Take it to Heart:

Talking Drugs, Supplements, and Cardiovascular Health with Bob Lefkowitz

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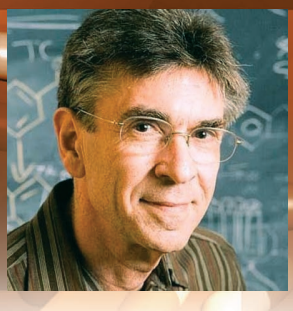


Conversing with Bob Lefkowitz to learn how he takes care of his own heart is like meeting with Warren Buffett to learn how he handles his own personal investment portfolio, or like hitting a practice round with Tiger Woods to learn the secret techniques he uses to hone his golf swing. When it comes to matters of the heart, Bob Lefkowitz knows what he's talking about. In addition to being one of the most-prolific and most-cited molecular cardiologists of all time, with over 800 career articles, Lefkowitz is also a cardiac patient.

In 1994, after suffering repeated angina attacks, Lefkowitz underwent quadruple bypass surgery. He was fifty-one years old. His mother and father had both suffered from severe heart problems that began early in their lives, so it's fair to say that Bob Lefkowitz has long had genetics working against him. He acknowledges that he became a cardiologist in part because of his family history. Over the years, he has developed a deep understanding of the factors that control cardiovascular health, viewing the topic as he does from the distinct perspectives of clinician, basic researcher, and patient. His focus as a researcher has been on fundamental studies that might eventually lead to new therapeutic drugs in the future, but his focus as a patient has

been on assessing available drugs that might be used as part of a personal daily regimen to optimize his own cardiovascular health. Admittedly, there has been no shortage of popular advice about cardiac health over the past few decades, and today one can choose from any number of regimens recommended by TV doctors, New Age gurus, or Internet websites. But anyone wondering how to keep their heart in good working order would do well to consider the advice of Lefkowitz. At sixty-six, he looks a decade younger than his actual age and exudes a youthful energy. Clearly, whatever regimen he's been following since that quadruple bypass surgery fifteen years ago has been working. This is a guy whose secrets of cardiovascular health are truly worth knowing.

RH: It is well-established that genetics plays a huge role in cardiovascular disease. What is your family history of cardiovascular problems?

Lefkowitz: I have a very striking history of coronary artery disease on both sides of the family. My father had his first myocardial infarction at age fifty and died after his fourth myocardial infarction, at age sixty-three. My mother had her first myocardial infarction at age fifty-seven, and then she continued to suffer from angina attacks for a number of years until undergoing triple bypass surgery and aortic valve replacement. Her own mother died at quite an early age from coronary artery disease.

RH: Did this family history of heart problems influence you to go into cardiology when you were a medical student?

Lefkowitz: Unquestionably. It also influenced certain aspects of my lifestyle. I took to a regimen of regular jogging in my mid twenties, which in retrospect began a few months after my father's death. I also began to reduce fat in my diet, although I wasn't very serious about it at that point. But it was always on my mind. After my father's early death, I definitely felt like I was a marked man.

RH: When did you first experience cardiac problems of your own?

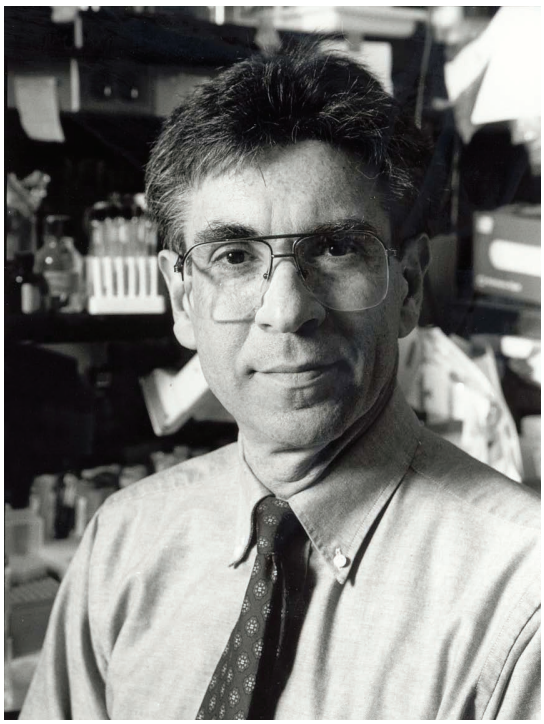
Lefkowitz: In the early 1990s, I developed what I should have immediately recognized was classical effort-related angina. It was manifest as a sensation of tightness in my chest on most of my morning runs. I would notice it about a mile into the run, then it would go away, and then I would often notice it again during the cool-down period. This is a fairly typical pattern, but I used the fact that the discomfort faded during the run as the basis for an elaborate scheme of denial. For more than a year, and despite my background in cardiology, I managed to convince myself that this was not angina.

RH: How did you eventually come to seek treatment?

Lefkowitz: I confided to my main running partner, Ralph Snyderman, who was then the CEO of the Duke University Medical Center, about my symptoms, and he helped me to see the light. I got evaluated and had a stress test, which revealed profound depression of the ST segments on my electrocardiogram. I also had an angiogram, which revealed significant two-vessel heart disease. This was the spring of 1994, and I was fifty-one years old. In June of 1994, I had quadruple bypass surgery.

RH: Following your recovery from the surgery, did you make any lifestyle changes to enhance your cardiovascular health going forward?

Lefkowitz: I did. I continued my jogging regimen, although of course it took me a number of months following the surgery to build back up to where I could jog multiple miles. Furthermore, I got much more serious about my diet. I began adhering to a diet known as the Dean Ornish diet, which is fairly draconian: it's strictly vegetarian and demands very low fat intake, with fat accounting for less than ten percent of total calories. Few people can stick with this type of diet over the long term, but having grown up in a kosher home *(laughing)*, I am accustomed to the mandates of inflexible dietary guidelines. I followed this diet very strictly for about six years.



RH: But no longer?

Lefkowitz: I would like to believe that most of the decisions I've made over the years about my health regimen have been driven by the available data. Over the past decade, a large number of studies have been published suggesting that extreme low-fat diets might not be optimal for one's blood lipid profile. Thus, I've basically switched over to what is often called the Mediterranean diet, with the main difference from the Ornish diet being the liberalization of the intake of monounsaturated and polyunsaturated fats. A typical Mediterranean diet allows for the consumption of fish, but having been a vegetarian for a number of years, I have remained a vegetarian out of personal preference. However, I have liberalized my fat intake, and now regularly eat legumes, peanut butter, hummus, olive oil, et cetera, although my total caloric intake has not changed.

RH: Are there any other lifestyle changes, beyond diet, that you have implemented since the quadruple bypass?

Lefkowitz: I have tried to reduce stress, although I have to say that out of all aspects of my regimen, this is the one that I've been least successful in controlling. I have the same stresses as most career-oriented people, but I do take certain small measures to reduce anxiety levels. For example, I travel a fair amount, and one thing that always makes me anxious is rushing to catch a flight. Thus, I try to get to the airport early, usually several hours in advance, so that I don't feel stressed. My wife does not get as stressed by travel as I do, but she very kindly humors me in my desire to leave for the airport many hours in advance.

RH: Few people would argue with your perspectives about the importance of diet, exercise, and lifestyle. However, given the pharmacology-focused readership of MI, and given your background as a molecular cardiology researcher, most folks reading this article are probably interested in hearing about your daily regimen of drugs and supplements.

Lefkowitz: First of all, I take aspirin. The numerous studies and reams of data on aspirin are unequivocal in terms of its beneficial effects for the cardiovascular system, especially with regard to platelet aggregation and antithrombotic effects.

RH: What dose of aspirin do you take?

Lefkowitz: That's an important question. The recommended doses range from one baby aspirin (75 mg) to one full aspirin (325 mg) per day. I've decided to split the difference and take two baby aspirin per day, roughly equivalent to half of a regular aspirin tablet. I've read some studies suggesting one baby aspirin might not be quite enough for the full beneficial effect, and I've seen other studies suggesting that the risk of bleeding is higher for people taking a full aspirin per day over a long period. So, I figured that I'd split the difference and take half an aspirin.

RH: What else beyond aspirin?

Lefkowitz: The other drugs that I take are intended to modify particular risk factors that I possess based on my genetics, namely hypercholesterolemia and hypertension. Let's start with hypercholesterolemia. When I was a young medical student, age twenty-two, in the summer of 1965, I had my cholesterol determined for the very first time. It was 260.

RH: Wow.

Lefkowitz: Wow is right! Amazingly, though, if you consult medical textbooks of that era, what you'll find for "normal" serum cholesterol is anything less than 280, with no breakdown numbers for HDL or LDL. So, I wasn't particularly concerned about it at the time. You can see how dramatically attitudes have changed since then, as now people start to get concerned if their cholesterol is over 200.

RH: When did this shift in medical thinking about cholesterol occur?

Lefkowitz: Mostly in the 1980s. Based on the studies that were coming out at that time, I began to think more seriously about my cholesterol levels and then, in the late 1980's, when the statins first came out, I was one of the first patients to

start taking them. I began on lovastatin, which succeeded in lowering my cholesterol from 250 down to about 190, and lowering my LDL down from 170 to around 100. Recently, I switched to a stronger statin, rosuvastatin, and have continued to have excellent results.

RH: Any side effects?

Lefkowitz: No. A certain percentage of folks taking statins have side effects in liver or muscle function, but I'm fortunate to have no problems at all. Some patients with high cholesterol who can't take statins switch to niacin. I actually take statins and niacin together as part of my regimen. Niacin is a fascinating compound. It's a vitamin, of course—vitamin B3—but the recommended daily allowance of niacin as a vitamin is around 10 mg per day, whereas the dose for treating dyslipidemia is in the range of 2 grams per day, or even higher, so this is a completely different pharmacological action of niacin, quite distinct from the action of niacin as a vitamin.

Niacin was actually the very first cholesterol-lowering agent to show a mortality benefit in clinical trials. One advantage of niacin over the statins is that it not only lowers LDL, the "bad" cholesterol, it also raises HDL, the "good" cholesterol. Niacin is nowhere near as good as the statins at lowering LDL, but it lowers triglycerides and raises HDL, which the statins really don't do as well. That's why I added niacin to my regimen in addition to a statin.

One of the nice things about this day and age is that you can basically use the available therapeutics to dial your cholesterol numbers to whatever you want them to be. Right now, using niacin and rosuvastatin in addition to the Mediterranean diet, my cholesterol in less than 150, and my HDL is actually higher than my LDL, so I'm a model citizen in terms of my cholesterol.

RH: So that takes care of the hypercholesterolemia. How about your approach to lowering blood pressure?

Lefkowitz: Like most patients with hypertension these days, I take a beta blocker. The particular one that I take is atenolol, which is selective for the β_1-adrenergic receptor. Beta blockers basically prevent the heart from being over-excited by adrenaline. They decrease the force with which the heart pumps the blood through the vasculature, so that's one way that they lower blood pressure, but there are other beneficial actions as well that are still under investigation. A major side effect, for me at least, is that beta blockers really cut down what I can do in terms of exercise. I simply cannot generate the type of maximal heart rate that I used to be able to achieve during a workout. But, you learn to live with it.

RH: Anything else in terms of controlling the hypertension?

Lefkowitz: The other drug that I take to lower blood pressure is an ACE inhibitor, enalapril. This drug reduces the rate of synthesis of angiotensin, which is a very potent vasoconstrictor, so ACE inhibitors like enalapril induce blood vessel relaxation and lower blood pressure. As with cholesterol, you can essentially dial whatever blood pressure values you want. So even with my family history of hypertension and my frenetic daily schedule, I am able to use the beta blocker and ACE inhibitor to manage my blood pressure to the point where it hovers around 110/60 during the day and is even lower in the evening when I'm relaxing.

RH: OK, so what I have down for your daily regimen thus far is: aspirin, niacin, a statin, a beta blocker, and an ACE inhibitor. Any other drugs?

Lefkowitz: That's it for the drugs. However, I do take a few supplements that are worth mentioning. First, I take a daily multivitamin. The benefits of multivitamins have been somewhat controversial over the years, but on the whole they seem to be beneficial. In addition to the multivitamin, I take two more specific vitamin supplements. The first is vitamin B12; the reason for this is that I'm still a vegetarian, and even though B12 is in my multivitamin, I take extra (500 micrograms) just to make sure that I'm getting enough. This isn't specifically for cardiovascular health, but just for general well-being, and I only take it because my vegetarian diet does not supply me with it.

RH: What is the other vitamin supplement you take?

Lefkowitz: Vitamin D. This is a vitamin that all of us normally make when sunlight hits our skin. But more and more studies are showing that vitamin D levels in the general population are quite low, and a significant fraction of the population in the USA may be deficient in vitamin D. People don't get as much sun as they used to, and when they do go outside, they put on a lot of sunscreen, which blocks sunlight-induced vitamin D production. There are many reports that vitamin D deficiency can contribute to cardiovascular disease and a host of other health problems. So I've been taking 1000 international units per day of vitamin D3, in addition to the amount of vitamin D that's in my multivitamin.

RH: Beyond the vitamins, are there any other supplements that are part of your daily regimen?

Lefkowitz: The final component of my regimen is fish oil. There is a lot of data from clinical trials establishing the salutary effects of fish oil in the prevention of heart disease, so fish oil has truly withstood the barrier of rigorous testing. The key actors in fish oil are omega-3 fatty acids that go by the names of DHA and EPA, and they have a variety of effects in the body, including beneficial effects on blood lipids as well as anti-arrhythmic effects on the heart. I take two capsules of fish oil per day, a gram each, but each capsule only has 600 micrograms of the good stuff, so my total intake is 1.2 grams.

RH: Are there any supplements that you took at one point but are no longer part of your regimen?

Lefkowitz: Yes. When I was diagnosed with coronary disease in 1994, my cardiologist put me on high doses of vitamins C and E, doses far beyond what you might see in a multivitamin. At the time, such high doses of vitamins C and E were being widely touted for beneficial cardiovascular effects due to their antioxidant properties. It made a lot of sense, and everyone took it as gospel. However, in the ensuing decade, a number of large, well-controlled clinical trials revealed no cardiovascular benefits of any kind for such high doses of vitamins C and E. Thus, I have discontinued taking those supplements.

Another supplement that had its day was folic acid. For a number of years, I was taking a couple of milligrams per day of folic acid, when it was recommended for a variety of reasons that made eminent good sense. However, folic acid hasn't panned out to have any cardiovascular benefits when studied in a number of large, well-controlled clinical trials.

Practicing medicine is the art of making important decisions based on insufficient data. You just can't wait around until all the studies are completed. Whether the patient is yourself or someone else, you've got to make decisions *now*, so there's a lot of judgment and best guesses involved. You win some and you lose some. However, the drugs and supplements that are currently part of my regimen are compounds that truly have withstood the test of time and proven over and over again to have demonstrably beneficial effects on cardiovascular health.

RH: Are there any drugs or supplements out there that you might consider adding to your regimen in the future?

Lefkowitz: There are a lot of folks interested right now in resveratrol. This is a polyphenolic compound that is found in red wine, although you probably have to consume fifty gallons of wine per day to get a physiologically relevant dose of resveratrol. Fifty gallons is a little high for most folks, so a lot of people are taking resveratrol in pill form. A number of excellent labs are working in this area, and companies have been formed to develop resveratrol-related compounds, so undoubtedly we'll know a lot more very soon about resveratrol. I'm adopting a wait-and-see attitude.

RH: Has your lab ever worked on any of the drugs or supplements that are part of your daily regimen?

Lefkowitz: Yes. We've worked a lot on beta blockers, because of the focus that we've had over the years on β-adrenergic receptors *(1)*. Recently, we've had some very interesting insights into differences between various beta blockers. A few years back, we found that the adrenergic receptors and other G protein–coupled receptors, in addition to signaling through the canonical G proteins, can also signal through interactions with another family of intracellular proteins known as the β-arrestins. More recently, we and others have shown that it is possible to stimulate receptors with "biased agonists," that is, agonists that preferentially activate G protein–mediated signaling but not β-arrestin-mediated signaling, or vice versa.

In a recent study *(2)*, we screened about sixteen different beta blockers, comprising basically all of the beta blockers that are used clinically around the world, for their effects on G protein–mediated versus β-arrestin-mediated signaling induced by the β_2-adrenergic receptor. All but one of the beta blockers turned out to be unbiased, meaning that they blocked G protein–mediated and β-arrestin-mediated signaling equally. However, one of the beta blockers, carvedilol, turned out to be a β-arrestin-biased ligand, meaning that it blocked G protein–mediated signaling but weakly stimulated signaling through β-arrestins. This was interesting because carvedilol has increasingly come to be seen as the beta blocker of choice for treating heart failure, so it was intriguing to achieve some mechanistic insight into how this beta blocker is different from other beta blockers.

RH: Are there any other connections between the drugs that you take for personal health reasons and the research that goes on in your lab?

Lefkowitz: I mentioned earlier that I find niacin to be a fascinating compound, and my lab has recently done some work on niacin. The main side effect of niacin is that it causes severe flushing in many patients, and this flushing can be very uncomfortable. The only way to get around this side effect for most people is to gradually increase the dose, which is what I did over a period of months, and so now I experience almost no flushing at all with niacin after taking it for 12 years and gradually building up. In any case, the flushing phenomenon is clearly an adverse side effect of niacin that would be desirable to avoid if possible.

Several years ago, it was shown that both the therapeutic effects of high doses of niacin, as well as the unfortunate side effect of flushing, were mediated by a G protein–coupled receptor known as GPR109A. My colleagues and I became interested in the question of whether these two effects might be separable, even though they're mediated by the same receptor. We published a paper very recently *(3)*, just a few months ago, demonstrating that the effects of niacin on blood lipid profiles in mice are due to G protein–mediated signaling, whereas the flushing effects are due to β-arrestin-mediated signaling. These data suggest that if one could develop analogs of niacin that were biased toward activating G protein–mediated signaling by GPR109A, without activation of β-arrestin-mediated signaling, such compounds might possess the health-promoting benefits of niacin without the flushing side effect.

RH: A premise of this interview is that biomedical researchers possess detailed knowledge about disease processes and therefore should have especially keen insights into how to manage their own personal health. Do you think it's true that biomedical researchers, in general, take better care of their health than people who are not professional scientists?

Lefkowitz: I would say that biomedical researchers, with notable exceptions, typically take better-than-average care of their health. For example, I know of very few colleagues who smoke. The percentage of smokers amongst scientists I know is certainly not zero, but it's much lower than the population average. Similarly, I would say that the incidence of regular exercise amongst researchers is significantly higher than the population average, and additionally scientists are probably better than average at going for regular check-ups.

One area where researchers are probably no different than the general population, alas, is in terms of diet. Most scientists I know just seem to eat whatever is available, without much thought to it, and I have many colleagues with frankly atrocious dietary habits. Additionally, in terms of stress levels, most researchers are probably at least equal to the population average in this area, if not more stressed out than average.

RH: Speaking of stress, when you attend the annual Duke-UNC basketball game and the game is close in the final few minutes, doesn't that put extra stress on the heart?

Lefkowitz: It does. But that's a situation where the beta blockers are especially helpful! doi:10.1124/mi.9.5.4

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Randy Hall, PhD, author and interviewer of this article, was a postdoctoral fellow in the Lefkowitz lab at Duke in the late 1990s. He is currently on the faculty of the Department of Pharmacology in the Emory University School of Medicine and serves on the Editorial Advisory Board of *Molecular Interventions*. He has no conflicts of interest to declare. The subject of the article, Robert Lefkowitz, of the Howard Hughes Medical Institute and Duke University Medical Center, likewise has no conflicts of interest to declare; he currently consults for Genentech, Lexicon Pharmaceuticals, and Five Prime, but these companies do not manufacture any of the drugs or supplements that are discussed in the article.