DANNY LENNON: So I think maybe to start us off I'll kick it over to you Dave first, number one, I know that you heard at least some of that discussion and particularly in reference to that point, but maybe you can just recap to get everyone listening on to the same page – what exactly was that point that was most of interest to you, what is your position on that, and then also any clarification so that we're clear on exactly what your position is before we get into any other...?

DAVE FELDMAN: Well, once again, thank you for having me on. I really want to credit you guys for speaking to this particular combination. We're going to be saying the word triad a lot I'm sure in this podcast, and it's certainly a term that I've used quite a bit, and I think the best way to approach this is to sort of recap on a central point that you made within that podcast really that's already in the literature, it's something known as atherogenic dyslipidemia, and atherogenic dyslipidemia is typically characterized by having low levels of HDL cholesterol, high levels of triglycerides which is a measure of fat in the blood, and typically a high preponderance of small LDL particles. Now, what's fascinating is that we find within the low-carb community many people who go on a low-carb diet see an almost exact reverse

of that, they tend to see that their HDL cholesterol will go up, their triglycerides will go down, and separately their LDL may also increase, so that third one whether or not it's a high preponderance of small dense or not, typically they'll see that actually it's not a high at least proportion of small dense LDL particles. But in general, no matter who you are and whatever diet you're on, if your HDL is low and your triglycerides are high, you typically will have a higher preponderance of small dense LDL particles at least as a proportion; and conversely if your HDL is high, and your triglycerides are low, you tend to see the reverse, you tend to see a very small proportion of small LDL particles. So a lot of what we're about to talk about is going to have to do with those three markers together, and in particular, I'm especially interested in not just the high HDL and the low triglycerides but when it's combined with high LDL cholesterol – and that's a lot of what I really credit you guys for addressing probably in a more distinctive way than most of the podcasts I've heard that are outside the low carb community, because you wanted to address that in particular.

So I think a good jumping-off point is the one place where I kind of want to break out our differences is I think conventional medicine, especially in lipidology has a kind of lipoprotein centric viewpoint which is to say that lipoproteins are themselves pathogenic or in particular at least Apo B containing lipoproteins, LDL particles especially that they themselves at a certain concentration level will drive atherosclerosis. And what I sort of want to put on the table is something that I would call a kind of lipid profile centric model, which is to say that I want to distinguish how much it is that a lipid profile drives the disease especially of atherosclerosis or whether or not it's the disease that drives the lipid profile, and that's why talking about this triad, these two variations of this triad are going to be extremely relevant. And so if you don't mind, I'm going to actually read this quote that is

straight from the last podcast you had which kind of gives us a good opening and this is from you Alan, you were saying to dismiss the body of evidence, people are left clutching at straws, at very nuanced, very niche hypotheses. What they seem not to realize or heavy degree of cognitive dissonance in relation to is that all the nuances they put forward are inherently accounted for in the totality of the evidence base, and then you go on further – so inflammation is probably the best example of that when people say, well it's not LDL that's the problem, it's inflammation and you only get penetration of the arteries and oxidation in the context of inflammation. We have intervention stratifying people by their high sensitivity CRP and putting them on a statin intervention to reduce LDL and independent of whether their C-reactive protein levels are really high or really low, reducing LDL reduces heart disease risk independent of the presence of inflammation. And so I think from there this is where we're going to kind of get into really sort of the crux of this. See what I would be very interested in are those people who would have low cardiovascular risk markers across the board save the one of interest which is high LDL. And we can all acknowledge that this is kind of uncharted territory, because we really haven't had a population like we're seeing right now in the low carb community where that exists at a fairly large scale. There really are a lot of people who have not just high HDL, low triglycerides, but also low C-reactive protein which is a great marker for inflammation.

So that was one place where I literally stopped and I took the note down and I was like, oh okay, I really want to reach out to Alan and I want to find this out because I am yet to find a study that did, in fact, stratify for people with really low C-reactive protein, and see that the reduction of LDL, as an intervention against the control group, would show that. So I guess that would be my first question to Alan: do we actually have such a study that's stratified

especially for this very low risk population that we would expect to see this with?

ALAN FLANAGAN: Yes, so the lead author was a Storey, if I remember correctly, and I wouldn't say, I wouldn't characterize C-reactive protein in that study as extremely low because the participants were all in a cardiovascular risk profile, but what it – so the stratification was over three or under three, and so it's not a complete absence but it's certainly a delineation of what we would consider high levels of high sensitive C-reactive protein. And I think coming back to the point that I was illustrating by reference to that example and there are others is that for me, looking at a body of evidence, understanding that nothing is ever proven to be true in science which is why evolution is still a theory although Mike Pence never seemed to wrap his head around that one, but the idea that, I think you're right in the sense of the, what did you characterize as a lipid centric, in so far as historically the focus has been on LDL per se. Now, the nuance that's been added to that particular marker is a Apo B containing lipoproteins, and even before direct measurements of Apo B containing lipoproteins became more of the standard clinical recommendation, non-HDL cholesterol provided a more somewhat crude marker of atherogenic lipoproteins in circulation. And so while LDL per se has been the independent focus, we're talking about the sum of all potential atherogenic lipoproteins and it was something that we were quite clear or trying to be as clear as we could in the article series and in the podcast was the potential for a lipoprotein to be atherogenic is a function of its diameter size and also Apo B as a factor that both of which contribute to either entry into the artery intima in the first place, but the inability to come out through the adventitia.

And so the only way those lipoproteins can get back out is against a concentration gradient of blood flow, and then coupled with retention and those other factors, we have the processes

– and I think from a pathological perspective, I think those mechanistic aspects of atherosclerosis cardiovascular disease I don't think are necessarily that controversial anymore. The extent to which various lipoprotein subclasses may contribute to that is something that is more appreciated now in terms of the various nuances, and I think that is something where people maybe look out and say, oh well, maybe we were somewhat wrong about LDL, whereas the point that I was trying to make in the podcast was that nothing that has gone before has necessarily been invalidated even if we go back to Framingham. So we start with total cholesterol, we realize from that body of research at that time point that up to 35% of heart disease was occurring in people who had – were defined as normal levels of cholesterol, and the focus moves on to LDL and it doesn't invalidate the relationship with total cholesterol, it just adds another nuance, and when we get to this point in time where all of those preceding markers don't have the value that they once did but we've become more refined in our ability to be predictive, and that encompasses a pool of atherogenic lipoproteins from smaller VLDL particles to IDL to LDL of various subclass particle size and lipoprotein A. And I think when we take that as a total picture of atherogenic lipoproteins, we have something that independent of HDL and triglycerides remains the most robust marker of the potential for atherosclerosis plaque to develop and over the course ASCVD to develop.

And I think that the difference for me just to round this out in relation to the triad, the difference for me between that pool of atherogenic lipoproteins, for example, and HDL and triglycerides is I personally don't necessarily consider HDL and triglycerides to necessarily be independent risk factors, I would rather characterize them as different measured exposures that are somewhat correlated, and I think that there's a big difference between risk factors that are correlated in an overall

assessment versus an exposure that's an independent risk factor, and that's something we can dig into.

DAVE FELDMAN: Yeah. Well, there's a few things that you just mentioned that I would definitely like to dig into. The first is the emphasis on Apo B as opposed to LDL which is certainly something I'm very interested in from the lipid profile perspective. So Apo B, for anybody who's listening, Apo B, of course, encompasses the entire lineage, it's not just the LDL, and it's usually in the context of Apo B 100 to get a little technical, but basically it's VLDL to IDL to LDL. And that's kind of relevant because if you have, for example, high triglycerides, you probably have a higher preponderance of VLDLs, and that does tend to be associated with atherogenic dyslipidemia. This is also commonly known as remnants, basically remnants are those lipoproteins that are not LDL, in particular, or for that matter, not LDL or HDL. And remnants are, as a profile, is definitely highly associated with cardiovascular disease and thus the easy way to determine if Apo B is independently atherogenic is to subtract the remnants to determine how much LDL particle count actually plays a part in it, and it's one of the advantages of actually looking at triglycerides especially as triglycerides are low but there's very high Apo B, there's probably very low remnants because of course they tend to be triglyceride rich. And that's why a lot of the stratifications that I've been doing especially with NHANES was to take Apo B, particularly high levels of Apo B but against this triad of high HDL and low triglycerides. And what I find is quite astonishingly in especially all-cause mortality, it's the reverse of what you would expect it would be. Those people with very low Apo B, but yet high HDL and low triglycerides, tend to have worse mortality outcomes than those with very high Apo B and high HDL and low triglycerides.

In fact, the best combination, I probably shouldn't speak too much about this because I'm working with a biostatistician and we're ultimately going to turn this into a paper, but the best combination of those three markers is actually not just high HDL and low triglycerides, but specifically high Apo B as opposed to low Apo B, at least as far as the association goes, and I fully acknowledge it's an association, we'll probably be talking about reverse causation here in a second. But I also want to talk just real quick because you mentioned the concentration gradient is the means by which these Apo B containing lipoproteins can get into the subintimal space. They are actually, it's not entirely the case, we also know that there's a family of receptors on endothelial cells for both modified and unmodified particles, there's a means by which the cells can either endocytose or even transcytose. And the thing we haven't fully worked out is just how much these particles end up in the subintimal space by design through that process of, for example, perhaps transcytosis, that's something that's still yet to be discovered, we don't fully know that. But one other thing that should be mentioned is there's also the means by which these particles could end up in the subintimal space because, of course, in the case of the site of an inflammation, endothelial cells can't separate from each other. In fact, they intentionally become porous in order for immune cells like macrophages to be able to gain entry.

ALAN FLANAGAN: So I think, just to clarify, the point I was making about the concentration gradient was in relation to the difficulty that those lipoprotein as – one of the difficulties those lipoprotein sizes have of returning back out because they can't pass through in the way that HDL does, but I fully acknowledge that there's other in terms of receptors and binding other factors that lead to retention. So yeah, nice clarification. I think the interesting thing about the Apo B factor in the context of higher or low HDL, so first off, just in relation to HDL, I

think of all of the lipoproteins subclasses that are studied, I'd actually argue perhaps that HDL, and I am interested to get your views on this Dave for the associations that we have typically had at a population level between HDL and a protective effect, one, that has never translated in terms of interventions targeting increasing HDL for the most part. I think HDL remains and this was our title for HDL when we addressed it in the series is still somewhat of an enigma. And so, as the primary lipoprotein in reverse cholesterol transport and associated with the protective effects and it has other effects as well, I think that our understanding of HDL probably lacks behind our understanding of other lipoproteins in a more comprehensive sense. And so I think there are a few we don't knows over HDL and its exact role and I think the discrepancy between the population research where you do generally see a protective effect of higher HDL, I think there are various contexts in which that can be looked at and again this is where I think it's important to stratify risk factors that are correlated versus independent risk factors in and of themselves that are a target for treatment. And so...

DAVE FELDMAN: I'm really glad you're bringing this up. By the way, I would love to address this.

ALAN FLANAGAN: Yeah, so there is, I mean, for me there is a difference. So HDL is clearly important in the picture of cardiovascular risk, I don't think we fully understand what its role necessarily is in an independent context, I think the associations at a population level with lower HDL, generally speaking, they also depend, so if we look at hunter-gatherer populations, they have just low everything, they have low total cholesterol, they have obviously very low LDL but concomitantly lower HDL. And the idea that it's low HDL per se, that's the independent risk is the difficulty that I have currently with the extrapolations that are made from the population research. And the lack of an independent effect of directly increasing HDL

certainly through pharmacological means makes me somewhat hesitant in the context of our risk evaluation to consider it a specific target for treatment or conferring a specific reduction in risk from a change in its status. So I think, and that's where again it's correlated, but for me not necessarily an independent risk where again when we look at LDL or atherogenic lipoproteins in totality, and the evidence for a reduction in atherogenic lipoprotein burden whether that's in the classic high LDL context per se or in the context of the atherogenic lipoprotein phenotype which is the combination of the elevated triglycerides, LDL remodeling into small dense particles and low HDL in relation to that phenotype, we know mechanistically why HDL ends up low. But independent of those different phenotypes, there's a net benefit to cardiovascular risk when atherogenic lipoproteins are reduced, and I think that that is for me where there's a delineation between HDL as a correlated factor in the overall picture of risk versus an independent risk factor that's a target for treatment which is for me atherogenic lipoproteins.

DAVE FELDMAN: Yeah. So definitely I'm excited to be talking about HDL because I think it so effectively exemplifies what I'm talking about from a lipid profile perspective. What you're referring to, I'm sure, for example, the most dramatic example of this is the CETP, Cholesteryl Ester Transfer Protein inhibitors, and those, what they did was, it's kind of a banana shaped protein that allows for an exchange between a cholesteryl ester cargo and triglyceride cargo between, for example, HDL and VLDL or LDL, it's kind of a means of exchange. And when they inhibit that, it results in an increase in HDL cholesterol and a decrease in LDL is very successful at that. But I for one was not at all surprised that that was – definitely a huge help, it didn't work out very well at all, because I think

that the lipid system is in many respects just like a network, you want to think that if you go into a network and piece by piece take a packet and reduce its content or add to its content, you're not thinking of the whole. And that's why it's not so much what it is that you can do to raise or lower the lipoproteins per se as though that will increase or decrease their capability, it's why was that profile associated with better outcomes in the first place. And those things that people do that result typically in higher levels of HDL lifestyle wise, that's not chemically changing the lipid system itself tends to have that better association with the lower, not just cardiovascular disease, but lower all-cause mortality. HDL, and for what it's worth, I actually really like HDL because it truly is one of these things that I think we barely have cracked the book open on, there's so many subspecies of it, there's so many proteins we found on, and I think that we're still fighting on it that can be trafficked. And not a lot of people know this, we have way more HDLs in our system than we do LDLs. I think it's something in the neighborhood of I want to say 500 to 1000 roughly but HDLs to LDLs, I'd have to double check my math on that, but it’s really kind of a fascinating process with the lipoproteins.

I forgot the other aspect that you were bringing up that I wanted to launch into but it had to do, it has to once kind of come back again to how it is that we look at it from a profile perspective. There's two studies I would like you to take a look at if you get a chance, and I can link it to your listeners. One for example is isolated low high-density lipoprotein cholesterol cardiovascular disease risk factor, and this is one of the few studies that actually did stratify for those three

so that we could actually see this triad that's the reverse of atherogenic dyslipidemia where we see high HDL and low triglycerides coupled with high LDL.

ALAN FLANAGAN: Dave is that the Framingham Offspring study?

DAVE FELDMAN: Yes.

ALAN FLANAGAN: Okay.

DAVE FELDMAN: Where the odds ratios is extremely low, it's actually very close to that with the LDL being low. I really wish that they had done all-cause mortality myself, but even the fact that it shows that it's low, even if just slightly higher than that which has got the lower LDL, that's extremely relevant and I loved how they actually didn't have that much adjustment. So what I liked was they had, I think it was, yeah, I've got it in front of me, 3590 men and women from Framingham Offspring, and what I really enjoyed about this was that they took out people who are in cholesterol-lowering medication, so they helped to stratify those people for which their lipid profile was unlikely to be modified by medical therapy. And the other one, of course, is isolated low, high-density – I am sorry, no it's not that one, it's the – no, I think it is this one. No, here we go, low triglycerides, high-density lipoprotein cholesterol and risk of ischemic heart disease, and this is the Jeppesen study. This one's really neat because they had stratified two groups between very low – sorry very high LDL cholesterol, in your units it'd be millimoles, they had those that were under 4.4 for LDL in millimoles and those above 4.4, and then they sub-stratified to three groups below that. And so effectively the group that's at the

highest HDL and the lowest triglycerides are nearly identical to the group on the other side with the very high LDL cholesterol level, and I wish that we actually could just get these studies done more often rather than focusing just on the sick populations and just on those who have atherogenic dyslipidemia. Let's see just how much there is or isn't risk with especially cardiovascular disease, and those that see very high levels of HDL and very low levels of triglycerides, because I believe that the profile is extremely relevant in this regard.

And moreover, I really can't emphasize this enough, I think that the key – I think the key thing I want to get across to great people like yourself Alan is that the discussion on all-cause mortality needs to happen because we have already so much in literature on how much LDL is associated with the immune response. I have a long list of studies, you may already be familiar with it, but I'd be happy to go over some of these on the many different ways in which it binds to pathogens, for example, how it also carries out the tocopherol in our system, otherwise known as vitamin D, and how that's relevant to lipoprotein contact with reactive oxygen species. And many of these things may turn out to be clues as to this association with cancer, and it may not be, I don't know for sure, but the bottom line is I do think that we need to be able to see this triad especially as it associates with all-cause mortality so that we can make a better decision on how it is that this is or isn't associated with risk.

ALAN FLANAGAN: I think a couple of things on those specific points, the first in relation to Framingham Offspring, if I remember

from looking at that, and you're right, it was nice the way that they presented the different measures for triglyceride LDL and HDL. But when I looked at the risk reduction in that study, what stuck out to me was, yes, in that population, it appeared that low HDL confers a particular risk in individuals and the high HDL low triglyceride combination appeared to associate two things, if I remember from that study, one was that that association wasn't necessarily linear and it was somewhat inconsistent. But the second was when I looked at the relative risk reductions in those various phenotypes as they presented them or those various profiles, the ones with the greatest relative risk reduction were still the ones with the lower LDL. So with the low triglycerides high HDL the ones that were stratified according to that context, the ones between different levels of LDL that had lower risk were the ones with lower LDL. So again that to me is something that comes back to this idea that I was saying of the difference between risk factors that are directly associated with an outcome in a causal sense versus risk factors that are correlated in some way, in an overall profile. And I think then just in relation to the second point about the kind of the – and please correct me if I'm wrong – but the second point you were making about the kind of the difference between say the LDL and HDL levels in terms of kind of mortality outcomes, but is that related to the idea of, and I know this is something that in the last couple of years has become much more appreciated is the difference between concordance and discordance in terms of lipoproteins, either Apo B or LDL or the particle number and the correlation with LDL cholesterol or non HDL cholesterol, and because if that is what you were broadly referring to or

certainly that's what we – I think this is coming back to this point I've said or the quote you said at the start of a nuance – so we previously had discord or disconnect in, I think disconnect is the better term here, because in the population research there has been a disconnect between some of the profiles that we would expect to be atherogenic, when there is just a measure of LDL per se, for example, and also low Apo B. And so the potential for high LDL cholesterol or high non HDL cholesterol in an encompassing sense but low Apo B, and that still confers a high risk, whereas the Apo B predicts a lower risk in cases where there is groups with low LDL cholesterol or non HDL cholesterol but high Apo B and they have the reverse.

So that is discordance, in my understanding of discordance, but I think from what we know currently, I think it's important to relate back to the literature on discordance seeming to suggest that it's probably about 20 to maybe, give or take, 20-25% of the population. So in terms of thinking probabilistically about risk management for the population, while I absolutely appreciate that there is this subset of a cardiovascular risk factor population where LDL or non HDL cholesterol and Apo B are not in concordance with each other and therefore differentially related to risk, that still is again a subgroup of the population. We should be investigating that further as science does, but it still for me comes back to the fact that if we're talking about risk management at a whole population level, there's still going to be a vast chunk of people at risk for cardiovascular disease or atherogenic cardiovascular disease who in the context to my mind of the available literature are going to benefit from a net

reduction in LDL and that's going to be independent of the Apo B factor because there will be relatively concordance between those two markers.

DAVE FELDMAN: So let me see if I can restate your position in the way that I think you're stating it. This is, in a sense, you would be classically as its associated with LDL, you would feel that LDL is kind of like smoking, in the sense that whatever two groups you compare it to, even if one group is healthier because of having a higher HDL and lower triglycerides, that said, comparing that group with low LDL to a likewise group that's identical in virtually every other way but has high LDL, the first group is at lower risk overall towards death period.

ALAN FLANAGAN: Yes…

DAVE FELDMAN: Right, towards an all-cause mortality.

ALAN FLANAGAN: That's what I'm saying and that's illustrating the point that the difference between a risk factor that is correlated in an overall picture versus a risk factor that is independently causal and for which then is a direct target for treatment.

DAVE FELDMAN: I actually would agree with you, I would actually agree with you if that's what the evidence showed. I would agree that basically if we could look at high and low LDL in every possible cohort group at scale, and it shows that those people with high LDL are dying more than those likewise cohorts with low LDL then it's comparable to smoking, you're just better off having lower LDL.

ALAN FLANAGAN: To my mind that's what the Framingham Offspring study somewhat showed in terms of risk. I know

mortality wasn't an outcome if I remember correctly.

DAVE FELDMAN: No it shows it with cardiovascular disease, and that's the what you die of, not the when. So looking at a particular stratification of a particular outcome is not something I was interested in as I am in all-cause mortality.

ALAN FLANAGAN: So this is something in your kind of writing and just your work generally that I've picked up on is you're quite focused on the actual outcomes themselves, I wonder if you would elaborate for me somewhat on, one, why the emphasis on all-cause mortality if for me we're specifically kind of talking about something that relates to a specific disease, I'm just interested to get your thoughts on why all-cause mortality for you is a particularly important or more important outcome.

DAVE FELDMAN: Well, for sure and, I mean, it's absolutely the case that if the reduction of LDL would have no other pleotropic outcomes, I mean, that's basically how we think of smoking right now, there's effectively no benefit – there's no group for which if that group smoked, its likewise cohort that doesn't smoke would have a better outcome for not just lung cancer and ischemic heart disease but for all-cause mortality. That's really what I focused on in quite literally the first couple of weeks after I got my initial blood test in November 2015 before I knew anything about cholesterol or lipids or anything. I immediately went to the literature and I said, okay, well, I should be able to find that those people who naturally have low LDL would live longer than those people than – well, for that matter, than the population average. For example, PCSK9 loss of function that should

confer a longevity benefit, people should just be straight-up living longer if they had that. Or for that matter that those people who took steps to lower their LDL in a very material way would show that just as we would see with smoking, and I wasn't finding that. I was finding that indeed, particularly in later ages, there were plenty of studies that were showing that it was a higher LDL tended to associate with lower all-cause mortality, and that did lead me down the road of, well, is this reverse causation, is it because what's actually happening is the disease such as say cancer or some forms of cancer could be associated with lower LDL, and that's creating this association for which you would see some people with low LDL dying sooner. And that further took me down the rabbit hole trying to find every single piece of evidence I could that especially took us out to longer and longer ranges. You mentioned Framingham – Framingham actually has one such study that found that indeed it was a cancer risk and it wasn't just within a few years, they took it all the way out to 18 years. And this is why I brought up immunity and the immune response and how much LDL is associated with it, what there is already in the literature is because if we look only at how you can die of one particular disease, then we have to feel confident that that intervention or that change isn't affecting other possible endpoints, other possible ways one can die. And I don't think we're anywhere close to determining how much lipoproteins, especially LDL has engagement with the immune response, and unfortunately the immune response such as almost all major diseases. Does that make sense?

ALAN FLANAGAN: Yeah, it does.

DANNY LENNON: To me it seems like there's some really interesting discussion we can have about all-cause mortality for sure, and so we'll definitely circle back to that. But just to clarify a couple of points, because I know this is where, or at least to me what I had presumed, some of our disagreement may center on Dave was really in two very related but kind of separate things. One was obviously directly looking at this lipid triad and the risk that confers and then more generally the causal nature of LDL which we may have a disagreement on, but presumably that was in relation to cardiovascular disease, and I think I've seen at least in some of our Twitter exchanges but also in maybe some of your presentations the hypothesis that this lipid triad of high LDL, high HDL, low triglycerides, you would suspect that confers a lower cardiovascular disease risk, so regardless of what that LDL number is in the context of those other two, you wouldn't see an increased risk of cardiovascular disease with increasing LDL. So I just wanted to confirm first, is that an accurate representation of how you see the relationship between that lipid triad and cardiovascular disease risk?

DAVE FELDMAN: I think that the lipid triad likely confers a below-average risk of dying of cardiovascular disease. I don't know that I can elaborate beyond that other than that's the evidence that I've seen up to this point. I think you and Alan, to steelman argument this, I think you and Alan would rightly say, okay, whatever evidence is out there that does show that it's below average, it's still in relative terms higher than when compared to a likewise cohort that has lower LDL cholesterol. Right?

DANNY LENNON: Correct.

DAVE FELDMAN: And this is where I have to say this, and I don't say this to be contrarian, but here's the one problem: the one problem is saying that you're dying less of disease X is exactly equivalent to saying I'm dying more of disease non-X. So we have to be able to determine, and it's hard to do, we have to be able to determine that those things a population is dying of that is not disease X, didn't change timelines on us, didn't possibly move up in timeline. Does that make sense?

DANNY LENNON: So in that context, if we're talking specifically about atherosclerosis development and therefore cardiovascular disease, would you be comfortable with then the LDL being causal in that, but your point is more that, yeah, even if that is true, we should look at all-cause mortality because maybe this lower LDL is causing something else, or are you still in the position that LDL doesn't have a causal role to play in cardiovascular disease specifically?

DAVE FELDMAN: Oh let me correct that real quick, I don't believe I've ever said, and certainly I'll correct the record now for anybody who might have the misimpression, I think Apo B containing lipoproteins are a part of atherosclerosis, a part of the process of atherosclerosis. To be fair though, so too are macrophages, right – it's that the question isn't whether they're a part of the process, the question is whether they are the initiator of the process and/or whether they are the progressor of the process, and that's the key, that's the key distinction we're kind of breaking down, like is – and really this kind of predates us by a lot, this goes back to the 70s, is this response to retention or is this response to injury. And I certainly feel I'm leaning much more into the camp of

response to injury, I think you guys would say you're leaning more towards the response to retention, would that be accurate?

ALAN FLANAGAN: Well, so personally, I right now think that that is too crude of a delineation, and I've seen those arguments, response to injury versus response to retention, and I think for the kind of biological systems that we're talking about, for me that's too crude a delineation. I think there is a response to injury and a response to retention, and I don't know how much it helps us in our analysis of the progression of atherosclerotic cardiovascular disease risk to stratify the most. Retention is a big part of the process, sure, but so is the initial injury. But what I tend to come back to and I think of the injury part is that, and this is where all of these other factors like inflammation come into play or even coronary artery calcium which has become a kind of popular marker to focus on, but it's not a biomarker of risk, it's a biomarker of damage retrospectively, and in order for the damage to take place there has to be atherogenic lipoproteins penetrating the arteries and depositing cholesterol and all of those other processes that happen from that. And I think when I focus on this idea of is it driving or is it a consequence, I think the most persuasive evidence to my mind in relation to that is the fact that populations, we have a couple of strands of evidence from populations in the kind of natural world and hunter-gatherers for example, in addition to the effects of interventions by various means, not necessarily statins but PCSK9 inhibitors or a combination, for example, of statins and ezetimibe because of the evolving use of tracers in nutrition science, I think that stable isotope tracers are

going to really open up a new level of our ability to understand postprandial dynamics in particular, not just for lipids but for everything, for all substrates.

So I think that's a case of kind of watch this space, I definitely think that endothelial function in the context of cardiovascular disease is a hugely important factor. I think that I've always had a hesitancy with the studies about LDL in the elderly because I think two factors play into that, one, I think we are opening up somewhat of a multiple worms in a can when we look at populations above 65, 70, 75 which is from what I can see uniformly where the idea of LDL being protective or associated with longevity comes from populations that have already got to that stage. We're then taking this snapshot of a point in time at that life stage and saying this relates, but there's two issues for me with that, one is that it doesn't speak to levels over the course of a lifetime; two, what we know about certainly exposure or, I mean, all chronic lifestyle diseases but particularly cardiovascular disease is that it's the cumulus of life long exposure. And this is another point that we were kind of really going out of our way to make with the Sigma statements is that it’s not that you have a stake and your LDL goes through the roof, it's a cumulative integrated exposure over the course of the lifespan. And the autopsy studies from Vietnam and Korea were probably one of the first places where that was realized, oh atherosclerosis can develop from the second decade of life.

So it's a cumulative exposure, and so I think that a problem when you start to look at populations that are 70 plus is that, for the most part, a lot of people

that have atherosclerotic cardiovascular disease are going to be in and around dead by, for the most part, when you look at kind of average life expectancy and it's increased in the last 20 years, 40 years, sure – certainly in the 1950s, 60s, 70s you were looking at people succumbing to cardiovascular or coronary heart disease at 50, 55 years of age. So I think that there's a time course difficulty with that relationship between higher LDL in the elderly and longevity, and the second issue I think with that is if it's an effective of cumulative exposure over the lifespan, what we understand about the treatment, and this is something that I've seen a couple of the kind of, the lipid skeptics in the UK present is the data that they use to show that there's a lack of a net benefit to lowering LDL is also in this age demographic, they're generally studies in the kind of 60, 70s, 75 plus where at that point, interventions, particularly statin interventions to lower risk are not necessarily that effective, but that's a reflection of this cumulative lifelong exposure and it's a reflection of the fact that after atherosclerotic cardiovascular disease is already so advanced that the net benefit to treatment at that stage is essentially too little too late, whereas in the analyses that have stratified reduction relative to age when you intervene, you get this greater magnitude of effect as you go down the decades. So if you intervene in the 40 to 50 age bracket, you get it low, then you've got this much more pronounced risk reduction. And that for me comes back to the idea of a more viewing atherogenic lipoproteins and LDL over the course of the lifespan as a risk, as opposed to at any isolated point in time, the Mendelian randomization studies for me kind of added something concrete to that idea.

DAVE FELDMAN: Yeah, let's say, we put a pin in the MR, because I want to get back to that in a second, what's the best evidence in your opinion for early intervention showing a net benefit in all-cause mortality?

ALAN FLANAGAN: This is the thing, in relation to all-cause mortality, I can't answer that question, because I've generally not had the kind of focus on this subject in relation to all-cause mortality. So I've viewed this through the lens of ASCVD and CHD quite particularly, and that's why I was keen to ask you about why you consider all-cause mortality a particularly important outcome. So in relation to that all-cause mortality, I can't necessarily answer that, but obviously in relation to cardiovascular and coronary heart disease, it's there.

DAVE FELDMAN: But there's two – I think the problem is we all naturally make two assumptions, when we're talking about the reduction of – let's get off cardiovascular disease for a second, let's say cancer. If I, let's say, I had a pill for you that I said this cures cancer – your instinct is to make two assumptions – if you believe I'm right, then the first assumption is, good, the world will not have to deal with cancer; there's a second sort of assumption you don't realize you're making, which is that there's no tradeoff, that in the reduction of cancer you haven't increased the risk of some other disease or multiple diseases. And that's what I think is a major disconnect that I'm anxious to have this possibility that's being put on the table to be disproven, that if you reduce LDL – or for that matter that when we look at populations that have low LDL and they have higher rates of cancer and it doesn't seem to be just within a few years of the study, but within half a

decade, a decade later, like if you go to the NHANES data right now, I mean, your listeners could go to the CDC, they could pull down the NHANES data, they can do the same stratifications I've done, you look at people with low LDL and you even eliminate everyone that died within say five years or even 10 years of when they got their blood work done, they are more likely to die of cancer. If they're more likely to die of cancer, they're less likely to die of non-cancer related diseases, and that includes cardiovascular disease. That's why all-cause mortality has to be a part of the conversation whenever you're wanting to make a claim of mortality benefit.

ALAN FLANAGAN: Yeah, I think for – and I absolutely see that thinking and why it can be important, and I think the only thing for me is, well, certainly when we specifically talk about cancer with other lifestyle diseases like cardiovascular disease or type 2 diabetes even or even neurodegenerative disease which interestingly there's a big overlap between the lipid, I mean, the net reduction in dementia from people on statins is enormous, it's like 30%. So there's this overlap between cholesterol hypotheses, between heart disease and the pathophysiology of dementia and Alzheimer's which is interesting. But anyway the point I'm making is that these diseases are diseases that we have somewhat more of a handle I think on the pathophysiology of, and that's something that we're still evolving our own knowledge of, but with type 2 diabetes of the various risk factors, but we can still hang our hat on the twin cycle of peripheral insulin resistance, progressive pancreatic beta-cell dysfunction, and ultimately failure and these pathophysiological processes. My thing with cancer, this is a general thing

by the way, it's not even related specifically to this conversation is I have a reluctance with pulling cancer into, as a disease, a comparison – one, cancer in the singular doesn't exist, it's an umbrella term for diseases that have somewhat similar unifying characteristics, but in their actual behavior in terms of metastases and otherwise are completely different; two, I think our understanding of cancer is still in many ways evolving to a point where the underpinnings of cancer like with pancreatic, for example, cancer, the hypothesis that in fact the cancer only appears in the pancreas has been ultimately in the body and growing prior to it manifesting – so people historically are assuming, well, it means once you get a diagnosis that the cancer has appeared in the pancreas; there's a hypothesis now that, well, it's appeared elsewhere and it's only showing for the first time in the pancreas.

If these underpinnings of cancer somehow have an impact on blood lipids then that's something that may be specific to cancer and it may be something that is indicative of a time course of cancer progression but that it relates to LDL being low as a causal factor, I'm hesitant to think what is the relationship that people who when they start to develop cancer in its earliest form begin to have both their impacts on physiological processes including LDL and other lipoproteins. And so, I'm really, I have a reluctance to looking at cancer in relation to low LDL, and I accept certainly in the elderly there is that relationship, but I have a reluctance of relating it to low LDL being a risk for cancer versus some sort of impact of the time course of the disease itself. And I think that's why for me, I mean, in terms of talking about mortality outcomes,

yeah, we can relate other lifestyle diseases to potential benefit to treatment but I just – yeah, that's just a personal thing, I have a reluctance with linking cancer into the comparisons with other lifestyle diseases. But I have that in all of these conversations.

DAVE FELDMAN: Yeah, and I think that, as I kind of emphasized before and I will emphasize again, it's associative and I don't think, as is the case with epidemiology, I think epidemiology is not good at proving causation, it is however fairly good at knocking down claims of causation. If we had – and let's kind of bring in the centenarians, there's a good example, I need to have the biostatistician double check my math on this, but I looked at the centenarians that are in the NHANES dataset right now, and unfortunately we only have one cycle for which there could have been centenarians and it's because the total amount of time that it covers right now, that includes both lipids and mortality is from 1999 to 2015.

ALAN FLANAGAN: Right.

DAVE FELDMAN: Right. But if you look at the 1999 set, I think it may be 1999 and 2001, but if you look at that set, you can only find five people that have made it to age 100 and later and are currently under the status of assumed alive, as in those are the five that made it to age 100. All five of them have high LDL in 1999 and 2001, as in they had it 15 years before they were then recorded as still being alive, they all had high HDL and four of the five had low triglycerides. Now, if you're one of these people who'd be like, you know what, this is still associative, we can't say anything about it, but it turns out that the five people who became centenarians were all three pack

a day smokers. We would suddenly stop and go, what, how is that even possible. That's why I bring it back to let's find out those things that may associate and may be relevant and see if there's also further mechanistic data that suggests LDL may be incorporated in these other processes, and then just also do the smoke test to try to actually see how that relates back to what we see in the real world when we do a headcount to see those people that survive and don't survive. You brought up a little bit earlier that it could be survivorship bias, right, that maybe those people who survived into middle age with high LDL are more likely to go the distance with high LDL.

ALAN FLANAGAN: Well, just to clarify on that, what I'm not ruling out, what I think maybe possibly also happening is that in the elderly is it possible that they actually had lower LDL over the course of most of their lifespan and LDL starts to increase as a function of age. And I don't think we necessarily, I would really like to see a bit more data on the time course, a long-term kind of profile of LDL because – so just to clarify that what I'm careful not to assume is that the people that are 75 with high LDL have high LDL for their whole life, and I find it difficult for me to make that assumption simply because of the cumulative lifetime exposure. So there's a possibility that they start to have increasing LDL as a function of age potentially – I don't know and the data isn't clear on that, which is one of those nuances I think needs to be teased out a bit more.

DAVE FELDMAN: And if my memory serves correctly, I have seen that at least as far as where we do have longitudinal data, it does tease out that, typically speaking, as you're younger and as you get older – when

you're younger, your LDL tends to be lower; and as you get older, particularly coming into middle age, it kind of plateaus off and then it typically starts to slightly decline if you're looking at the population as a whole and just tracking the mean. But to your point, I think that's a 100% fair, I think that we should be looking more at longitudinal data. Period. I would like to be seeing people who have been – part of the problem is though is right now people who tend to have higher LDL in prior datasets were already getting treatment, especially if it was extraordinarily high, especially if it was double the recommended amount. It's only just now with low-carbers, this includes myself, for which we're saying, well, given the evidence that we know up to this point in time, I'm going to go ahead and not take steps to lower my LDL, because I feel that the evidence as it stands right now has not led me to do so, but it doesn't mean that my mind's not going to change with the evidence. Naturally, I'm going to have to plug just because it kind of gives me the opportunity, I don't know if you guys knew this that I'm actually trying to get together a – I'm trying to put together some data that may ultimately become a study on this phenotype of a special interest to me, the lean mass hyper-responders because they tend to have extremely high levels of LDL, and also have the triad and have a high HDL and low triglycerides, and we're going to do CT angiograms on them and have a very strong comparison on the geography changes with their cardiovascular system. And we'll find out, I mean, that's the best way to actually...

ALAN FLANAGAN: Are you enrolling long-term follow up with that cohort, like plan to do five to 10-year?

DAVE FELDMAN: That's what I want. But, I mean, it's going to be dependent on their interest in participating. We have from a very high-level expert, somebody who you would know and who I can't name at this moment in time, but I guarantee you'd know who this person is, who is definitely very high expert in CT scans imaging, who says – because we were originally planning this to be a five-year follow-up – he says it's more than fine at one-year given how high the effect size is for their LDL because, of course, their LDL starts... I think in your units it starts at around 5, LDL starts at around 5 and goes up, basically 200 milligrams per deciliter, that's like the starting, that's the floor. So I think our mean average will probably be close to 72 or 300, something in the neighborhood, very close to heterozygous FH levels.

ALAN FLANAGAN: Okay. So you'll do one-year follow-up before and after?

DAVE FELDMAN: Yeah, and this is a good time – what would you predict, do you predict that we'll see rapidly progressing atherosclerosis in this cohort?

ALAN FLANAGAN: I would predict that we would see a progression, yeah, whether it's rapid or not, I'd be to scientifically conservative to say what the rate would be, but I would predict that perhaps there would be a progression, that would be my hypothesis that I would support at this point. And I think that for me a big part of this phenotype or this triad is the triglyceride part because, again, the historic emphasis on triglycerides as an independent risk factor have tended more recently to be attenuated or fall away when non-HDL cholesterol is adjusted for. So it's the triglyceride content of atherogenic lipoproteins that is problematic. I think there's one

phenotype that we can kind of just say it is a risk, which is the atherogenic, the ALP where someone has high triglycerides; and as a function of the level of triglyceride they have, there is a remodeling of LDL and HDL and that is some – and you mentioned CTEPH earlier, but the exchange of lipid for cholesteryl ester is equimolar, otherwise the weights are unbalanced. And with that high triglyceride level, you get a dumpling essentially of triglyceride onto lipoproteins that don't have that lipid capacity, and so we end up with HDL catabolism and an LDL remodeling. So that phenotype aside, in the triad, we're looking at, and the reality is that within that phenotype, you have a high burden of triglyceride within atherogenic protein, so VLDL, LDL, IDL. With the low triglyceride component of your triad, what I still can't, I think, mechanistically wrap my head around – and again you can elaborate on your ideas on this – is that there is still a pool of atherogenic lipoproteins, from what I understand, that is going to be present in the form of the transcendence from dietary intake to LDL. It may not be liver synthesized via LDL but a really nice, very recent tracer study, stable isotope tracer study indicated that in response, and it stratified participants relative to triglyceride levels, but what previously has been the focus has been chylomicron remnants and it may be that that term gets done away with if this research is replicated because chylomicrons have been hard to study because they are rapidly – triglyceride in chylomicrons is rapidly broken down. What was really interesting about this study was that the greatest concentration of lipoproteins of Apo B containing lipoproteins in the postprandial periods were in the VLDL density range. And so, I think that while historically just looking at this kind of,

again this discrepancy between chylomicron triglycerides from dietary intake, triglyceride and VLDL from liver synthesis, I think in your triad I can certainly understand why there would be less liver synthesis of VLDL, but I still see with a very high, there's still fat coming in through the diet, right?

DAVE FELDMAN: Yeah, and I should correct you, I believe that there actually is enormous secretion of VLDLs, particularly for lean mass hyper-responder. This is sort of a disconnect with a lot of people is that including – you'll probably be able to get this, a lot of people may not, what I believe is the mistake people keep making is they assume that the turnover rate for the triglyceride cargo on the VLDLs is at a constant, it's at a constant rate in the periphery, and I categorically reject that. I believe that there's absolutely a variable amount of turnover and has a lot to do with the existing demand, especially in the peripheral tissues, and if that demand is high, particularly if you're powered by fat, then you're going to have a lot more turnover of triglycerides, both in the VLDLs and the adipocytes, and that's creating the downstream higher levels of LDL particles.

ALAN FLANAGAN: And so it's interesting that you say that because what this tracer study shows, and it was literally published in January, was that the chylomicron – the intestinally derived lipoproteins that were in the VLDL density range, the time course of them was extensive. So in chylomicrons Apo B returned to near zero at around 24 hours in everyone, independent of triglyceride levels. But while they were cleared quickly, so the normal period of fasting kind of, generally speaking, before the analysis, the intestinally derived VLDL

lipoproteins were present in both VLDL 1 and VLDL 2 at increasingly higher concentrations over the course of the day. Now, I will say that that effect was most impaired, as in the area under the curve, for VLD 1 and VLD 2 intestinally derived, as in from dietary intake, was significantly higher in the high triglyceride subjects compared to the average and lower triglyceride subjects; plus there was still a significantly long time course that's over the – and so what that's saying to me is that the reality is that total plasma Apo B in the LDL and plasma Apo C3 increased in everyone but then there was a relationship between the magnitude of increase relative to triglyceride concentration. So with that in mind, I would view the low triglyceride aspect of the triad as not – I'm not convinced that that's entirely an independent marker of no risk or low risk, so to speak, because I still think that there is a time course here of circulating atherogenic lipoproteins that are intestinally derived.

DAVE FELDMAN: And this is where we're at a division that goes all the way back to the beginning. You're thinking about in terms of a lipoprotein centric model. I'm still thinking about in terms of a lipid profile model. I'm thinking the disease gets reflected in the lipid profile, and what the count of the HDL and the triglycerides and the LDL are relative to other things that were used to being present. You mentioned Apo C3, it's a good example. Apo C3 you tend to see less of when somebody's much more insulin sensitive, and I think that's not by mistake. I've changed my own lipid profile to an atherogenic dyslipidemia profile by eating a whole bunch of white bread and processed meat, and I did it in one week. Actually, I helped to tank

my LDL particle count in my LDL C just by eating preposterous levels for it, because – go ahead.

ALAN FLANAGAN: Well, that's eating a week of refined carbohydrates.

DAVE FELDMAN: Right.

ALAN FLANAGAN: But we know that that means you didn't eat oats...

DAVE FELDMAN: We know that that's – exactly, if I continued on that diet, you would expect that I would probably have a more atherogenic dietary profile, you would agree with that, right, like you wouldn't even need to look at my lipids. You'd say, Dave, if you keep eating like that, you're probably going to give yourself a heart attack ultimately, right? And if I came back to you, but you don't...

ALAN FLANAGAN: No, no, I – yeah, I'm agreeing that the atherogenic lipoprotein, the ALP is a significant risk factor, yes absolutely.

DAVE FELDMAN: And so I could come to you and I could say, look, I got my lipid profile done, and I only looked at LDL, and my LDL was 83 which by the way was what it was in my overfeeding because that's part of what I was trying to prove, I was trying to prove how fast going from a fat based metabolism to a glucose based overfeeding metabolism would look like. But it's profile based – how do we determine that it's not profile based and is in fact lipoprotein centric? All we have to do is look at high LDL and subtract the atherogenic dyslipidemic profile, that's all we have to do. And if we find that those people with high LDL, in spite of having high HDL and low triglycerides have a high rate of cardiovascular disease, then it is, it's like smoking. At that point we can feel more

confident. And per the two studies we just mentioned earlier, where they do stratify by those three, I think at a bare minimum, well, maybe I'm wrong in this, I think at a bare minimum we can agree that the combination of HDL and triglycerides is definitely far more predictive of cardiovascular risk than LDL alone – or do we agree on that?

ALAN FLANAGAN: So that's I think going back to the point I was making about the correlating factors versus an independent risk factor. So for me, I think we need to have caution when assuming that an exposure is an – or independent risk factors, when they're actually measured, when there are measured exposures that are tightly correlated. And so for me, triglycerides and HDL are correlated as exposures but they're not independent risk factors, and LDL for me satisfies the criteria for a causal independent risk factor that there is a benefit to targeting for treatment. That's not necessarily to say that those other parameters don't give us an indication, they do, and I think if, for example, the REDUCE-IT trial, so we know that there can be a residual risk in interventions that lower LDL that's generally related to the remnant aspect, so the increase in plasma triglycerides. And in the REDUCE-IT trial they put people that were already on statins for reducing LDL on 4 grams a day of EPA of the long-chain omega-3 fatty acid, it was a pharmacological version, it was like icosapent ethyl, and further reduce their cardiovascular events by 25%. So I'm not saying that those factors like triglycerides and HDL are irrelevant. I'm saying there's a difference for me between a factor an independent risk versus correlation factors that can be in the equation but don't necessarily individually tell us about risk over the long term.

DAVE FELDMAN: I have a funny offer I'd like to make that I've never done on any podcast. Are you ready? You work with the UK Biobank Data, my guess is, right, as a researcher?

ALAN FLANAGAN: I don't but, I mean, I'm very familiar with Biobank.

DAVE FELDMAN: Okay. I would love to run this stratification in the Biobank Data, for example, looking at high HDL and low triglycerides, and then having as the stratified variable LDL looking at low LDL to high LDL in this context, and I'm going to make a prediction without actually knowing because I don't have this data at all in front of me, I don't have any access. I believe that you're going to find, if you compare, likewise aged groups, you're going to find an association with lower all-cause mortality with higher Apo B in particular, not just even LDL, but higher Apo B where HDL is high and triglycerides are low. You would predict the opposite, right?

ALAN FLANAGAN: If we were stratifying people by triglycerides and HDL with LDL remaining constant?

DAVE FELDMAN: With age parity, that's also important, that you're not looking obviously at a young group versus an old group because that's not going to work.

ALAN FLANAGAN: Absolutely. I think the age comparison is really important when we talk about these risk assessments, and my prediction in that context, my hypothesis would be, and this comes back to when we were discussing Framingham a bit that if you had people with low triglycerides and high HDL and you stratified that relative to LDL, but the lower LDL would have reduced risk,

relative to the same profile of triglyceride and HDL but with higher LDL.

DAVE FELDMAN: And I think that would be very meaningful to the people who follow my work, because right now I'm looking at NHANES data and I see the opposite. And so I would like to check that against other datasets, I would like to actually...

ALAN FLANAGAN: ... against a dataset with them with some genetic component as well which the UK Biobank is one of the largest datasets with genetic information as well.

DAVE FELDMAN: The only requirement is, I'm sure you would know if you follow my work at all, is it's got to be no to minimally modified, and I'm glad you actually brought this up in the prior podcast, I'm not a big fan of a lot of adjusting, I don't like how – because we're working with large datasets these days researchers, especially depending on what the goals of the funders are, can start with such a large dataset that they can know a conclusion they'd like to get to and then work their way backwards through sometimes very convoluted methodologies and so forth. I like it like I like my food, whole and unprocessed with as little additives as possible.

ALAN FLANAGAN: Yeah, I think in epidemiology, in particular, I think there's a cult of over-adjustment particularly currently. I think we seem to have confused confounders with effect modifiers, and if you read Sander Greenland's work or Kenneth Rothman or even Austin Bradford Hill, these guys really understood those differences and still do. But I think that in the wider space everyone just assumes that any relationship in epidemiology is a confounder and that's just categorically

incorrect, and confounders and effect modifiers are completely different. And yeah, I think there is a tendency to obscure true relationships when a factor that may be a related factor but not in any sort of confounding or causal senses is over adjusted.

DAVE FELDMAN: I agree, and I can't possibly emphasize enough, if I really was somebody who felt that epidemiology was good enough to make the claim of causation, well, then I would just close the book on that, you know, tell everybody it's all good, go home, don't bother doing any further research. But I mean, part of the reason I like the opportunities to do what we're doing right now, to engage with people of different opinions, for that matter in this documentary I'm putting together to get more interviews with people of a wider spectrum of opinion, it's because I really wish more people especially in the nutrition space would get exposed to lots of good opinions on both sides, try to find the best arguments on each side, and then see where you feel the data is lining up.

ALAN FLANAGAN: Yeah, I think when it comes to nutrition, that’s wishful thinking. I think there's a problem with belief systems in nutrition that means that these conversations can be intractable unfortunately. So yeah, I'd love to get to that point where we can sit back and have measured discourse with different opinions, but it can be difficult in nutrition unfortunately. But yeah, I think you're right, it would be great to have more productive dialogue on these issues. I think for me, as Danny will know, I am a big fan of epidemiology, not because I distort what it can and can't show, I just think that too much of the conversation around all of these factors, nutrition related or otherwise are generally dismissed as well.

Association isn't causation, and that's the statement of fact, it's not critical appraisal. Association is association and association when it's temporal and crosses populations and it's consistent and has a degree of strength to it, can be a powerful indicator of a causal inference, not demonstrable causality. And for me, for example, I made this, you know, we made this point in the lipid series, the relationship between saturated fat, for example, and heart disease is evident when you don't control for blood lipids. Of course every analysis goes and adjusts for blood lipids, and then boom, the association becomes weak positive or slightly null, and you have an attenuation of a relationship that's a statistical over adjustment and not necessarily a reflection of a causal chain because it's not direct. So I think observational epidemiology and nutritional epidemiology is incredibly useful, and we should, I think if we're having these conversations, it's incumbent on us to get to know it and to understand it better so we can have more productive conversations rather than simply say observational research is all confounded and nonsense and we can't trust it.

DANNY LENNON: One thing I did want to maybe pull back on and ask about Dave, because I think we've gone into lots of really interesting details, and I think why these types of conversations are so at least interesting to me and why I like having them is because there's all these areas we need to think about a bit more, here's a particular type of case that we don't have enough data that we would ideally like to have, and therefore we can think about all these different types of studies that we would like to see in the future to get some clarification on that. But in lieu of getting to that point, we still need to

have a particular position on this topic, and so to me that brings it back to I think one of the things that we now have discussed on the podcast as well of what do we take to be our default hypothesis for the moment, because there's these different hypotheses we can have of, hey, I've got high LDL that's conventionally through the roof but there's this hypothesis that suggests I'm not actually at increased risk. So that's one hypothesis versus lipid hypothesis, and again in the most accurate and robust form of that, not the strawman version some people paint, but the one that takes into account other risk factors are part of that, it's not just LDL that's going to cause you to definitely have a heart attack, it's that it takes into account inflammation, endothelial function, and so on, and is a matter of risk as opposed to this guarantee, that this one individual is going to succumb to this. But in those cases what I worry about whilst a lot of your hypotheses are very interesting and make really good points, what I worry about is how some people might interpret that, right, and interpret that to mean oh Dave Feldman says X, that means now my LDL is through the roof, but I'm not on any risk because I follow a certain dietary pattern. Now I think through the course of this conversation and if you look at any of your longer form piece of writing, I think what I do like is you're very good to place caveats on things to state that certain things are hypotheses or areas that we need to look more, and I totally get that. So my fear is how people may interpret that and see that there's these different hypotheses, and in some way think that they are equivalent, because my position would be that in terms of the evidence that we currently have, they are not necessarily equivalent in the probability of them being most accurate.

And I would just be interested to hear your response to hearing that.

DAVE FELDMAN: Yeah definitely. So I'm actually kind of glad you brought that up. If I just had a dollar for every time somebody quotes me in a way that's not exactly what I said, for that matter like the meaning completely changes, I could totally fund 10 studies just fine. No, your point is well-taken, I actually had to settle on a terminology, a two-word terminology that I use often which is to say that I'm cautiously optimistic. I like those two words together, cautiously optimistic, about the context of high LDL in where it's matched with high HDL low triglycerides and otherwise excellent cardiovascular markers. And the cautiously optimistic I think I like because a cautiously is to say, no, by no means am I at a point of certainty; optimistic is yet even further it's an outlook based statement. So I don't know, I genuinely don't know, and I'm comfortable saying to people I don't know. Somebody says one of my least favorite things that people will bring to me, but I get all the time is here's my lipid profile, should I worry, and I say it's not for me to ever tell anybody if they should worry. It is up to you to learn for yourself what it is that you can, I can tell you how I feel. And I can tell you, for example, if you showed me your lipid profile and we were to be hypothetical in that if it were my lipid profile, would I like it or not like it, and so forth. But to that extent yet there's no question, the lipid hypothesis could be true, it very well may be the case that right now in operating at a higher level of LDL particle count as well as LDL cholesterol as well as higher Apo B, in fact I think right now I'd be at the 99th percentile for the population according to NHANES, maybe 99.7. I have an LDL

of, I think I last clocked in at around 270 milligrams per deciliter.

So this isn't just waxing philosophic. I really am operating under what I believe to be, given the moment, an evidence based position, but that's not in the same way as saying, oh I have such overwhelming evidence to support the position that I'm in, that there's no reason for me to look any further. There are things in my life that do meet that standard where I'm like, oh well, I know enough like say flying in an airplane, I'm going to continue flying in an airplane because I feel confident enough and the odds that I'll be okay. Do I feel confident enough in the odds that having my high LDL is not an independent risk for atherosclerosis, or for that matter that I'm not shortening my life? No, I'm not at that level of confidence. But I can say this, I can say this, I can say that given every single study I've been able to find that does stratify out this triad, given the corresponding research on the other end of the spectrum with the atherogenic dyslipidemia, and given my getting a hold of a lot of raw data such as NHANES, and for that matter there's other datasets that I want to get a hold of and I'm working with some potential academic partners to do so, given also a Mendelian randomization, I kind of went – we didn't get a chance to touch on it yet, but I went down the rabbit hole of working with MR base and looking at LDL against age of death, which turns out, if you don't do a lot of modifications, it ends up being a wash.

But in particular, just really getting my head deep into why it is that it makes more mechanistic sense to think about this in terms of a lipid profile versus a lipoprotein centric model that the former makes just much more sensical

rationale, that the process just, everything just kind of falls into place a lot more for me as an engineer, that's led me to feel at least confident enough to continue on the journey that I'm on, but not so much so that I don't continue doing this additional work, like I mentioned, with it's the citizensciencefoundation.org that I started up that's helping to put together this study. I want to go and get that data, I would argue that there's nobody working harder to prove me wrong than I am, like I'm literally out there trying to raise a couple of hundred thousand dollars to make this thing happen and the net outcome may ultimately be that indeed, no, sorry, if you have this triad, even if you do have excellent cardiovascular risk workers across the board, it doesn't look good for you, you do have rapid progression of atherosclerosis, in which case, yeah, like a third of the low-carb movement by my estimation is going to need to take steps and some people bigger steps than others. Let's get to that answer as soon as we can. My hope though is that if it does prove to be true that the lipid hypothesis does need to at least add this additional context that there'll be that level of receptivity outside of the low-carb community, that there will be a lot of people like yourselves who will say, well, actually this may not falsify the lipid hypothesis because I'm not making the claim that it does, but it does mean that this additional context of mechanisms, it may deserve some more merit, it may be something that we should consider a little bit strongly.

DANNY LENNON: And I would suspect that would be the case because – and I hope how we communicated things before was very much in line of this is an interesting observation and there's areas that you

can point to if we don't have specific data on this right now, but the conclusions still have to be made probabilistically and I think that's where hopefully it's understandable why the lipid hypothesis or at least I feel should be the default position because of that current evidence, but if something adds to that then that can be of course amended. But Alan you had something to...

ALAN FLANAGAN: Yeah, it goes back to that idea that we spoke about earlier of nothing so far, and Dave one of our colleagues at Sigma talks about science as an error correcting machine, but so far all of the – they haven't necessarily been errors in the emergence and development of the lipid hypothesis, it's been the addition of more nuance and more context. So I absolutely acknowledge what you're saying is that what this may add is an additional nuance to the overall picture, and I do hope always with any sort of scientific advancement if the body of evidence that emerges in support of it is robust, that it isn't met with resistance and is met with receptivity as you put it. And I imagine that it would be because of our understanding of cardiovascular risk becoming more nuanced, but I also imagine that the barrier to it or potentially what would make an environment less receptive is the community itself, and the way that they would behave if in such a finding came out.

DAVE FELDMAN: Yeah, and to be sure, this goes both ways. I mean, I guarantee, there's going to be some people who listen to this podcast, they may be doing it right this moment as they're hearing me talk; there's going to be some people who follow my work who are going to say, you know what, these guys keep kind of

just defaulting back to where they were, Dave's trying to explain this kind of lipid profile, is it going to be something that will ruminate with them to where they'll start to understand it and start asking those questions back towards their peers, will they start to – as I mentioned earlier, will you start looking into the data and see, hey, can I at least help to disprove Dave's position and confirm that indeed even for those people at a very low risk and who have that lipid triad that indeed they will have worse all-cause mortality outcomes when compared to those people who have lower Apo B. I think that that's where we see where the next steps take us.

ALAN FLANAGAN: Yeah.

DAVE FELDMAN: Yeah, and I think the reason why in my and Alan's original episode where we referenced your triad essentially, the part of that, the reasoning is that we want people to be aware of – we are aware of these arguments, we have looked at these different cases and are aware of counterpoints that it wasn't, we didn't put out these statements, and what we didn't want people to do is who are of an alternative position to read them and say, oh they're just like parroting the old lipid hypothesis, blah, blah, blah, they're not aware of argument X, Y, and Z, right; or, oh if they just read Dave's work, or whoever is making other counter points, we wanted to make it clear that there are some counter points out there, there's some validity to some of the points that you make and that we're aware of them and hopefully trying to account for them; and yeah, there may be just differences in interpretation and conclusion, but it's very much not a, hopefully, on my part at least not, I kind of blindly just ascribing to a certain view that I am

trying to look at the point you're making, reading your stuff and being aware of that and that was all factored in before releasing any of those statements for that podcast. So at least that's from my perspective.

ALAN FLANAGAN: Yeah, and from mine, I mean, I think, and some of the things that I've heard you talk about previously on other platforms Dave is, I don't think – I think on the extreme end of the pro side there can be this idea of, oh we'll just get it to zero LDL, for example, and oh it doesn't, you know, we just treat and we don't consider all these other factors, I mean, any of the lipidologists and the people in the cardiovascular space publishing that I have a lot of respect for and read, I don't think any of them, I've never seen any of them say that, they're all aware of the nuances, there's an acknowledgment that if having lower LDL cholesterol from a population health perspective, it may be better for reducing risk, then lowering it with pharmacotherapy is a different matter, it matters how we get levels low and it matters – the population demographics matter for what kind of interventions are used. So just this whole blanket, you know, get it low by any means possible, I personally don't see that, I know that there are some people that would take that extreme view. But certainly the people that I pay attention to in the literature would be acknowledging that there are nuances and that we need to be careful about inpatients who are at risk, you know, where are they in this risk spectrum, what are their characteristics, do they need just a basic statin intervention or might they need an adjuvant therapy, whether it's ezitimibe or might they respond better to a PCSK9 inhibitor, all these kind of variables, but that's the total picture of encompassing

cardiovascular risk assessment and then treatments.

And so I don't think it's just blanket, I don't think healthcare ever, ever should be, and I think our interventions should always be specific to the individual. But I think where I lean right now, and I do find your triad interesting, and I do welcome further, and like we talked at the start, HDL still being an enigma, I'm looking forward to our research and our knowledge of HDL expanding, I think tracer studies will add a lot to our understanding of what's happening with Apo B containing lipoproteins particularly in a postprandial state, and how that might relate to risk. For now, my position for the general population, for managing cardiovascular risk specifically, the evidence for me is overwhelmingly in favor of lowering LDL, and atherogenic lipoproteins as a broad subclass, but I do say that specific to coronary heart disease and cardiovascular disease, and I do say that from the perspective of population health and what would serve a majority risk reduction in the population. And yeah, and that's where I currently stand on it, but I'm certainly interested in your triad and acknowledge that we, in terms of profile, definitely have not a complete picture in relation to all aspects of lipoprotein metabolism at this point.

DANNY LENNON: Yeah, and I think it's actually the point you make on about those researchers that you'd have respect for and acknowledging the nuance in this area only last week was the new consensus statement from the EAS where you had like Ron Krauss, Chris Packard...

ALAN FLANAGAN: Yeah.

DANNY LENNON: Yeah, Jan Boren, Brian Ference...

DAVE FELDMAN: I actually love that paper. I love so many things about that paper. It has so many aspects that come back to the inflammatory response, it gets into efferocytosis. I wish that that paper existed five years ago. It actually has many things that I particularly appreciate about it.

DANNY LENNON: Right, and I think that to me that's a perfect example of where the actual current state of real true lipidologists are in terms of reference and stuff. It's not this over simplistic LDL cholesterol is the only thing that matters, no, this is a clear rundown of all these interesting concepts, and I think maybe there is some room. And I know you'd probably disagree with some of maybe the conclusions but the bulk of the actual paper is just phenomenal, and that's kind of where we are with this stuff...

DAVE FELDMAN: I agree with that actually, and it's exactly what you just said, I disagree with some of its conclusions, but it was one of the rare times where I've really seen a much stronger acknowledgement towards the process of inflammation and its association back with atherosclerosis. And again with full acknowledgment, as I did earlier, that we haven't yet been able to fully elucidate how much LDL particles initiate and progress the disease, but how much they are involved, how much inflammation for that matter and the inflammatory response is involved, that's about as strong as it gets. I don't know anybody who would try to argue otherwise with that.

DANNY LENNON: Yeah. So before we wrap up, because of both you gentlemen have been very kind with your time so far, I did want to open up, if anyone did want to leave any final

remarks or mention anything that you didn't get a chance or even just something to leave people with if you wanted to before we start wrapping up.

DAVE FELDMAN: No...

ALAN FLANAGAN: I mean, I think we've had a pretty good discourse and I think my last statement was where I kind of stand on the current evidence, and particularly where I stand in terms of how we approach this from a population risk management perspective.

DAVE FELDMAN: I think I would say just real quick, I mean, we didn't really get a chance to go over this, and I feel like this isn't said enough. I do feel sometimes like LDL, and I've only more recently realized this particularly with doctors, I feel like LDL ends up becoming kind of a low-hanging fruit for people to feel that they've done something to reduce their risk a little too conveniently. I really feel like people aren't giving enough weight towards lifestyle and diet changes that really would make an enormous difference, not just a cardiovascular risk but to mortality overall, and that oftentimes it's kind of looked at as though health can be acquired pharmacologically. And I like that your podcast addresses this a lot, I like that there's a lot more focus on the health aspects. I appreciate anybody and everybody who just puts more emphasis on that, because if you really do sit down and look at the numbers, you don't get that much advantage from pills without doing a lifestyle intervention if you're already in a bad way, you really should take the time and the effort to put toward yourself and really adopting a new lifestyle that's going to give you greater longevity because there's really strong data behind that.

DANNY LENNON: Okay gentlemen, well, I'm sure there's probably things that we could have talked a lot more about and there may actually be points or questions that people listening to this bring up that they would have liked us to get into or something that they would like clarification of, so maybe after this episode is released and we collect some of those, maybe some months down the road we can maybe come back to this and get into some more stuff because I think these, like you say, Dave, can be extremely useful conversations, hopefully for most people listening and add a layer of required nuance to this. So maybe that's something to look forward to. But before I let both you go, maybe starting with you Dave, let people know where they can find you on the internet if they are interested in knowing more a bit about you and what you do.

DAVE FELDMAN: Sure, of course, they can visit cholesterolcode.com, and not only there do we document a lot of our existing research, I will proudly tout the fact that the, I think strongest article for the case for lowering LDL on a low-carb diet which is written by my good friend Spencer Nadolsky is there. So certainly, I practice what I preach in trying to have as much of both sides represented. That said of course Cholesterol Code probably has a little bit more of my and Siobhan's work which might be a little bit more on the skeptic end. Of course you can also find me on Twitter I'm very active as DaveKeto, and otherwise we also have two Facebook groups for those people going low-carb and who see this higher rate of cholesterol, there's the Cholesterol Code Facebook group and then there's the Lean Mass Hyper-responder Facebook group itself.

DANNY LENNON: Awesome, and that will all be linked in the show notes for everyone listening. And then turn it to you, Alan, where can people track you down on the internet?

ALAN FLANAGAN: They can track me down at Sigma Nutrition and the Sigma statements that are there on the podcasts and they can also track me down on Instagram @thenutritional_advocate which is really my only social media platform, and they can also track me down at my website which is alineanutrition.com, and that is a nutrition science specific focused research review platform.

DANNY LENNON: Perfect. And so with that, thank you guys for doing this, it's been enjoyable for me to be able to listen through a lot of this and to be able to try and clarify some of this, and I appreciate both the input but also the time you've given up today, so thank you both for doing this.

ALAN FLANAGAN: Thanks for having us, it's been great, thanks Dave, it was really good to chat.

DAVE FELDMAN: Yes likewise, thank you.