Understanding the Mechanisms That Link Alcohol and Lower Risk of Coronary Heart Disease

Bob Barrett: This is the podcast from *'Clinical Chemistry'*. I am Bob Barrett. For more than 75 years, pathologists have recognized that alcohol consumption has a surprising link to atherosclerosis. In those early studies, postmortem examinations of deceased heavy drinkers identified less atherosclerosis than was expected, suggesting that alcohol consumption is somehow atheroprotective.

Studies attempting to draw the full links between alcohol consumption, coronary heart disease and the pathways that connect them remain important. In the April 2012 issue of *'Clinical Chemistry'* Dr. Kenneth Mukamal, Associate Professor of Medicine at the Harvard Medical School examined several studies that attempt to address the relationship between alcohol consumption and atherosclerosis.

Dr. Mukamal is our guest in this podcast. Doctor, what is already known about the association of the alcohol consumption and the risk of coronary heart disease and does the risk relate to the type of beverages and drinking patterns?

Dr. Kenneth Mukamal: You know we have known for really now probably 30 years or so, that individuals who consume, what I will call moderate amounts of alcohol which typically runs in the range of about half a drink to two drinks a day, have a lower risk of coronary heart disease, particularly lower risk of myocardial infarction.

That's been seen in observational studies going back to the early 70s, although to be honest there was evidence from pathological studies going back probably a century suggesting that individuals who consumed at that point large amounts of alcohol seem to have less atherosclerosis than might be anticipated based on their other risk factors of their age. That is to say, they seem to have cleaner coronaries or cleaner other vessels than we anticipated.

So we have had some sense of this now I think already for about 30 years. Bringing all of that evidence together, the suggestion has been that on average people who drink, say about a drink per day have some where in the range about 25% lower risk of myocardial infarction than do complete abstainers. There is still quite a lot of controversy on both ends of that spectrum though. On the lower end, it's not quite clear sort of where benefit begins or doesn't begin.

In our work, we have seen that lower risk seems to be conferred certainly but half a drink per day, but there are certainly studies that particularly in women have suggested that there might be benefits from even lower amount, whether that's biologically possible or not, I think remains uncertain.

On the other hand, sort of rightward end with heavier drinking, there is also I think some uncertainty, many compilations of studies have suggested that risk basically seems to plateau at about one drink per day such that heavier drinkers don't necessary have higher risk, they necessarily have lower risk as to say something of an L shape.

Other studies have suggested that we begin to see an increase in risk with heavier drinking perhaps related to adverse effects of really heavy drinking, on things like blood pressure.

So it's been a little bit unclear. I think the cumulative body of evidence, it's pretty secure that moderate drinkers serve to have a lower risk of myocardial infarction, but exactly where that tips back up, it gets back to level of non-drinkers, is a little bit uncertain. It's hard because clearly on observational studies, we just don't see lots of people who are very heavy drinkers. And the very heaviest drinkers tend to have adverse risk profiles in other ways. They tend to be more likely smokers and have adverse diets and so on. It's little bit hard to tease that out.

It's interesting to then move that forward though and try to give that -- I think a little bit more of the subtlety. The beverage type as one of the really common questions that certainly the lay public has. There are undoubtedly interesting chemicals present in, particularly in red wine, but frankly also in white wine and to some degree in dark beers. The coloring in virtually all of the beverages comes from polyphenols, and polyphenols have some of the most interesting biological properties of many chemicals around.

However, with that being said, to be perfectly fair, there is much more alcohol in any of these beverages than there is in phytochemicals and so the polyphenols, while of interest, and although they may have biological activity at high doses, I think what we've seen is at the level of intake, most patients have that really frankly it's hard to see that there is difference in risk between drinking beer, or

wine or spirits. Basically, these seem to be relatively similar.

It is certainly true that many studies have found particular benefits to red wine, but in most of those studies, they haven't necessarily been able to fully account for the fact that people who drink wine tend to be different than people who drink beer and spirits, and in particular, they tend to have very clearly healthier diet. So that if they are drinking red wine, they are also eating more fruits and vegetables for example, and eating less fat, soda and simple snacks.

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But that also gets into I think another interesting area because drinking pattern is clearly I think an area where we have seen a lot of importance. So you might decompose average alcohol consumption into 3 pieces and these basically represent the recommended ways that the National Institute on Alcohol Abuse and Alcoholism recommends that we ask about drinking, that is to say drinking frequency, drinking quantity and binge drinking.

Specifically, so drinking frequency would be how many days say in a given week does one consume alcohol of any type. Drinking quantity, how many drinks typically on average does one consume when one drinks alcohol and then binge drinking how often does one consume large amounts of alcohol all at once.

The reason that binge drinking tends to be separated as in part because it tends to be something of a different kind of activity but also because there is good evidence that people don't incorporate binge drinking well into their matrix of average drinking. And so it really does seem to reflect sort of different behaviors that individuals can't average well into their average alcohol consumption.

So to take you to those separately, virtually all the evidence we have would suggest that drinking frequency is the most important determinant of lower risk of alcohol consumption. That is to say, drinking frequency trumps quantity in individuals who drink alcohol consumption frequently seem to have the lowest risk of myocardial infarction even accounting for differences in quantity.

In contrast, almost all the evidence we have would suggest that the harms from alcohol consumption come from drinking quantity, and there seems to be very little relationship of drinking quantity per se with lower risk, and in fact, some evidence with higher risk.

So, but differently it seems as though, the pattern of alcohol consumption that's associated with lowest risk based on observational studies is a pattern of small amounts of alcohol consumption consumed frequently, say one drink a day as opposed to not the other extreme seven drinks once a week.

Binge drinking has been hard to study and part again because it hasn't always been asked in a separate way and so we tended it to conflate it with other elements of drinking. Although there is some evidence that would suggest that binge drinking per se is associated with higher risk of myocardial infarction. The evidence for that is modest at this point in time.

So although there is a suggestion that binge drinking may confer particularly higher risk independent to other drinking patterns, we don't have strong evidence for that.

And it's interesting to see that it's possible that some of what we see in beverage-specific effects, they actually relate instead to drinking patterns. That is that in countries in which say wine seems to be the beverage that is particularly associated with lower risk, it appears that wine is also the beverage consumed most frequently. It's a dominant beverage in that population.

In contrast, in populations in which say beer is the most frequently consumed population that seems to be what's most strongly associated with lower risk and so we maybe attributing to beverage specific effects may really be nothing more than just reflecting underlying relationships of drinking pattern with risk, with drinking frequently conferring lower risk and with drinking quantity potentially conferring higher risk.

Bob Barrett: So what are the biochemical pathways thought to relate alcohol consumptions with lower risk, and how have these been investigated in the past?

Dr. Kenneth Mukamal This is particularly important question these days, particularly in relationship to some of what's been

done very recently. So I think it's important to try to tease these out. So maybe to take the second question first, there are at least a couple of different ways that industries in this field have tried to get at this, at least in humans, where I think the questions are most interesting. I will emphasize that a little bit more in just a moment.

So one way that these have been looked at is to do feeding studies. So to take individuals in a very controlled setting, typically for shorts periods of time, say 3 to 4 weeks and ask them to come in every day and drink one, or two, or three drinks of alcohol, typically these doses are on the higher end, it's easier to see effects of those in a short time period and then to cross people over from alcohol to a non-alcoholic controlled beverage or vice versa.

And then to look at the effects of alcohol consumption relative to the controlled beverage on a host a different things, and a host of different types of potential cardiovascular risk factors and then occasionally what we will see done next is to say well, here is how much of a difference we saw with alcohol consumption on biomarker X, how much would that change in biomarker X be expected to influence risk of myocardial infarction? For example, although we don't see effects of alcohol consumption on LDL cholesterol, you might ask if we had if we had seen effects, how much would that magnitude of change in LDL cholesterol be anticipated to lower risk of myocardial infarction from other studies?

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Dr. Kenneth Mukamal: And if we could sum up all the effects of alcohol consumption, we would have a guess of how much alcohol consumption will be anticipated to affect risk of myocardial infarction itself. And if those two matched up, we might guess that we can sort of identify all the important biological pathways.

There are some important limitations to that method although there are some benefits as well. The strengths very clearly are that in feeding studies, we know absolutely positively that it's the alcohol consumption itself that's causing the effects. We have the ability to control for fluid intake; we're doing it in a controlled setting. So we have the strongest causal inference possible. We know that it is the alcohol itself that's doing it at least in studies that are done well.

The downsides however are also sort of clear. These are studies that are typically done over a course of just a few weeks. So if something -- if alcohol has an effect on something in the short-term, but on the long-term we'll have misspecified that. We'll have guessed wrong about what alcohol is really doing in the long run. And it requires us to make some assumptions about how a change in a given biomarker affects risk of myocardial infarction.

So typically we're doing a feeding study in one population and trying to guess that how much the changes that we see translate into long-term risks from a different population. So there are strengths and there's weaknesses.

That approach has shown a few very interesting things however. So feeding studies have very consistently shown that perhaps the single thing that alcohol affects most consistently is HDL cholesterol. And its effects on HDL cholesterol have been replicated in virtually every feeding study that have been done, although there's different magnitude that appears to be something fairly close to a straight line, in the short run with basically increasing HDL cholesterol with greater alcohol consumption administered.

The magnitude of that is relatively large. So on average what we've seen is that say alcohol intake in the range of about two drinks typically raises HDL cholesterol on average something in the range of about 4 milligrams per deciliter. That's quite a lot, certainly more than, at this point in time, any approved pharmaceutical agent that we have.

The same feeding studies have shown some other effects. So particularly at high levels of alcohol consumption, we've seen effects on triglycerides at the same time with high levels of triglycerides. That does seem, again, to be a dose-dependent effect with only very little effect of alcohol consumption of small doses but potentially larger effects at high doses.

The other thing that in feeding studies it's sort of -- or the two things that consistently kind of come out have been, number one, fibrinogen. Fibrinogen is an acute-phase reactant and so it's not clear that reflects an effect of alcohol consumption on clotting per se or on inflammation more generally. But the effect of fibrinogen seems to be stronger than the effect of alcohol and other inflammatory markers. If

an effect of higher levels of fibrinogen are associated with higher risk myocardial infarction, again, we might assume that lowering fibrinogen would lower risk of MI.

The last biomarker that's shown up relatively consistently in feeding studies is adiponectin, obviously a well-studied adipokine and perhaps the biggest constituent of fat cells by mass. So adiponectin has been consistently found to be increased by alcohol consumption in feeding studies and indeed it seems to be the high molecular weight form which seems to be increased the most.

Now the relationship of adiponectin at least with myocardial infarction is a little bit unclear. So it's something that, I think, at this point in time is not quite easy to say how that increase in adiponectin will be expected to lower risk.

The second way in which investigators have approached this question about how does alcohol lower risk is to work in reverse. And that is to say, particular population to look at how alcohol consumption relates to coronary heart disease and then to, in the same population, measure different biomarkers, and ask how does adjustment for any given biomarker change the observed estimate relating alcohol consumption to coronary heart disease.

So for example, if we saw that alcohol consumption is associated with a 25% lower risk of myocardial infarction, you might try say adjusting for HDL cholesterol and see how does that 25% estimate change. If the 25% estimate doesn't change, then we would say, gee!, it doesn't look like HDL cholesterol is in the pathway linking alcohol to coronary heart disease.

In contrast, if when we adjusted for HDL cholesterol, it entirely went away if there was then no effect of alcohol consumption once we countered for HDL. And we might say, gee! It looks like HDL by itself explains -– this is virtually all the benefits.

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Now this method too has its strengths and weaknesses. On the one hand, one of the strengths that it has is that all of the material that we need to do these analyses is present within the study itself.

That is to say we don't need to take any information from outside sources. So that's a real strength.

On the other hand, it relies on a variety of assumptions some of which are kind of hard to test. And that becomes an important limitation when we look at studies that have tried to do this. For example, it requires that the biomarker that we're studying in any given population be associated with risk in sort of the way we expect from other populations. If, to be specific, HDL cholesterol isn't very strongly associated with risk in a given population, then we wouldn't expect it to account for very much of the benefit of alcohol consumption even if HDL does account for large amount of the benefit of alcohol in a different population. So these studies aren't always readily, easily interpretable.

Nonetheless, they have generally shown a few different things. First, is that HDL cholesterol, in addition to being the biomarker that's most consistently related to alcohol consumption, feeding studies also seems to account for most of the benefit that you look at most studies, typically somewhere in the range of about half. So that about -- it appears that when you adjust for HDL cholesterol, about half of the benefit of moderate drinking goes away. And that hasn't always been seen and it's important to recognize why.

At least, a couple studies that have shown no particular mediating effect of HDL cholesterol have been in populations of older adults. That's important because in older adults, lipids just don't predict risk of myocardial infarction very well. And so it may or may not be a surprise that HDL doesn't serve as a strong mediator in those populations.

Far and away, the best evidence that we have so far is for HDL cholesterol even though it's not, as I said, universal.

The other potential sort of pathways that we've seen that seem to account for some of the benefit at least for myocardial infarction do include inflammation. So things like fibrinogen, as I just mentioned, fibrinogen or other inflammatory markers seem to account for somewhere in the range of 10%-20% of the benefit. And so this anti-inflammatory effect of alcohol may also be at least partly contributing.

We have not yet done studies similar to this for adiponectin, but we have done them for other

markers related to glucose metabolism. And those again seem to account for a similar amount of benefit as for inflammation. So across the board it would appear that for most people, if there is a benefit to gaining from alcohol consumption is by raising their HDL cholesterol, but with the proviso that in populations in which HDL doesn't seem to really provide much benefit, it looks like there maybe other mechanisms involved.

Bob Barrett: Doctor, studies seem to differ on the importance of some of these pathways including HDL cholesterol. Why might studies not agree on this basic question?

Dr. Kenneth Mukamal: There's a really important lesson to be, I think, gleaned from some of these sorts of studies. Part of it, clearly is that we don't anticipate the same pathways to be at work in everybody. And indeed it's likely that the pathways that are particularly important for one person and for another person are going to differ just on the basis of their pre-existing risk factors alone.

So we don't necessarily expect every single population to look similar in terms of the pathways involved. For example, one of the things that we've seen relates to the genetics of alcohol consumption. Alcohol consumption or ethanol consumption in humans is predominately driven first by a series of enzymes in the alcohol dehydrogenase or ADH family. There are multiple ADH genes. The key ones seem to be the ADH1 genes in humans. And there's always three genes within that fat; ADH1A, ADH1B, and ADH1C.

So the interesting thing is that ADH1C at least has a very common functional polymorphism in Caucasians. And the interesting thing is that for example, for coronary heart disease, the polymorphism that leads to slow metabolism of alcohol consumption which would sort of seem to make alcohol linger longer in one's body and circulate longer seems to be associated with a particularly strong bump in HDL cholesterol and with a particularly big drop in myocardial infarction.

But, the interesting thing is that that same polymorphism has not been associated with a particularly big bump in adiponectin and indeed has seemed to be associated with a smaller benefit of alcohol consumption on risk of diabetes, which is another area of interest. And so the same genetic makeup seems to activate different sets of pathways

in relationship to alcohol consumption, both of which might be expected to lead to lower risk. In one case, someone's genetic makeup may lead to a big bump in HDL which lowers risk. In another case, somebody may be particularly likely to have a lower risk of diabetes which then lowers the risk of myocardial infarction.

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So some of the differences across population may simply be related to the underlying genetic background in those populations. But clearly in addition to this, we need to worry about methodological differences. There are studies in which, for example, of HDL cholesterol, this isn't measured very well, then, we're not going to find it to be much of an important mediator just because it is not measured well. And so, we have to take those studies with a grain of salt unless we have good evidence that both HDL is related to alcohol consumption and HDL is related to risk of MI in that population, have to be concerned that the inferences we can draw from that may not be correct.

Bob Barrett: Well finally, are there any potential pathways that have not been extensively investigated that might relate alcohol consumption to lower risk?

Dr. Kenneth Mukamal: That's, I think, a really interesting area going forward. On the one hand, we have some reason to think that we've gotten the major pathways down, because for example in some studies that have had relatively large numbers of biomarkers available, we have found that when you would account for all those biomarkers that you can explain a very large portion of the apparent benefit of alcohol consumption. In some cases, you can explain more than 80%.

So those studies would seem to suggest that there may not be a lot of additional things to be studied. However, it's clear from these studies for example that haven't found HDL to be a particularly strong biomarker that there must be other things involved as well. And in many of those studies, we have yet to identify what it is that seems to be driving the lower risk.

Some of the really interesting ones I think that are going to need to be studied particularly relate to issues of glycemia. So as I said, adiponectin seems to be associated with lower risk of diabetes. But what's not so clear is how it relates to risk of

myocardial infarction and it's possible that it explains some of the apparent benefit of alcohol consumption.

I think there are some other really interesting ones as well. One of the things that we've known perhaps the longest about alcohol consumption is that it's linked to an antiplatelet effect that's additive to aspirin. And that's been known for quite a long time. For example, drinking alcohol consumption extends bleeding time in an additive way beyond aspirin. But if that's the case, we might expect that that would contribute to the lower risk of myocardial infarction associated with drinking, since we know that at least from most individuals that myocardial infarction is triggered by a localized clot.

If that's the case, then it'd be really important to study differences in platelet effects of alcohol consumption with different levels of drinking and try to relate those to what's happening with risk of myocardial infarction. That hasn't been done.

So although we have done studies that have very clearly shown that alcohol consumption leads to less platelet activity both in vitro and in vivo, we don't have large-scale studies that have asked the question, how much of the apparent benefit of alcohol consumption might relate to those platelet effects. And so that's really important and I think that those sorts of functional studies are going to need to be done to help us get at this.

Another area that has yet to be kind of tackled and although there's some interesting methodological challenges, I think, represents one of the most interesting areas to do this is the whole revolution in genomics.

Although we have some kind of candidate genes that seem to modify how alcohol consumption relates to lower risk of myocardial infarction and the ADH genes are but one example of that, what we haven't done yet is really ask across the entire genome what are the genes or what are the genetic regions that seem to modify the apparent benefit of alcohol consumption on risk, the most. Are there areas that we haven't even considered?

And given the fact that GWAS have sort of suggested that we don't really understand the genetics of coronary heart disease all that well, given that some of our most prominent hits have been in relative gene deserts, one of the genetic regions that we

really did not anticipate to be associated with risk, all of that would suggest that trying to get at in a large-scale way, what are the different genetic regions that seem to modify a risk may help point to pathways by which alcohol consumption is associated with lower risk that we may not have anticipated. And so I think those are also some studies that we can expect to see in the years to come.

Bob Barrett: Dr. Kenneth Mukamal is an Associate Professor of Medicine at Harvard Medical School. He has been our guest in this podcast from *'Clinical Chemistry'*. I'm Bob Barrett. Thanks for listening!

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