Cardiometabolic Chronicle

CMHC Cardiometabolic Health Congress

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DELIVERING THE LATEST
developments in cardiometabolic health

Special Article Collection

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A Cardiometabolic Subspecialty? Not Such A Crazy Idea

The global epidemic of metabolic syndrome, a constellation of cardiometabolic risk factors, and that of obesity, type 2 diabetes, atherosclerosis, and cardiovascular disease (CVD) have become the modern-day health hazard across the world. In the US, the numbers are particularly striking. Even with the recent reports that the incidence of diabetes fell by 35% in the last 20 years[1], there are more than 30 million US adults living with diabetes, 1.5 million Americans are diagnosed with diabetes every year, and 84 million have prediabetes.[2] The increasing prevalence of obesity (now estimated to affect more than 93 million, or nearly 40% of all US adults), high cholesterol (95 million US adults have cholesterol levels of >200 mg/dL), and hypertension (46% of US adults using the new guidelines), together with type 2 diabetes (T2D) are some of the major drivers in cardiovascular morbidity and mortality, and altogether causing billions if not trillions of dollars to the US economy.[3-5]

At Cardiometabolic Health Congress, we have been at the forefront of looking at the whole spectrum of cardiometabolic disease, including obesity, diabetes, lipids, hypertension, cardiovascular disease, and practical ways to address them. We strive to synthesize and translate the latest developments across the different fields to promote evidence-based strategies to tackle this growing epidemic. As these diseases or risk factors exist in a continuum, they can't be addressed individually or in a vacuum, which is unfortunately what tends to happen in clinical practice. As CMHC Chair Robert H. Eckel, MD and Michael J. Blaha, MD, MPH describe in a powerful editorial published in The American Journal of Medicine, "patients are shunted back and forth among cardiologists, endocrinologists, and primary care physicians—with uncertain "ownership" of different aspects of the patient's care." As such, meaningful change in patients outcomes continue to elude us, as the statistics above show.

Arguably, the times have never been better for cardiometabolic medicine. With the results of cardiovascular outcomes trials of newer diabetes drugs like sodium-glucose-cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs), we now have real means to prevent heart failure (HF), stroke, myocardial infarctions, and all-cause mortality in patients with T2D and existing CVD, and perhaps, soon enough, even in patients without T2D, or for primary CVD prevention.[7,8,9] Furthermore, these agents have shown real promise in tackling the massive challenge of slowing kidney disease progression in patients with diabetes, in addition to having beneficial effects on hypertension and overweight and obesity.[7,8] We have discovered the 'metabolic face' of heart failure, which has led to not only improved treatments for the often ignored spectrum of patients with heart failure and diabetes, but also in characterizing a new subset very tightly related to cardiometabolic risk factors, or HF with preserved ejection fraction (HFpEF).[10] These developments only represent a small portion of the exciting advances that are poised to revolutionize the care for patients with cardiometabolic disease or risk.

But will they do so, or will they be subject to the slow uptake (sometimes in decades)[11] that usually is associated with newer therapies and approaches? The early indications do not seem promising. A recent study from the GOULD registry, an on-going US-based registry designed to describe real-world treatment patterns among patients with ASCVD, including those with T2D, showed that in eligible patients with existing ASCVD and T2D, only 9% and 7.9% were using an SGLT-2 inhibitor or a GLP-1 RA, respectively.[12] In this study, the use of therapies that, at best, have no cardiovascular benefits in high-risk patients with T2DM, such as sulfonylureas and DPP-4 inhibitors, was significantly higher than that for GLP-1 RAs or SGLT-2 inhibitors.[12] Because of the cardiovascular benefits of these agents, there is considerable discussion about using them (particularly SGLT-2 inhibitors) in the cardiology setting, and even calls to merge diabetes and cardiology.[13] But, cardiologists still seem skeptical about using these agents, or may be ill-equipped to do so.[6,14] Also, what is it to say that even if we get past the hurdle of the widespread adoption of these agents across specialties, that we can really address the tremendous impacts of cardiometabolic diseases without taking into account nutrition, physical activity, smoking, hypertension, or lipids?[6]

Optimizing and coordinating a comprehensive treatment plan for a patient with cardiometabolic disease that takes into account all these factors can be extremely challenging, confined not only by deficiencies in training, but also financial and health system barriers. While there are no easy solutions to this, an interesting proposal is to create a new cardiometabolic subspecialty training track in internal medicine, so in the near future we can have physicians that are better equipped and specialized to address all these different aspects. The proposal, as laid out by Drs. Eckel and Blaha[6], would involve 3 years of specialized training that would be a composite of cardiology, endocrinology, and advanced concepts in lifestyle medicine. The endocrinology component would include extensive training in obesity, diabetes (both type 1 and type 2), as well as lipids and lipoprotein disorders, while the cardiology component would be focused primarily on the primary and secondary prevention of ASCVD. Lifestyle training would go beyond just inquiring about diet and exercise; the cardiometabolic clinician would have the ability to address nutrition and diet, smoking cessation, and recommend individualized physical activity goals. Although the idea is in its initial stages and a lot of groundwork needs to be done, the authors make a compelling argument for challenging the current status quo for the care of patients with cardiometabolic disease. As the authors conclude: "it's time to move forward and not wait until we wish we had. The answer should not be to add more training, but to sharpen and focus existing education concepts to produce the product we know we need."[6]

Shpetim Karandrea, PhD
Editorial Director

References:

1. Benoit, Stephen R., et al. "New directions in incidence and prevalence of diagnosed diabetes in the USA." BMJ Open Diabetes Research and Care 7.1 (2019): e000657.
2. American Diabetes Association. "Statistics about diabetes." Available at http://www.diabetes.org/diabetes-basics/statistics/, accessed August 6, 2019.
3. Centers for Disease Control and Prevention. "Adult obesity facts." Available at https://www.cdc.gov/obesity/data/adult.html, accessed August 6, 2019.
4. Centers for Disease Control and Prevention. "High cholesterol facts." Available at https://www.cdc.gov/cholesterol/facts.htm, accessed August 6, 2019.
5. Benjamin, Emelia J., Paul Muntner, and Márcio Sommer Bittencourt. "Heart disease and stroke statistics-2019 update: a report from the American Heart Association." Circulation 139.10 (2019): e56-e528.
6. Eckel, Robert H., and Michael J. Blaha. "Cardiometabolic Medicine: A Call for a New Subspeciality Training Track in Internal Medicine." The American Journal of Medicine (2019).
7. Carbone, Salvatore, et al. "Glucose-lowering therapies for cardiovascular risk reduction in type 2 diabetes mellitus: State-of-the-Art Review." Mayo Clinic Proceedings 93.18 (2018): 1629 – 1647.
8. Das, Sandeep R., et al. "2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways." Journal of the American College of Cardiology 72.24 (2018): 3200-3223.
9. Gerstein, Hertzel C., et al. "Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial." The Lancet (2019).
10. Sunder, M. D. "Heart Failure with Preserved Ejection Fraction: A Review of the ACC/AHA Guidelines and Evidence-Based Management Strategy." The Medicine Forum 20.1 (2019).
11. Packer, Milton. "Why it's still 1989 for primary care." Medpage Today. July 03, 2019, available at https://www.medpagetoday.com/blogs/revolutionandrevelation/80822, accessed August 7, 2019.
12. Arnold, Suzanne V., et al. "Use of Guideline-Recommended Risk-Reduction Strategies Among Patients with Diabetes and Atherosclerotic Cardiovascular Disease: Insights from Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management (GOULD)." Circulation (2019).
13. Vardeny, Orly, and Muthiah Vaduganathan. "Practical Guide to Prescribing Sodium-Glucose Cotransporter 2 Inhibitors for Cardiologists." JACC: Heart Failure 7.2 (2019): 169-172.
14. Young, Randy. "Cardiology & diabetes: collaborating to defeat a dangerous duo." CardiovascularBusiness, available at https://www.cardiovascularbusiness.com/topics/lipids-metabolic/cardiology-diabetes-collaborating-defeat-dangerous-duo, accessed August 9, 2019.

Advancing Education in Cardiometabolic Disease

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With the principal objective of advancing education in cardiometabolic disease, the *Cardiometabolic Chronicle* delivers the latest updates and insights in the field of cardiometabolic health.

Previous *Chronicle* publications have incorporated a broad array of articles focusing on various facets of cardiometabolic health including advancements in the field of cardio-oncology, appropriate nutritional plans for the cardiometabolic patient, and cardiometabolic risk factors in the female population. Additionally, the publication has outlined updates from critical trials in cardiometabolic medicine, as well as important real-world studies --to help readers stay at the forefront of cutting edge information in the field.

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Technology in Cardiometabolic Health – Challenges and Solutions

The increasing impacts of cardiometabolic risks and cardiometabolic disease, including obesity, hypertension, type 2 diabetes, dyslipidemia, atherosclerosis, chronic kidney disease, have led to significant therapeutic innovations that have undoubtedly helped improve cardiometabolic health in the last decade. Conventional approaches to care, such as landmark clinical trials, updated clinical practice guidelines, and population-level efforts in screening and diagnosing cardiometabolic disease have helped to improve outcomes. However, a significant proportion of the population is still at a high-risk for developing cardiometabolic disease or for exacerbated effects from existing cardiometabolic conditions.

Since patients may respond differently to therapy, many conventional approaches are unable to answer these differences at the individual level, and several approaches to help bridge this gap and individualize therapy are emerging. One of such emerging cutting-edge approaches with significant advances in the last decade is healthcare technology. Inclusion of technology has brought a remarkable revolution in healthcare, for instance, health and fitness apps promote the idea of patient self-management and bring innovation in individualized health care by converging with genomics, genetics and systems biology. As the evidence-base for technology in healthcare, and specifically in cardiometabolic health, continues to increase, its utility is increasingly recognized by experts and incorporated as part of clinical practice guidelines. In this context, we had an opportunity to talk with ***Patrick Wayte, Senior Vice President of the American Heart Association's Center for Health Technology & Innovation***, about the role of technology in health care.

Today an individual can self-monitor their health by using smartphone-enabled fitness apps, as well as wearable scanners to monitor their weight, sleep, blood glucose levels, electrocardiographic activity, blood pressure, body temperature, heart rate, and more. Latest statistics indicate that there are more than 97,000 health and fitness apps available in the marketplace in 2019. The cardiometabolic health space is increasingly being influenced by this tech-realm, and according to Mr. Wayte "one of the extraordinary opportunities with technology is the combination of high fidelity and high volume data coming through the body sensing devices tied to ultimately nudging systems analytics and AI systems that allow the individual to make much better decisions about their health". "If this approach is further linked with pharmacotherapy, genetic sequencing, and what physicians know about treating disease, we have a great opportunity to have a deep understanding of the individual patient, how they process medication, perhaps even what are the precursors to disease, allowing for rapid interpretation of increasingly sophisticated amounts of data", he mentioned.

The use of technology is very powerful and confers numerous advantages to both the patients as well as providers, including massive amounts of data, which can also bring additional challenges. Hence, it becomes very pertinent to know the answers of many important

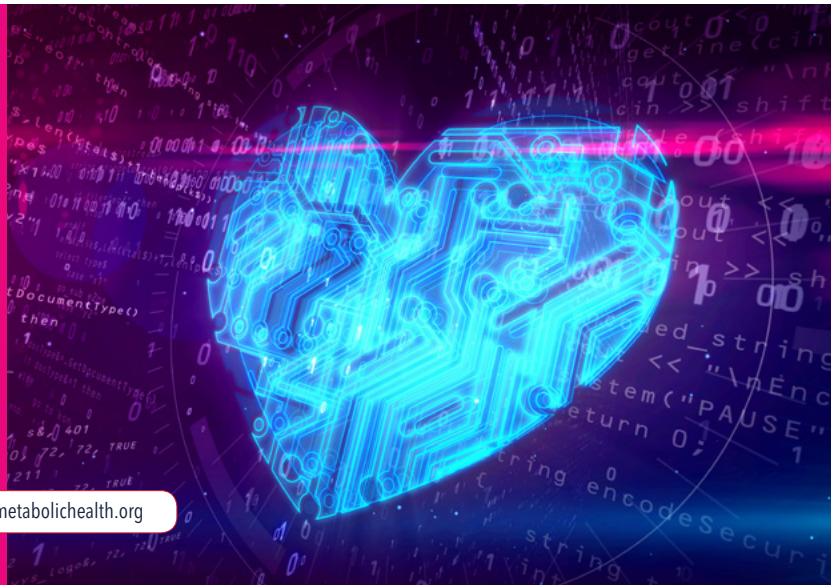
questions, including how to streamline and filter through this information and leverage it for the benefit of patients. Mr. Wayte told us that the American Heart Association has been working very diligently to answer these questions. "We are always talking with healthcare providers on how to best use the data, and it is a very difficult endeavor. The Association recently worked alongside the American Medical Association (AMA), Health Information Management Systems Society (HIMSS), and the DHX group to lauch Xcertia, a non-profit dedicated to promoting best practices in the development and use of healthcare mobile applications. Another step on which the American Heart Association is actively working with different stakeholders to create a sort of "healthcare outcomes clearinghouse," something that works throughout the body of evidence and consolidates the outcomes data with technology which will help to filter and standardize the data beneficial for patient care.

The next very logical question is whether caretakers, as well as caregivers, are ready for this big, dynamic change that technology is bringing to healthcare. The answer can be effortlessly reflected from the current statistics, approximately 52% of smartphone users collect health-associated data, and around 93% of doctors indicated that mobile apps can enhance patient health care quality. "The healthcare community is already experiencing this, because patients are bringing in data. On the other hand, patients and consumers are very ready for it. But there is definitely a gap in terms of determining what information is relevant for patient care and for making clinical decisions, and the traditional healthcare systems' ability to make sense of it right now" – Mr. Wayte mentioned.

We now have several evidence-based technology approaches in cardiometabolic health, but if patients are not adequately using them, it can undermine their clinical value, similar to the impact that medication non-adherence has on overall outcomes. As such, the importance of patient engagement and education cannot be overstated. Mr. Wayte mentioned that the American Heart Association is working to aid patients as well as clinicians to eradicate the barriers for an easier adoption of technology. "We are trying to bring together clinical algorithms, health content, care plans, and digital solutions, including remote patient monitoring with the intent of trying to get alignment with evidence-based care. We believe that this would be beneficial to both clinician and patient engagement with technology, in terms of sticking with the regimens, believability and credibility" – he mentioned.

Not only this, technology has the potential to bridge the socioeconomic patient care gap by optimizing and improving healthcare in rural areas. However, there are significant challenges with the affordability of technology, particularly in rural areas, due to the slow absorption of technology reimbursement in the healthcare payer systems among others. "One of initiatives that we are developing to address this aspect, is to create a health equity plan for technology that aims to improve access to various healthcare thechnologies across socioeconomic status to give everyone the same opportunity to improve health and prevent deadly diseases" – said Mr. Wayte. "Lastly, we are also pioneering an effort that will encourage our own clinical professional members to volunteer their time through telehealth systems for consults to federally-qualified health centers and community clininics, which will reach rural and medically underserved communities" – Mr. Wayte mentioned.

Healthcare technology is emerging as a major player to bridge real clinical gaps and improve patient care. As we continue to evaluate its role in the prevention, diagnosis, and treatment of cardiometabolic disease, it is important to educate clinicians about best practices and current evidence base. CMHC, in collaboration with MedTech Impact, organized the ***Cardiometabolic Technology Summit: Digital Advancements and Practical Solutions***, which took place during the 14th Annual CMHC meeting in Chicago, IL and further explored these issues and much more. During the summit, Mr. Wayte overviewed some of these efforts in his presentation titled "New Generation Engagement: The New Frontier.



Edward S. Horton, MD

Prevention of Diabetes and Metabolic Syndrome: Lessons Learned from the DPP and DPPOS Trials

Prediabetes is a high-risk state for developing diabetes, and currently, more than 84 million adults in the US have prediabetes.[1] Diagnosing and managing prediabetes is essential, considering that it increases the annual risk for developing diabetes by 10%, and individuals with prediabetes have a 70% lifetime risk of progressing to diabetes.[2] As with diabetes, prediabetes increases the risk of atherosclerotic cardiovascular disease (ASCVD), nephropathy, and retinopathy.[3,4] The exponential rise in obesity has contributed to the overall impact of prediabetes; individuals with prediabetes that are also overweight or obese have an increased risk of progressing to diabetes.[5]

However, despite the increased morbidity and mortality, prediabetes is underdiagnosed and undertreated. It is estimated that 90% of individuals with prediabetes in the US are not aware that they have the condition.[6] The treatment of prediabetes is a complex and controversial topic in the clinical community; many clinicians are reluctant to screen and manage patients with prediabetes.[7] Studies have shown that clinicians rarely provide lifestyle modification counseling, refer eligible patients to an intensive behavioral lifestyle intervention modeled on the successful Diabetes Prevention Program (DPP), or prescribe metformin; all of which are recommended in the ADA guidelines for prediabetes.[7-10]

The reasons for undertreatment are multifactorial; clinicians may not view prediabetes as a disease state that warrants intervention or believe that treating prediabetes does not prevent diabetes or its complications, as well as a lack of FDA approved pharmacotherapies for prediabetes.[7-9] However, several approaches to prevent or reduce diabetes progression in these individuals have been successful, including targeting overweight and obesity with intensive lifestyle interventions, pharmacotherapy, and bariatric surgery, as well as glycemic control with existing glucose-lowering medications.[11]

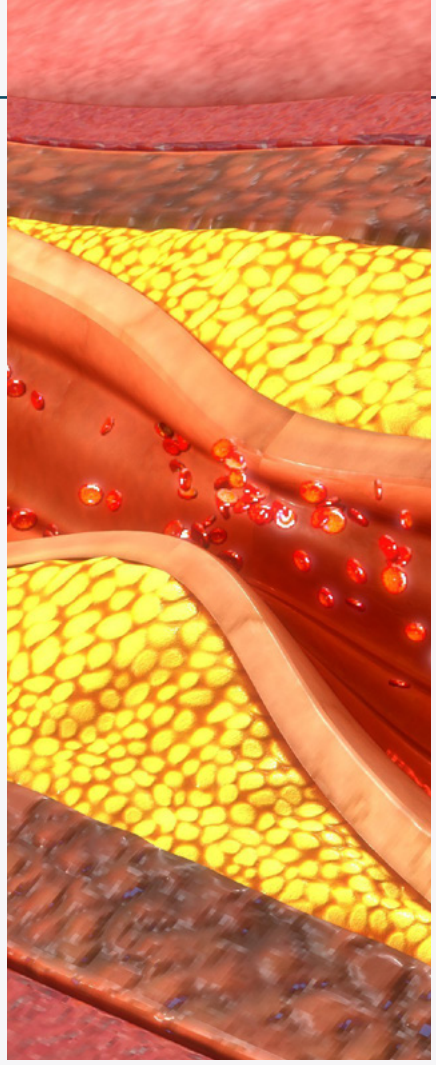
"Prediabetes occurs when fasting plasma glucose (FPG) levels or 2-hr plasma glucose (PG) levels following an oral glucose tolerance test (OGTT) lie between normal levels and the cut points for diagnosing diabetes. At present, fasting glucose levels of 100-125 mg/dL, or 2-hr PG levels following an OGTT between 140 – 199 mg/dL are considered to be prediabetic.[12] However, the criterion mostly used in practice is the fasting glucose as most clinicians do not routinely do an OGTT" – mentioned ***Edward S. Horton, MD***, Professor of Medicine at Harvard Medical School and Senior Investigator at the Joslin Diabetes Center in Boston.

Dr. Horton has played a pioneering role in several clinical trials that have looked at pre-

vention of diabetes or diabetes complications with intensive lifestyle interventions or metformin, including the Diabetes Prevention Program (DPP), DPP Outcomes Study (DPPOS), and the Action for Health in Diabetes (LookAHEAD) Study. Some of the strongest evidence for lifestyle modification in the prevention of diabetes comes from the DPP program, which was established by the Centers for Disease Control and Prevention (CDC) to bring evidence-based lifestyle change programs to Americans at high-risk for type 2 diabetes.[13]

"At first, the DPP really looked at interventions to decrease progression from impaired glucose tolerance to diabetes, but as the study progressed, we began to look at prevention of cardiovascular disease and all of the long-term complications associated with diabetes, like retinopathy, nephropathy, and neuropathy. In this program, nondiabetic patients with impaired glucose tolerance or elevated FPG were randomized to metformin, intensive lifestyle modification, or placebo control. We chose metformin because along with effectiveness it conferred selective advantages such as low cost, long term safety data, and fewer adverse events compared to other potential candidates at the time which had also been shown to prevent type 2 diabetes, including troglitazone, rosiglitazone, pioglitazone, voglibose, and insulin glargine[14-18]" – mentioned Dr. Horton, further adding: "intensive lifestyle involved reducing dietary fat and overall calorie intake, increasing physical activity to at least 150 minutes a week of moderate-intensity exercise similar to brisk walking and to achieve and maintain at least a 7 percent reduction in their body weight. As reported[13], the study was highly successful; the lifestyle intervention reduced the incidence of diabetes by 58% and metformin reduced the incidence by 31% compared to placebo. Furthermore, the incidence of metabolic syndrome (MetS) was reduced by 41% in the lifestyle group and by 17% in the metformin group compared to placebo. Quite remarkably, in people diagnosed with MetS at baseline, 18% in the placebo group, 23% in the metformin group, and 38% of the lifestyle group no longer had the syndrome at 4-years.[19] Because the results of the study were so dramatic, it was stopped ahead of schedule, and we gave everyone an intensive lifestyle program including those in the original placebo and metformin groups. We asked the individuals to continue taking metformin in addition to lifestyle modification, which is what is known as the DPPOS, the long-term follow-up of the DPP study, which is still ongoing."

Recent results from more than 11 years of follow-up in the DPPOS study have demonstrated the longer-term effectiveness of metformin, showing a 18% risk reduction for the development of diabetes, a 28% decreased risk for microvascular complications in patients who did not develop diabetes, as well as reduced risk for atherosclerosis in men.[20,21] Indeed,



the remarkable results of the DPP and DPPOS study call at least for a reflection about the powerful role of lifestyle modification in the prevention of diabetes and metabolic syndrome. However, we know that implementing and maintaining life style changes is difficult to say the least. Dr. Horton shared some of the approaches used in the DPP to give an idea of what it takes to achieve and sustain meaningful lifestyle changes: "All the participants across different centers in the DPP program had a very intense course in lifestyle modification. Besides physicians, we had trained dietitians, exercise physiologists, behavior modification specialists to deal with some of the psychological problems, and we used the team approach to really work with people to help them achieve the lifestyle changes." Although most clinical practices do not have the resources to address all these factors, they should be at least be encouraging lifestyle changes or refer eligible patients to lifestyle specialists, nutritionists, or to a local DPP program in order to better address the rising impacts of type 2 diabetes and metabolic syndrome.

References:

1. Centers for Disease Control and Prevention. "Prevalence of prediabetes." February 19, 2018, available at https://www.cdc.gov/diabetes/data/statistics-report/prevalence.html, accessed December 20, 2018.
2. Bowen, Michael E., et al. "Building Toward a Population-Based Approach to Diabetes Screening and Prevention for US Adults." *Current Diabetes Reports* 18.11 (2018): 104.
3. Ali, Mohammed K., et al. "Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988–2014." *The Lancet Diabetes & Endocrinology* 6.5 (2018): 392-403.
4. Grundy, Scott M. "Pre-diabetes, metabolic syndrome, and cardiovascular risk." *Journal of the American College of Cardiology* 59.7 (2012): 635-643
5. DeJesus, Ramona S., et al. "Incidence rate of prediabetes progression to diabetes: modeling an optimum target group for intervention." *Population Health Management* 20.3 (2017): 216-22
6. Centers for Disease Control and Prevention (CDC). "Awareness of prediabetes--United States, 2005-2010." *MMWR. Morbidity and Mortality Weekly Report* 62.11 (2013): 209.
7. Mainous, Arch G., et al. "Prediabetes screening and treatment in diabetes prevention: the impact of physician attitudes." *The Journal of the American Board of Family Medicine* 29.6 (2016): 663-671.
8. Tseng, Eva, et al. "Survey of primary care providers' knowledge of screening for, diagnosing and managing prediabetes." *Journal of General Internal Medicine* 32.11 (2017): 1172-1178.
9. Kandula, Namratha R., et al. "Preventing diabetes in primary care: providers' perspectives about diagnosing and treating prediabetes." *Clinical Diabetes* 36.1 (2018): 59-66.
10. American Diabetes Association. "3. Prevention or delay of type 2 diabetes: standards of medical care in diabetes-2019." *Diabetes Care* 42.Suppl 1 (2019): S29.
11. Perreault, Leigh. "Prevention of type 2 diabetes." *Diabetes and Exercise*. Humana Press, Cham, 2018. 17-29.
12. American Diabetes Association. "2. Classification and diagnosis of diabetes: standards of medical care in diabetes–2019." *Diabetes Care* 42.Supplement 1 (2019): S13-S28.
13. Knowler, William C., et al. "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin." *The New England Journal of Medicine* 346.6 (2002): 393-403.
14. Azen, Stanley P., et al. "TRIPOD (TRoglitazone In the Prevention Of Diabetes): a randomized, placebo-controlled trial of troglitazone in women with prior gestational diabetes mellitus." *Controlled Clinical Trials* 19.2 (1998): 217-231.
15. Scheen, A. J. "DREAM study: prevention of type 2 diabetes with ramipril and/or rosiglitazone in persons with dysglycaemia but no cardiovascular disease." *Revue Medicale de Liege* 61.10 (2006): 728-732.
16. DeFronzo, Ralph A., et al. "Actos Now for the prevention of diabetes (ACT NOW) study." *BMC Endocrine Disorders* 9.1 (2009): 17.
17. Kawamori, Ryuzo, et al. "Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance." *The Lancet* 373.9675 (2009): 1607-1614.
18. Origin Trial Investigators. "Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention)." *American Heart Journal* 155.1 (2008): 26-e1.
19. Orchard, Trevor J., et al. "The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial." *Annals of Internal Medicine* 142.8 (2005): 611-619.
20. Aroda, Vanita R., et al. "Metformin for diabetes prevention: Insights gained from the diabetes prevention program/diabetes prevention program outcomes study." *Diabetologia* 60.9 (2017): 1601-1611.
21. Diabetes Prevention Program Research Group. "Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study." *The Lancet Diabetes & Endocrinology* 3.11 (2015): 866-875.

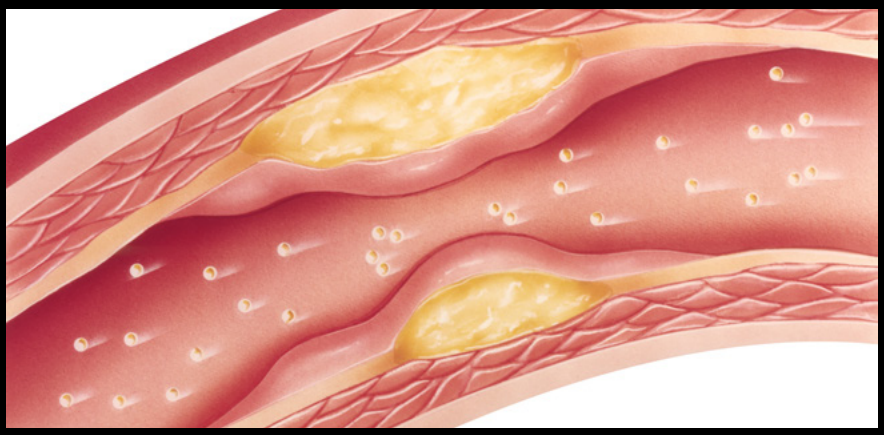
HYPERTENSION
which course of treatment to follow?

By Progga Sen, Ph.D.

High blood pressure is a dangerous medical condition that eventually leads to cardiac disorders and stroke if not regulated on time, and around 75 million Americans (~one in every three adults) are afflicted with hypertension at present, according to the Centers for Disease Control and Prevention (CDC). The American College of Cardiology/American Heart Association (ACC/AHA) 2017 guidelines has categorized blood pressure (BP) into the following groups: <120/80 mm Hg as normal blood pressure, 120-129/80 mm Hg as elevated BP, 130-139 mm Hg systolic pressure or 80-89 mm Hg diastolic pressure as stage-I hypertension, and 140/90 mm Hg as stage-II hypertension. In addition to re-categorizing the BP subdivisions, greater emphasis rests on out-of-office BP measurement for accurate hypertension monitoring and for prescribing required medication.[1-4]

With myriad factors causing the incidence and progression of high blood pressure, including several lifestyle-related risks- obesity, inactivity, improper diet, stress and alcohol; pre-existing medical conditions- diabetes, pre-hypertension and chronic kidney disease (CKD); and others- family history, race and gender; hypertension is considered a silent killer. In terms of disease management, lifestyle modification is essential; patients are advised to maintain a healthy diet (heart-friendly, sodium restricted, and lipid-lowering), exercise regularly, and monitor BP constantly. High BP is generally associated with high sodium and subsequent fluid retention in the body, that can lead to swollen lower extremities and hardening of the heart arteries; advanced cases of hypertension can show signs of headache, dizziness, shortness of breath, and eye problems. Moreover, prolonged hypertension can cause more serious ailments that include retinopathy, cardiac failure, cerebral stroke, or renal dysfunction.[5-7]

Hypertension can be either primary, where no root cause is known, or secondary, caused by other medical conditions, like diabetes or chronic kidney disease (CKD). The combination and type of medications prescribed to the patients depend on patient medical history, background, comorbidities, age, and lifestyle.



The ACC/AHA, in the latest guidelines, has emphasized individualized cardiovascular risk measurement by ambulatory and home BP monitoring as crucial steps, in addition to clinic BP checking. Also, the ACC/AHA advices the physicians, the nursing staff or the nutritionist to provide a much-needed lifestyle modification education to the patients- BP of 130-139/80-89- with a <10% cardiovascular disease risk over the next 10 years and a more aggressive approach for those with a >10% risk of the onset of cardiovascular disease.[3] Several types of drugs are prescribed to curb hypertension, such as diuretics; beta blockers; renin-angiotensin-aldosterone system blockers (RAASs)- angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs); and calcium channel blockers (CCBs).[8,9] Diuretics, calcium channel blockers, and RAAS blockers form the first line of treatment.

RAAS inhibitors either reduce angiotensin II synthesis, thereby inhibiting aldosterone secretion (ACEIs), or may impair the angiotensin II receptors (AT I) (ARBs). The CCBs reduce blood pressure by relaxing vascular smooth muscle and dilates blood vessels, and therefore, reduce peripheral resistance. The diuretics, on the other hand, curbs sodium and water retention by the kidneys and hence, reduces extracellular fluid volume.

Hypertension lies at the crossroads of significant health complications- cardiac dysfunction, stroke, and renal disorder. The diuretics, a prominent class of medication prescribed to treat hypertensive patients, targets kidney function by tightly regulating sodium and water load; they affect the renal tubules of the kidney to expedite their release from the body. According to the ACC/AHA guidelines, the diuretics are incredibly favorable for patients with diabetes, >65 years of age, of African origin, with a history of stroke or low renin, and even people who have suffered from cardiac failure. The thiazide-type diuretics constitute the only category of diuretics that dilates blood vessels, in addition to regulating sodium and water retention in the body, thereby reducing blood pressure. Though the precise functional mechanism is unknown, these diuretics target the distal convoluted tubules in the kidney. Several meta-analyses and clinical studies (on patients with varied medical histories) have tested the efficacy of the thiazide-type diuretics. These diuretics have exhibited favorable outcomes in these studies; their effectiveness proved to be comparable with other classes of hypertension medications.

The thiazide-type diuretics are grouped into two separate sub-classes: thiazides (with a bi-cyclic benzothiadiazine backbone) and the thiazide-like diuretics (lacking the benzothiadiazine backbone), both target the first segment of the distal convoluted tubule. Studies performed on diabetic and elderly patients show promising outcomes with the thiazide-like diuretics in comparison to thiazides, the main differences lie in potency, dose, and side-effects. The thiazides are administered in high doses that are responsible for harmful side-effects such as hyperkalemia, dyslipidemia, and dysregulated glucose levels, to mention a few. Evident from independent clinical trials, the thiazide-like diuretics have an edge- their efficacy in low sustained doses have proved to control almost every adverse metabolic reaction in patients with primary hypertension. Specific thiazide-like drugs are preferred for their role in improving renal and cardiac markers too; independent trials show the positive impact of these diuretics on reviving endothelial and arterial functions of the heart.

Interestingly, the thiazide-like diuretics have greater half-lives, and therefore, have a prolonged duration of activity- reported in several clinical studies. These findings are consolidated by the latest guidelines from the ACC/AHA and the Latin American Society of Hypertension that propose the use of thiazide-like diuretics or calcium channel blockers (CCBs) as a preferred route for hypertension therapy for black patients in U.S. (tested with thiazide-like diuretic, chlorthalidone, in ALLHAT analysis).[10, 11] Besides, meta-analyses reveal improved mortality risk only in hypertensive patients treated with thiazide-like diuretics.[4, 10, 12, 13]

Thus far, the thiazide-like diuretics fare considerably better than the thiazides- dose, half-life, potency, end-organ damage risk, and mortality. Therefore, the benefits with these diuretics place them at the forefront with other groups of antihypertensive treatments. The thiazide-like diuretics have the potential to be a primary candidate as a leading choice of medication to treat hypertension, although further detailed analyses are needed. Concludingly, every course of drugs has its upside and downside; we have to scrutinize each aspect of the drug (structure and functional mechanism) and the patient (medical history of self and family) before prescribing a particular combination of medicines to treat hypertension.

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References:

1. Vijayakumar, Shilpa, Javed Butler, and George L. Bakris. "Barriers to guideline mandated renin-angiotensin inhibitor use: focus on hyperkalaemia." *European Heart Journal Supplements* 21. Supplement_A (2019): A20-A27.
2. Burnier, Michel, George Bakris, and Bryan Williams. "Redefining diuretics use in hypertension: why select a thiazide-like diuretic?." *Journal of Hypertension* 37.8 (2019): 1574-1586.
3. Bakris, George. "Similarities and differences between the ACC/AHA and ESH/ESC guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults: a perspective." *Circulation Research* 124.7 (2019): 969-971.
4. Whelton, Paul K., et al. "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *Journal of the American College of Cardiology* 71.19 (2018): e127-e248.
5. Konstantinidis, Lazaros, and Yan Guex-Crosier. "Hypertension and the eye." *Current Opinion in Ophthalmology* 27.6 (2016): 514-521.
6. Pinho-Gomes, Ana Catarina, and Kazem Rahimi. "Management of blood pressure in heart failure." *Heart* 105.8 (2019): 589-595.
7. Palmer, Biff F. "Renal dysfunction complicating the treatment of hypertension." *New England Journal of Medicine* 347.16 (2002): 1256-1261.
8. Mann, Johannes FE, and Karl F. Hilgers. "Renin-angiotensin system inhibition in the treatment of hypertension." *UpToDate* (2016).
9. Yang, Yang, and Huilan Xu. "Comparing six antihypertensive medication classes for preventing new-onset diabetes mellitus among hypertensive patients: a network meta-analysis." *Journal of Cellular and Molecular Medicine* 21.9 (2017): 1742-1750.
10. Carey, Robert M., and Paul K. Whelton. "Prevention, detection, evaluation, and management of high blood pressure in adults: synopsis of the 2017 American College of Cardiology/American Heart Association hypertension guideline." *Annals of Internal Medicine* 168.5 (2018): 351-358.
11. Wright, Jackson T., et al. "Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril." *JAMA* 293.13 (2005): 1595-1608.
12. Olde Engberink, Rik HG, et al. "Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: systematic review and meta-analysis." *Hypertension* 65.5 (2015): 1033-1040.
13. Barbos, Eduardo, et al. "Guidelines on the management of arterial hypertension and related comorbidities in Latin America." *Journal of Hypertension* 35.8 (2017): 1529-1545.

LIFE IN THE TRENCHES: A Clinical Perspective On Cardiometabolics

By John C. Sciales, MD[1]

I work in the trenches. I am not an academic physician, I do not do research, and I spend all my time in patient care. I am an internist in a busy office as part of an outpatient setting of a large hospital network. My father[2] and mentor, an internist and keen diagnostician, made my focus in approaching each patient very easy. He said "whenever you see a patient, narrow down your approach to one question. What variable can you change that will improve the quality or length of his/her life?" He also said, "Be careful, every 7 years, half of what you know will change... However, you do not know which half".

This led me to the study of cardiometabolics. I realized that unfortunately many patients were being treated as if time stood still in medicine. Cardiologist were treating cholesterol, endocrinologist were treating sugars, and exercise was "going for a walk". Lipid issues were treated with the advice, "watch your diet" and many patients were told "be careful you have borderline diabetes". Unfortunately, death rates, though modestly improved, were still unacceptably high. High-profile people were getting ill and dying with traditional care. Tim Russert's death at 58 years old of a myocardial infarction with an LDL less than 70 mg/dL and a normal stress test 6 weeks earlier is a prime example, as well as Bill Clinton's bypass and subsequent stenting 2 years later. Both of these men had metabolic issues which should have initiated a full cardiometabolic work-up today.

Diabetes is not about sugars alone. In fact, glucose is the fourth variable I will look at with diabetes. The first is overall cardiometabolic health including percent body fat, exercise patterns, and fitness. The second is evidence of cardiovascular disease. The third is lipid patterns, especially the triglyceride to HDL ratio indicating atherogenicity. Last is the hemoglobin A1C level. Why is so much attention paid to glucose when other variables predict morbidity and mortality to a great extent? Unfortunately, many patients were told that if they did not improve their sugars, they would have a heart attack or stroke. This was proven wrong by the UKPDS[3], ACCORD[4], ADVANCE[5] and VADT[6] trials. In fact, overall mortality increased slightly! CVD-real[7], EMPA-reg[8], CANVAS[9], DECLARE[10], LEADER[11] and SUSTAIN-6[12] trials, to name a few, have all changed our "goal" when treating diabetes mellitus. The goal should not be hemoglobin A1C, but reducing the cardiovascular morbidity. Most clinicians do not know that the definition of diabetes with a hemoglobin A1C of 6.5% was defined based on diabetic retinopathy and not the associated cardiovascular disease.

Cardiologists must now remove their blinders when it comes to cardiovascular prevention. Lowering a diabetic's LDL from 90 to 70 mg/dL after a cardiovascular event with ezetimibe as in the IMPROVE-IT trial[13], resulted in a 2% absolute risk difference after 7 years and

is minimal compared with the risk reduction of discontinuing the sulfonylurea, adding an SGLT–2 inhibitor as well as a GLP-1 agonist and considering pioglitazone when appropriate. Additionally, as most patients with type 2 diabetes have elevated triglycerides, adding icosapent ethyl has been associated with a 25% to 30% risk reduction[14]. Bromocriptine, in its safety study[15] has been associated with a decreased cardiovascular composite endpoint by 40%, although further large-scale studies need to be undertaken. In statin intolerant patients or those not at LDL goal, a PCSK–9 inhibitor should be added. When a patient has progression of atherosclerosis, one has to change a variable besides mechanically opening up the vessel to prevent it from happening again. Frequently, this is not done especially if the lipid levels are "within normal limits". Einstein said it best with his definition of insanity, which is doing the same thing multiple times and expecting a different result.

All patients with evidence of diffuse inflammatory vascular disease should get a 2-hour glucose tolerance test, regardless of normal fasting blood sugar or normal hemoglobin A1C[16]. I have coined the term EUGLYCEMIC DIABETES MELLITUS to describe those patients that have a normal fasting blood sugar or hemoglobin A1C but have an abnormal 2-hour glucose tolerance test. The increased cardiometabolic risk demonstrated did not correlate with the degree of glucose abnormality, whether it was present on not. It's like being a little pregnant, you are or you are not. This is frequently seen in those patients who have early onset or diffuse atherosclerosis as this is a leading cause of atherogenic dyslipidemia and subsequent cardiovascular disease. Patients that scare me the most are those with diffuse cardiovascular disease. I label these the inflammatory vasculopathy as opposed to the discrete lesion. Diabetic heart disease is frequently seen as Diffuse Luminal irregularities or diffuse areas of atherosclerosis rather than the discrete lesion. Cardiac surgeons are seeing much more complex disease with the obesity epidemic seen today. Many have strong family histories of cardiovascular disease and many have normal or near normal LDL levels. I have seen these patients put on low-dose statins because "the cholesterol is normal". However metabolic issues in these patients related to insulin resistance and genetic variability play an even greater role. We need to recognize this vulnerable patient prompting a full cardiometabolic workup. Furthermore, new noninvasive imaging techniques are being used to identify these high-risk patients. These include computed tomography (CT) coronary calcium score, computed tomography angiogram (CTA) coronary arteries, and the fractional flow reserve (FFR) which helps predict the degree of stenosis and which patients would benefit from subsequent coronary angiography. The CTA coronary arteries with FFR not only show structure but demonstrate function as well. I predict that with the higher accuracy and a much lower radiation dosage, this test may ultimately surpass the nuclear stress imaging in cardiac risk stratification.

When it comes to exercise, I say, "less is more, and failure is success". High intensity interval training is superior to moderate intensity continuous training at improving cardiometabolic risk[17]. A program of less time but higher intensity leading to muscle failure is easy to achieve and leads to successful improvement in cardiovascular risk. Walking should be the baseline, exercise the goal.

The lack of recognition of the cardiometabolic syndrome has led to a failure of clinicians in looking at metabolic variables in heart disease as opposed to just "aggressive" statin lowering. An example of this is when one of my surgical colleagues, a 67-year-old non-smoker African-American male of above average physical condition and shape had chest pain and had a CABG x4 as well as a carotid endarterectomy. Triglycerides were 90 mg/dL, LDL was 86 mg/dL and HDL was 48 mg/dL. His coronary angiogram demonstrated at least 8 separate 90% stenotic lesions. He had a strong family history of cardiovascular disease. When he returned back to work, I was shocked to find out he was prescribed 10 mg of atorvastatin because his cholesterol was "fine". That was the dose that he had prior to his cardiac event! As a friend, I took control and I called the cardiac surgeon. I asked if his heart appeared to be a diabetic or inflammatory type of heart and he said definitely yes. As a matter of fact, he commented over the past 10 years the bypass surgical cases were becoming more complex as there were less discrete lesions and a lot more inflammatory type lesions. I ordered a 2-hour glucose tolerance test which revealed a 2-hour of 108 mg/dL with an average insulin response. His advanced lipid testing was significant for considerably reduced large HDL. Because of this, I started my friend on rosuvastatin 40 mg as obviously he did require a high intensity statin, icosapent ethyl 2 g twice daily as per the data from the REDUCE-IT trial, and pioglitazone 30 mg based on the IRIS trial[18]. There was no recognition of the metabolic state by his internist, cardiologist, vascular surgeon, cardiac surgeon or the hospital team taking care of him. Unfortunately, this is the rule rather than the exception. Prior to his diagnosis of advanced atherosclerosis, he was on atorvastatin 10 which was his discharge dose! Obviously, no one thought of changing a variable to prevent it from happening again.

I see 25-30 patients daily and I try to keep my focus simple–change variables to improve outcomes. Like most physicians, I use EMR and barely have time to take a deep breath. However, as Jack Nicholson said in the movie A Few Good Men "...you need me on that wall...protecting you. I have a greater responsibility". I feel I must be constantly vigilant in my role as a physician and coordinator of my patients' care. I am wary of the cardiologist who ignores metabolic issues in cardiovascular risk reduction, as well as the endocrinologist whose main focus is glucose lowering ignoring the metabolic issues related to insulin resistance and cardiovascular disease. Cardiometabolic issues involve not only lipids and diabetes but exercise, obesity, nutrition, brain health, inflammation, kidney disease, and even cancer. This list I am sure is not complete. Treating variables is easy but recognizing which ones to change is the difficult task. As Robert Eckel[19] told me "...the more we learn the more we realize what we do not know! ". Never lose focus and never stop learning as patient lives are in our hands.

References:

1. John C Sciales, MD – Internal Medicine – New York Presbyterian Medical Group Queens NY
2. William J. Sciales MD 1930-2016, SUNY Downstate 1956, Internist: Flushing, NY
3. Holman, Rury R., et al. "10-year follow-up of intensive glucose control in type 2 diabetes." *New England Journal of Medicine* 359.15 (2008): 1577-1589.
4. Action to Control Cardiovascular Risk in Diabetes Study Group. "Effects of intensive glucose lowering in type 2 diabetes." *New England Journal of Medicine* 358.24 (2008): 2545-2559.
5. ADVANCE Collaborative Group. "Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes." *New England Journal of Medicine* 358.24 (2008): 2560-2572.
6. Duckworth, William, et al. "Glucose control and vascular complications in veterans with type 2 diabetes." *New England Journal of Medicine* 360.2 (2009): 129-139.
7. Kosiborod, Mikhail, et al. "Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors)." *Circulation* 136.3 (2017): 249-259.
8. Zinman, Bernard, et al. "Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes." New England Journal of Medicine 373.22 (2015): 2117-2128.
9. Neal, Bruce, et al. "Canagliflozin and cardiovascular and renal events in type 2 diabetes." *New England Journal of Medicine* 377.7 (2017): 644-657
10. Wiviott, Stephen D., et al. "Dapagliflozin and cardiovascular outcomes in type 2 diabetes." *New England Journal of Medicine* 380.4 (2019): 347-357.
11. Marso, Steven P., et al. "Liraglutide and cardiovascular outcomes in type 2 diabetes." *New England Journal of Medicine* 375.4 (2016): 311-322.
12. Marso, Steven P., et al. "Semaglutide and cardiovascular outcomes in patients with type 2 diabetes." *New England Journal of Medicine* 375.19 (2016): 1834-1844.
13. Cannon, Christopher P., et al. "Ezetimibe added to statin therapy after acute coronary syndromes." *New England Journal of Medicine* 372.25 (2015): 2387-2397.
14. Bhatt, Deepak L., et al. "Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia." *New England Journal of Medicine* 380.1 (2019): 11-22.
15. DeFronzo, Ralph A. "Bromocriptine: a sympatholytic, D2-dopamine agonist for the treatment of type 2 diabetes." *Diabetes Care* 34.4 (2011): 789-794.
16. Jesús, M., et al. "Real incidence of diabetes mellitus in a coronary disease population." *The American Journal of Cardiology* 111.3 (2013): 333-338.
17. Ramos, Joyce S., et al. "Low-volume high-intensity interval training is sufficient to ameliorate the severity of metabolic syndrome." *Metabolic Syndrome and Related Disorders* 15.7 (2017): 319-328.
18. Kernan, Walter N., et al. "Pioglitazone after ischemic stroke or transient ischemic attack." *New England Journal of Medicine* 374.14 (2016): 1321-1331.
19. Robert H.Eckel MD, Univ of Colorado Charles A. Bottcher II Endowed Chair Of Atherosclerosis, Past President of American Heart Association and President Elect of The American Diabetic Association

Nutrition for Cardiometabolic Health:

Cutting Through the Noise

Despite a wide variety of dietary options available, a prolonged controversy still exists about optimal nutritional plans for cardiometabolic patients, which contributes to the challenges faced by clinicians while caring for these patients. A poor diet is a major contributor in exacerbating the impacts of the cardiometabolic disease; as well as a leading contributor to morbidity and mortality worldwide.[1,2] Thus, proper nutrition for cardiometabolic health is paramount, a view emphasized in several clinical practice guidelines.[3-5] However, defining proper nutrition for cardiometabolic disease is challenging and can be very controversial. Clinicians may not be aware of appropriate healthy eating patterns or the evidence for different dietary approaches on cardiometabolic health outcomes; this is more apparent by the fact that many clinicians do not receive adequate training on nutrition and are less likely to address nutrition as a topic during a clinical visit. To gain more insight in this area, we had an opportunity to talk with Stephen Devries, MD, FACC, a preventive cardiologist, and Executive Director of the Gaples Institute for Integrative Cardiology, a nonprofit dedicated to advancing the role of nutrition and lifestyle in medicine.

Because of all the diet and nutrition advice available, most people are puzzled with the concept of "the ideal diet." Recently, the EAT-Lancet commission report, a large-scale nutrition initiative by The Lancet, emphasized the consumption of plant-based diets over meat-based diets6, an approach that also is supported in the diabetes, hypertension, cholesterol, and primary cardiovascular disease (CVD) prevention guidelines.[4,5,7,8] Dr. Devries echoed this approach: "the diet that would be most helpful for the vast majority of people would be one that is predominantly plant-sourced, a diet rich in vegetables, fruit, beans, whole grains. Although frequently overlooked, it's best that these items be consumed in as close to their original state as possible–not ground into flour or extracted into juice." – *he told Cardiometabolic Chronicle.*

Often while talking about diets, people are focused on how much protein, carbohydrate, and fat they should consume. "For protein, the evidence is clear that a decisive shift to

more plant-sourced protein is ideal. Rich plant sources of protein include beans, whole grains, nuts, and tofu. Most people consume more protein than needed and can easily obtain more required from plant sources." Dr. Devries added - "with regards to fat and carbs, rather than focusing on amounts, it is most helpful look at the quality rather than quantity."

"With fats, cutting down on saturated fat is an important step, but the replacement is equally important and ideally includes foods with healthier fats like Omega-3s (like fish, walnuts, and flax) and monounsaturated fats (such as extra-virgin olive oil, avocado, and almonds). In contrast, replacing saturated fat with refined carbs–a historically common swap–yields no net benefit."

"Similarly, for carbs, rather than focusing on quantity, a good strategy is to improve the quality of carbs with an emphasis on whole grains, and fruits and vegetables-again, served whole rather than ground into flour or extracted into juice."

We can also help our patients by encouraging them to gradually transition towards more plant-sourced foods. And if there is one thing that the science is very clear on, it is the need to remove processed meats from our diets, like bacon or sausage; the World Health Organization has deemed processed meats as carcinogenic to humans[9], and there is clearly decreased risk for CVD or diabetes after eliminating processed meats from the diet[10]."

Paradoxically, several studies have shown that most physicians and other healthcare professionals receive exceedingly limited education in nutrition as part of their formal clinical training.[11] Only 25% of medical schools in the United States offer a dedicated nutrition course, and few medical schools achieve the 30 hours of nutrition education recommended by the National Academy of Sciences.[12] Furthermore, lack of nutrition persists even after formal training, as studies have shown that most clinicians that specialize in cardiometabolic care do not keep up to date with continuing education in nutrition.1 Dr. Devries was in full agreement with these facts as he pointed out that "unfortunately the state of nutrition education in medical training is dire, recently a study that we published in The American Journal of Medicine, which was a survey of over 600 cardiologists, showed that 90% of cardiologists reported receiving no or minimal nutrition education during their training. Interestingly, in the same survey, 95% of cardiologists reported that they felt it was their duty to at least begin the nutrition conversation with their patients".1 At the same time, he underscored the fact that nutrition counseling needs to be a team effort rather than the sole responsibility of the physician. Participation of experts, such as registered dietitians and other nutrition professionals is of the utmost importance.

> "I don't believe that most clinicians regard nutrition with the same degree of importance and urgency as pharmacologic interventions. I think it's critical that we change the mindset about nutrition. Nutritional interventions should not be considered an add-on and are not optional. Diet is fundamental to the health of every patient and needs to be considered an essential component of their care."

Nevertheless, clinicians may not adequately address nutrition with their patients, not only due to a lack of knowledge and training, but also due to the limited time they have to spend with each patient. Dr. Devries shared some practical pearls on how to circumvent this barrier: "given the time constraints, there are some efficient ways to make a meaningful difference with nutrition in your practice, including a quick dietary assessment that could be distributed to patients while they're waiting in the waiting room. Physicians can then choose one nutrition topic identified by the survey to discuss for a minute or two during each clinic visit.

Moreover, a critical nutritional intervention that takes even less time is for clinicians to make a simple statement to patients that emphasizes nutrition as a priority; and that makes clear that as essential as it is for them to carefully take their prescribed medication, that optimal health also requires attention to nutrition and lifestyle. From there, patients should be directed to appropriate nutrition resources, which could include appropriately trained dietitian/nutritionists, nurses, health-coaches, and chefs.

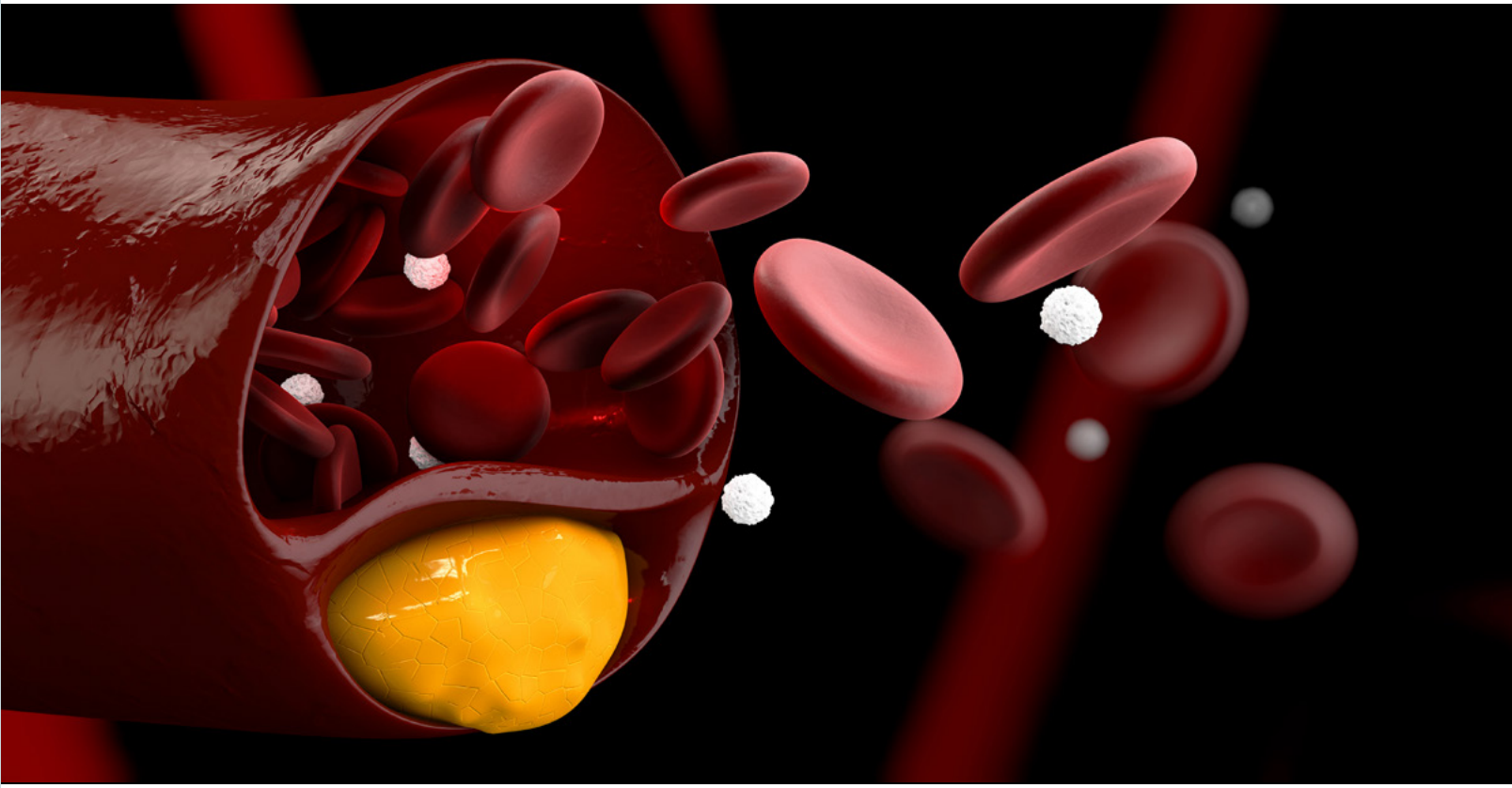
On being asked about the common questions raised by patients about the nutrition, Dr. Devries said, "many of the questions that patients have are specifically related to what sort of diet they should be on, e.g. a low-fat, a low-carb, or should it be a vegetarian, vegan or gluten-free diet". Physicians should, at minimum, have a solid foundation of nutrition knowledge that will allow them to begin the nutrition conversation with their patient and to make appropriate referrals.

Thus, it imperative that clinicians receive additional education on the benefits of nutrition and comprehensive nutritional approaches aimed at better managing patients with cardiometabolic risk or cardiometabolic disease. Dr. Devries and the nonprofit Gaples Institute have taken a leading role in tackling the nutrition education vacuum among healthcare professionals, offering a nutrition course and several other resources for the busy clinician across their platforms (more information on the nutrition course can be found on their website, https://www.gaplesinstitute.org/e-learning-physicians/).

References:

1. Devries, Stephen, et al. "A deficiency of nutrition education and practice in cardiology." *The American Journal of Medicine* 130.11 (2017): 1298-1305.
2. Forouhi, Nita G., et al. "Dietary and nutritional approaches for prevention and management of type 2 diabetes." *BMJ* 361 (2018): k2234.
3. American Diabetes Association. "5. Lifestyle Management: Standards of Medical Care in Diabetes–2019." *Diabetes Care* 42.Supplement 1 (2019): S46-S60.
4. Flack, John M., David Calhoun, and Ernesto L. Schiffrin. "The New ACC/AHA Hypertension Guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults." *American Journal of Hypertension* 31.2 (2018): 133-135.
5. Grundy, Scott M., et al. "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines." *Journal of the American College of Cardiology* (2018): 25709.
6. Willett, Walter, et al. "Food in the Anthropocene: the EAT–Lancet Commission on healthy diets from sustainable food systems." *The Lancet* 393.10170 (2019): 447-492.
7. Arnett, Donna K., et al. "2019 ACC/AHA guideline on the primary prevention of cardiovascular disease." *Journal of the American College of Cardiology* (2019): 26029.
8. Evert, Alison B., et al. "Nutrition therapy for adults with diabetes or prediabetes: a consensus report." *Diabetes Care* 42.5 (2019): 731-754.
9. American Cancer Society. "World Health Organization says processed meat causes cancer." Available at https://www.cancer.org/latest-news/world-health-organization-says-processed-meat-causes-cancer.html, accessed July 30, 2019.
10. Mozaffarian, Dariush. "Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review." *Circulation* 133.2 (2016): 187-225.
11. Kahan, Scott, and JoAnn E. Manson. "Nutrition counseling in clinical practice: how clinicians can do better." *JAMA* 318.12 (2017): 1101-1102.
12. Adams, Kelly M., Martin Kohlmeier, and Steven H. Zeisel. "Nutrition education in US medical schools: latest update of a national survey." *Journal of the Association of American Medical Colleges* 85.9 (2010): 1537 - 1542.

Addressing Statin Intolerance In Practice: Moving Beyond the Controversy



Low-density lipoprotein cholesterol (LDL-C) has been shown to be atherogenic and likely have a causal relationship for the development of atherosclerotic cardiovascular disease (ASCVD).[1] Thus, reducing LDL-C levels is imperative in decreasing the impacts of ASCVD, as demonstrated in several studies.[2] Since their introduction more than 30 years ago, statins, along with lifestyle modifications, have been the treatment of choice in lowering cholesterol. They decrease cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), a rate-limiting step in cholesterol synthesis.[3] Multiple large outcomes trials have demonstrated the efficacy of statins in not only lowering LDL-C but more importantly, reducing major adverse cardiovascular events both in the primary and secondary prevention of ASCVD.[4] Given the strength of evidence and the cost-effectiveness, statins remain the first-line treatment of patients with elevated LDL-C, which was also highlighted in the updated 2018 AHA/ACC cholesterol guidelines.[2]

However, a large gap remains between guideline recommendations and use of statins in actual practice, with studies showing that a large number of eligible patients are not on statin therapy, or are not adherent to therapy.[5-9] This includes patients at high-risk for primary or secondary events, including patients with diabetes or cardiometabolic risk, and statin underutilization and non-adherence can increase ASCVD morbidity and mortality.[8] Even when patients are initiated on statins, many discontinue statin therapy within the year of starting it.[6] Real-world studies have shown that less than 40% of patients persist in taking statins for primary prevention at the 3-year post-initiation mark, while these number is only 45% for secondary prevention.[8] One of the many reasons that lead to discontinuation of statin therapy can be statin intolerance, which is most frequently attributed to muscle-related adverse events.[10] Often patients will discontinue statins without consulting their physician, which increases their cardiovascular risk.[10]

"One of the reasons for statin underutilization is that patients frequently go on the internet and read the negative complications associated with statins and are afraid to take a statin therapy. Another reason is that hypercholesterolemia is a silent killer. One does not feel anything until something bad happens like a heart attach or a stroke, and it is always very hard to treat silent conditions. That is why, for example,

blood pressure is hard to treat, and we still do a dismal job in controlling it"– **Leslie Cho, MD**, Professor of Medicine and Section Head of Preventative Cardiology and Rehabilitation at the Cleveland Clinic in Ohio – told *Cardiometabolic Chronicle* in an interview.

The prevalence of statin intolerance is still widely debated mostly due to difficulties in identification and diagnosis.[10] "Statin intolerance is unfortunately very common, but when we look at randomized controlled studies, reported rates are as low as <1% of the study populations. Part of this is due to randomized studies enrolling healthier patients; also, patients that had statin-related adverse events during the run-in-period were excluded from the studies. Conversely, when we look at real-world registries, such as the French registry of primary care clinics[11] or US insurance database studies[2], statin intolerance is around 5-10%" – Dr. Cho added.

Statin intolerance can lead to statin discontinuation or suboptimal therapy, thus it is crucial to identify patients that are exhibiting true statin-associated side effects, and address these symptoms accordingly. "The most important thing for identifying statin intolerance is obtaining a very thorough patient history. Statin intolerance or its symptoms can be induced by concurrent medications that the patients are taking; for instance, several cardiovascular drugs and antibiotics can interact with statins, leading to reduced statin elimination, and increasing the risk of statin intolerance. Also, patients on fenofibrates and statins, or with underlying muscle issues, are at an increased risk for statin-associated myalgia. We should ask patients how long after initiating statin therapy they experienced muscle aches or weakness; if they report pain after just one dose than most likely it is not true statin intolerance, but if the pain appears a month after starting statins, is persistent and affects the patients' quality of life, then we may think about the possibility of true statin intolerance. Therefore, it becomes crystal clear that getting to know the medical history of the patient before stopping or modifying statin therapy is very crucial as there is no simple test or a questionnaire to determine statin intolerance. " – said Dr. Cho.

Very frequently, in patients with statin intolerance, it may be advisable to change the dose, switch to a different statin, or try an alternate-day regimen.[12] "The lipophilicity and hydrophilicity of statins plays an important role, as hydrophilic statins such as rosuvastatin and pravastatin are less likely to cause muscle aches than lipophilic statins such as simvastatin and atorvastatin. In our clinic, we often start with rosuvastatin once a week with the lowest dose, if the patient can tolerate it, we go to twice a week usually Monday and Thursday and then escalate the dose or the frequency depending upon their performance" – said Dr. Cho, while further adding "in our own study at the Cleveland Clinic[12] of more than 1600 patients that were intolerant to two or more statins, intermittent dosing was effective

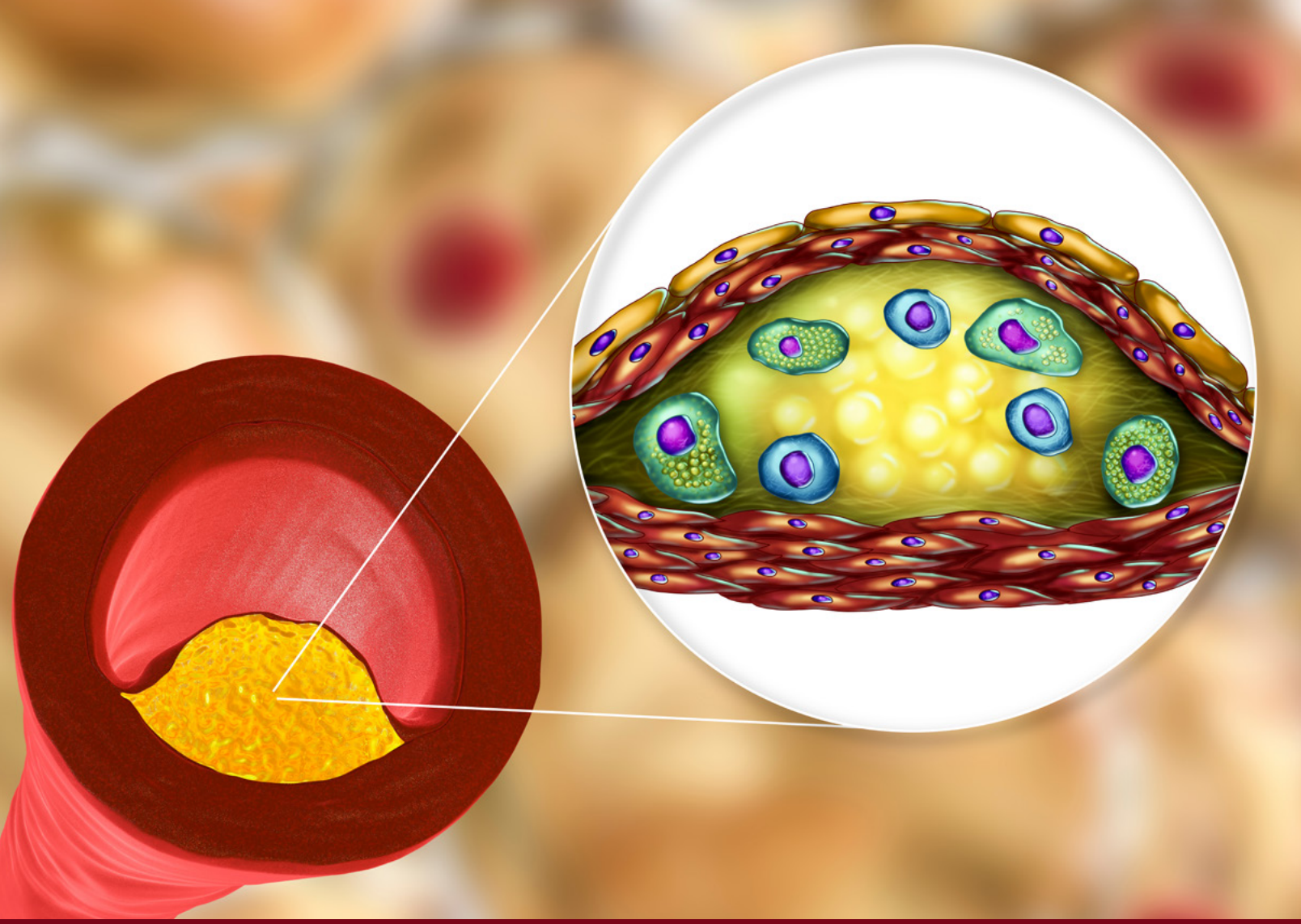
to achieve LDL-C goals and keep patients on statins; 72.5% of them could tolerate some form of long-term statin therapy, with 63.2% on a daily regimen, and 9.3% on intermittent dosiing, while 27.5% were statin-intolerant. Remarkably, the GAUSS-3 trial[13], which was a statin intolerance study with the PCSK9 inhibitor evolocumab, echoed our findings, reporting that about 40% of patients population had true statin intolerance."

The risk of incident diabetes is another common concern with statin therapy, with several studies suggesting that statin treatment may significantly increase the risk of type 2 diabetes onset in patients with hypercholesterolemia.[8, 14, 15] However, despite the increase in incident diabetes, the cardiovascular risk reduction with statins is similar in patients with diabetes and those without, and these benefits outweigh any potential risk, a view supported in clinical practice guidelines and position statements.[2, 8, 16, 17]

"Absolutely, the statin cardiovascular and mortality benefits outweigh the diabetes risk. This was also shown in the JUPITER trial,[18] where high-intensity statin therapy (rosuvastatin 20 mg) did not increase diabetes in patients with no major diabetes risk factors, but it did accelerate the average time to diabetes diagnoses in predisposed patients with diabetes risk factors. Unfortunately, the harmful effects of statins are more popular and it is remarkable how much negativity about statins exists in the internet and media. This has caused a "nocebo effect" regarding statins, in which patients develop symptoms because of preconceived negative expectations from its treatment. Lifestyle modifications, including diet and exercise, are the cornerstone of hypercholesterolemia management, followed by statin therapy. Statins have been around for 40 years, are extremely beneficial, cost-effective, have important pleiotropic benefits, and are generally safe. We can be seduced by the latest and greatest therapies, but the therapy that has proven to reduce mortality, myocardial infarction, and cardiovascular event rates, has been this oral medicine that now is cheap to take, so I believe that statins will still have a huge role going forward" – concluded Dr. Cho.

References:

1. Ference, Brian A., et al. "Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel." *European Heart Journal* 38.32 (2017): 2459-2472.
2. Grundy, Scott M., et al. "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *Journal of the American College of Cardiology* (2018): 25709.
3. Istvan, Eva S., and Johann Deisenhofer. "Structural mechanism for statin inhibition of HMG-CoA reductase." *Science* 292.5519 (2001): 1160-1164.
4. Baigent, C., et al. "Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials." (2010): 1670-1681.
5. Bradley, Corey K., et al. "Patient-reported reasons for declining or discontinuing statin therapy: insights from the PALM registry." *Journal of the American Heart Association* 8.7 (2019): e011765.
6. Brinton, Eliot A. "Understanding Patient Adherence and Concerns with STatins and MedicatION Discussions With Physicians (ACTION): A survey on the patient perspective of dialogue with healthcare providers regarding statin therapy." *Clinical Cardiology* 41.6 (2018): 710-720.
7. McClellan, Mark, et al. "Call to Action: Urgent Challenges in Cardiovascular Disease: A Presidential Advisory From the American Heart Association." *Circulation* 139.9 (2019): e44-e54.
8. Spence, J. David, and George K. Dresser. "Overcoming challenges with statin therapy." *Journal of the American Heart Association* 5.1 (2016): e002497.
9. Ueda, Peter, et al. "Treatment gaps and potential cardiovascular risk reduction from expanded statin use in the US and England." *PloS One* 13.3 (2018): e0190688.
10. Toth, Peter P., et al. "Management of statin intolerance in 2018: still more questions than answers." *American Journal of Cardiovascular Drugs* 18.3 (2018): 157-173.
11. Bruckert, Eric, et al. "Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study." *Cardiovascular Drugs and Therapy* 19.6 (2005): 403-414.
12. Mampuya, Warner M., et al. "Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience." *American Heart Journal* 166.3 (2013): 597-603.
13. Nissen, Steven E., et al. "Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial." *JAMA* 315.15 (2016): 1580-1590.
14. Ahmadizar, Fariba, et al. "Associations of statin use with glycaemic traits and incident type 2 diabetes." *British Journal of Clinical Pharmacology* 85.5 (2019): 993-1002.
15. Thakker, Divyesh, et al. "Statin use and the risk of developing diabetes: a network meta-analysis." *Pharmacoepidemiology and Drug Safety* 25.10 (2016): 1131-1149.
16. Blumenthal, Roger and Francoise A. Marvel. "AHA's statement on the safety profile of statins: big benefit with low risk." December 10, 2018. Available at https://professional.heart.org/professional/ScienceNews/UCM_503181_AHAs-Statement-on-the-Safety-Profile-of-Statins-Big-Benefit-with-Low-Risk.jsp, accessed August 2, 2019.
17. Arnett, Donna K., et al. "2019 ACC/AHA guideline on the primary prevention of cardiovascular disease." *Journal of the American College of Cardiology* (2019): 26029.
18. Ridker, Paul M. "The JUPITER trial: results, controversies, and implications for prevention." *Circulation: Cardiovascular Quality and Outcomes* 2.3 (2009): 279-285.



RESIDUAL CVD RISK:

Can you REDUCE-IT?

Residual Risk: Beyond LDL-C

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death in the United States, and its prevention and treatment continue to be an area of utmost importance.[1] Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established ASCVD risk factor and significant advances have been made to lower it by using established and new strategies, including statin therapy, ezetimibe, and PCSK9 inhibitors.[2,3] However, while lowering LDL cholesterol (LDL-C) remains central in the prevention and treatment of ASCVD, residual risk may be present even after the optimization of LDL-C levels.[4]

Current therapies that primarily target LDL-C may not address other drivers of atherosclerosis, including triglycerides (TGs), which seem to be part of the causal pathway in high-risk patients.[2] In certain high-risk patients, including those with pre-existing ASCVD, or that have type 2 diabetes and/or metabolic syndrome, intensive treatment with statins and newer therapies to lower LDL-C may not address the full spectrum of cardiovascular prevention.[4] In these patients, the interplay between phenotypes that promote both a proinflammatory state and atherogenic dyslipidemia (including elevated TG levels), requires additional measures to optimize both primary and secondary ASCVD prevention.[2,4]

Elevated TG levels increase ASCVD risk, but omega-3 trials have shown mixed results about targeting HTG for reduction of adverse CVD events, with the notable exception of the REDUCE-IT trial with icosapent ethyl.[5,6] The results of the REDUCE-IT trial represent an important change in how we address residual cardiovascular risk in practice in the near future, including a re-definition of what constitutes elevated levels of triglycerides.[2]

Lowering TGs: not a straightforward approach

Although we can debate whether triglycerides themselves or the lipid/lipoprotein company they keep are causal for ASCVD7, elevated TGs are being recognized as an important marker for ASCVD risk stratification.[3] Recent real-world studies and meta-analyses have shown that high TG levels are associated with an elevated CVD risk in high-risk statin patients with ASCVD and statin-controlled LDL-C.[8,9] A recent study evaluating the association between adverse cardiovascular outcomes and HTG (200-499 mg/dL) in ASCVD patients with statin-controlled LDL-C, reported greater adverse cardiovascular events in patients with HTG compared to normal (<150 mg/dL) triglyceride levels.[8] Over the course of a follow-up of 4.2 years, patients with high TG had a 30% increased risk for myocardial infarction (MI) or coronary revascularization, and a 13% increased risk for the composite outcome of non-fatal MI, coronary revascularization, and all-cause mortality compared to normal TG patients.[8] As such, in the 2018 multi-society cholesterol guidelines, TG levels of >175mg/dL are a risk-enhancing factor to determine need for statin therapy.[3]

However, there is a paucity of evidence for effective cardiovascular risk reduction with existing therapies that target elevated TGs. In all patients with hypertriglyceridemia, emphasis is placed on lifestyle modification, including weight management, increased physical activity and restriction or elimination of alcohol consumption. However, lifestyle therapy is not always sufficient to achieve adequate TG lowering. Statins are considered first line drug therapy for the management of hyperlipidemia, including for most patients with high TG, but there is substantial residual ASCVD risk among patients taking statins.[8,10] Trials with currently available agents to treat hypertriglyceridemia (HTG), such as fibrates and niacin, have not been efficacious in reducing ASCVD risk either as a monotherapy or when added to statins, and has contributed to the challenges that clinicians face in targeting HTG to reduce residual ASCVD risk.4 To date, trials with omega-3 fatty acids have shown mixed results in cardiovascular prevention, and clinicians may be confused in differentiating between the different formulations and evidence about these agents for reducing ASCVD risk.[4]

REDUCE-IT: The Emerging Role of Icosapent Ethyl

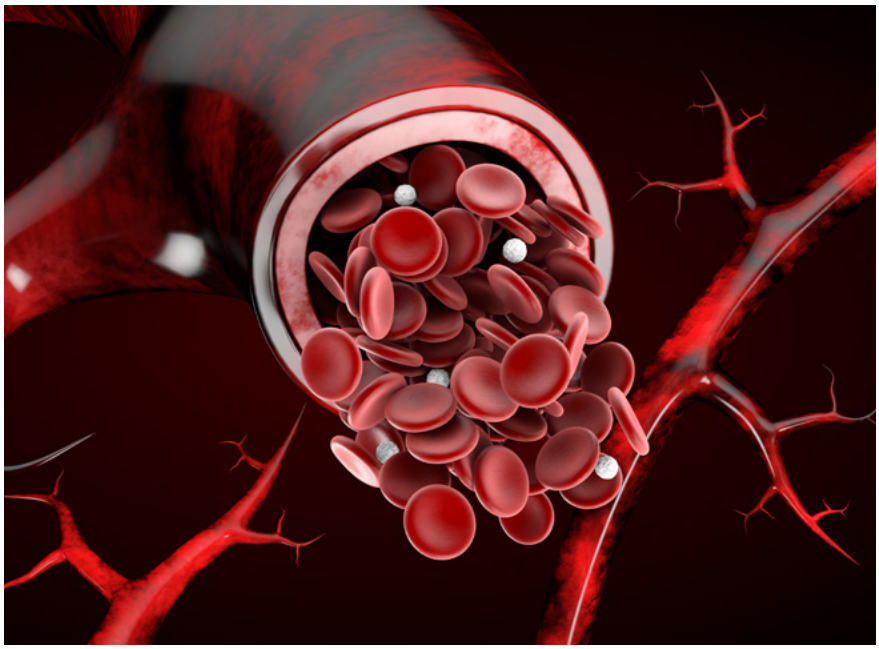
The omega-3 fatty acids (OM3FA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) lower TG through reduced synthesis and release of hepatic VLDL-TG and enhanced clearance of TG from plasma.[11] On a molecular level, omega-3 fatty acids have been shown to reduce endothelial dysfunction, plaque volume, and inflammation.[6] There are a variety of different prescription and generic OM3FA formulations available for the treatment of hypertriglyceridemia, including icosapent ethyl, omega-3-carboxylic acids, and omega-3-acid ethyl esters.[12-14] However, many generic fish oil supplements lack the sufficient pharmacological dose of at least 2g/day of omega-3 fatty acid needed to significantly reduce serum TG levels.[15] Several OM3FA concentrate prescription drugs are approved for the treatment of severe hypertriglyceridemia (TG ≥500 mg/dL).[16] These formulations provide EPA and DHA in either ethyl ester or free fatty acid (carboxylic acid) forms.

Omega-3 fatty acids have been shown to reduce TG levels by 22-33% in statin-treated patients with high baseline levels of TG (259-680 mg/dL) in short-term studies.[17,18] Recent meta-analyses did not provide support for the role of OM3FA supplements in CVD risk, however, different formulations were used in these studies, including not completely pure OM3FA, which makes their interpretation challenging.[4,19,20] To date, the one study that used a pure OM3FA agent (1.8 mg EPA) in addition to low-dose statin, JELIS, showed that EPA was associated with a 19% reduction in major coronary events.[21] The ASCEND trial, which assessed the efficacy and safety of daily supplementation with OM3FA (1 g EPA + DHA) in preventing CV events (a combination of non-fatal MI, non-fatal stroke or TIA, and vascular death) in patients with diabetes and no prior cardiovascular disease, showed that OM3FA supplementation did not prevent major adverse CV events.[22] However, these results of the ASCEND trial could be due to the dose of OM3FA used (1g), which has not shown positive results in previous trials, and authors suggest that higher doses (2-4 g) may yield more benefits.[4,22]

Recently, the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT), which used higher doses of a highly purified ester of EPA, icosapent ethyl, evaluated the effects of this intervention in preventing cardiovascular events in high-risk patients with established ASCVD or diabetes plus at least an additional risk factor.[5] A total of 8179 patients, who had fasting triglyceride levels of 135-499 mg/dL and an LDL-C of 41-100 mg/dL while on background statin therapy were enrolled and randomized to receive 2g of icosapent ethyl twice daily (4g total daily dose) or placebo.[5] In this trial, patients treated with icosapent ethyl had a 25% risk reduction in the occurrence of major adverse CV events (composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization) after a median follow-up of 4.9 years, which was significant compared to placebo.[5] This included a statistically significant 20% reduction in CV death, as well as statistically significant relative risk (RR) reductions for other prespecified individual endpoints, including myocardial infarction (31% RR), stroke (28% RR), hospitalization for unstable angina (32% RR), and urgent or emergent coronary revascularization (35% RR) compared to placebo.[2] Furthermore,

the benefits were consistent among several prespecified subgroups, including in patients with normal TG levels (<150 mg/dL), which represented 10.3% of the study population.[2] Thus, it is unlikely that the benefits observed with icosapent ethyl in the REDUCE-IT trial are merely a function of baseline TG levels, since the risk reduction in the primary and key secondary endpoints was relatively the same in those with baseline TG ≥200 mg/dL and those with what is TG values of ≥150 mg/dL, and these results are re-defining of what we perceive to be "normal" TG levels.[2,23] The specific mechanisms of action that lead to these benefits with icosapent ethyl are an ongoing area of investigation.[23] In this trial, icosapent ethyl was generally well tolerated; with a trend toward more bleeding-related disorders which did not reach statistical significance, and increased hospitalization rates for atrial fibrillation with icosapent ethyl compared to placebo.[5] A recent sub-analysis of the REDUCE-IT trial showed that in addition to the 25% reduction in first ischemic events, icosapent ethyl was associated with a 32% reduction in second events, a 31% reduction in third events, and a 48% reduction in fourth of subsequent events, with total events being reduced by 30% compared to placebo.[6]

Due to the results of this study, an application for an additional indication for icosapent ethyl to reduce the risk of major CVD events was submitted to the FDA in March 2019 and is pending. Currently, this agent is approved only to treat patients with TG levels ≥500 mg/dL to prevent acute pancreatitis.[23] Although not yet FDA approved for the CV indication, recent guidelines have been modified to recommend this agent in certain patients. The American Diabetes Association (ADA) issued an update in March 2019 to its standards of care, advising that icosapent ethyl be considered to reduce CV risk in patients with diabetes and ASCVD or with other cardiac risk factors who are on a statin and have controlled LDL-C, but elevated TG levels.[24]



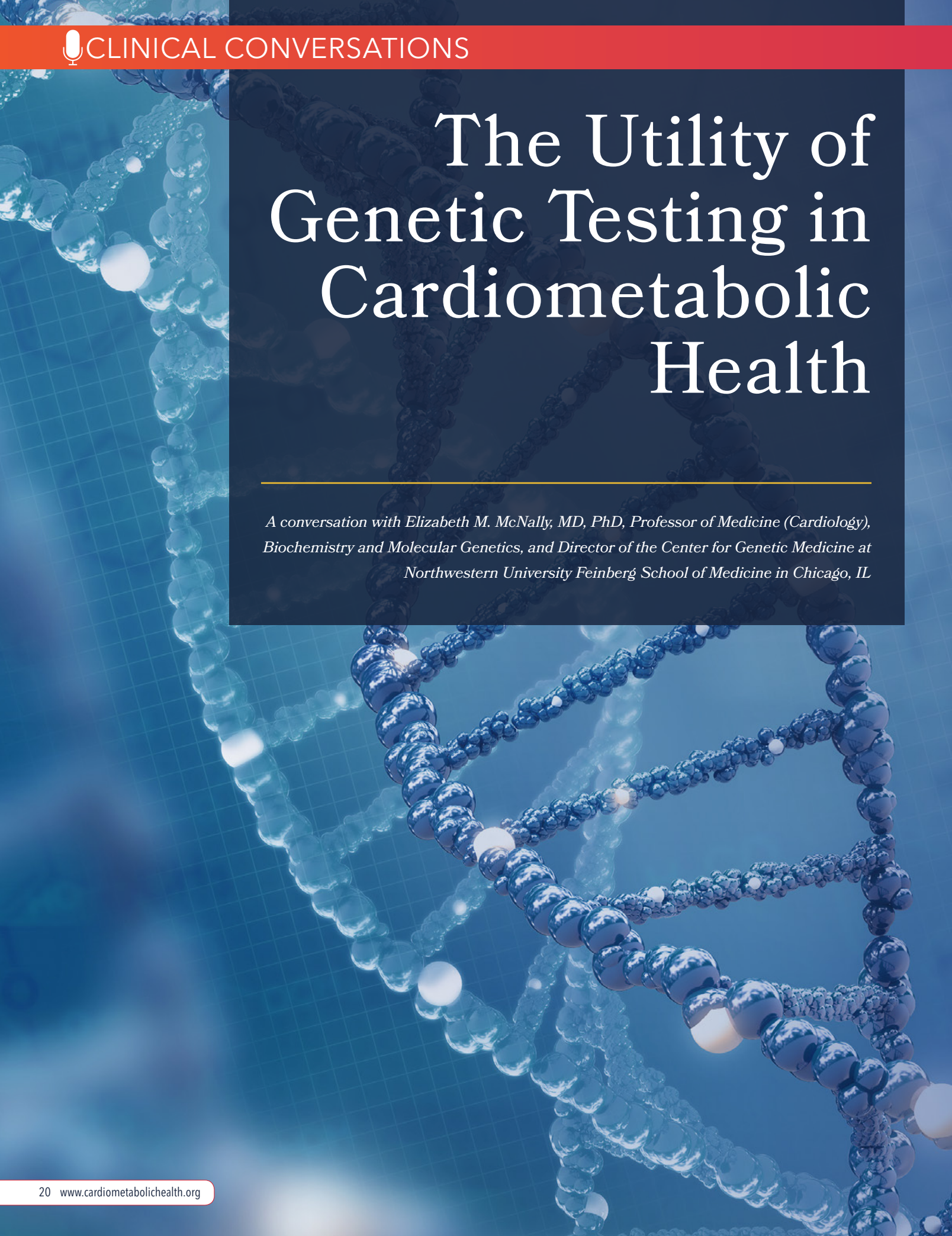
Recent results with icosapent ethyl, as demonstrated by the REDUCE-IT trial, have shown that it can significantly reduce atherosclerotic events in high-risk hypertriglyceridemic patients with clinical ASCVD or type 2 diabetes and additional markers of increased risk. As more evidence becomes available, it is expected that icosapent ethyl will play an important role in primary and secondary prevention in high-risk patients.

References:

1. Lloyd-Jones, Donald M., et al. "2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk." *Journal of the American College of Cardiology* 68.1 (2016): 92-125.
2. Bhatt, Deepak L. "REDUCE-IT: residual cardiovascular risk in statin-treated patients with elevated triglycerides: now we can REDUCE-IT!." *European Heart Journal* 40.15 (2019): 1174-1175.
3. Grundy, Scott M., et al. "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *Circulation* 139 (2019): e1082-e1143.
4. Ganda, Om P., et al. "Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management." *Journal of the American College of Cardiology* 72.3 (2018): 330-343.
5. Bhatt, Deepak L., et al. "Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia." *New England Journal of Medicine* 380.1 (2019): 11-22.
6. Bhatt, Deepak L., et al. "Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT." *Journal of the American College of Cardiology* 73.22 (2019): 2791-2802.
7. Eckel, Robert H. "What is it about very low density lipoproteins (VLDL) and cardiovascular disease in patients with type 2 diabetes mellitus: Is it the triglycerides or the cholesterol?." *Atherosclerosis* 237.1 (2014): 138-139.
8. Nichols, Gregory A., et al. "Increased cardiovascular risk in patients with statin-controlled LDL cholesterol and residual hypertriglyceridemia." *Circulation* 136.suppl_1 (2017): A14161-A14161.
9. Toth, Peter, et al. "High triglycerides and ASCVD are significant predictors of major CV events and increased costs in statin-treated patients: real-world analysis." *Journal of Clinical Lipidology* 12.2 (2018): 528-529.
10. Fruchart, Jean-Charles, et al. "The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia." *The American Journal of Cardiology* 102.10 (2008): 1K-34K.
11. Bays, Harold E., et al. "Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications." *Expert Review of Cardiovascular Therapy* 6.3 (2008): 391-409.
12. Ballantyne, Christie M., Rene A. Braeckman, and Paresh N. Soni. "Icosapent ethyl for the treatment of hypertriglyceridemia." *Expert Opinion on Pharmacotherapy* 14.10 (2013): 1409-1416.
13. Ito, Matthew K. "A comparative overview of prescription omega-3 fatty acid products." *Pharmacy and Therapeutics* 40.12 (2015): 826 - 836.
14. Weintraub, Howard S. "Overview of prescription omega-3 fatty acid products for hypertriglyceridemia." *Postgraduate Medicine* 126.7 (2014): 7-18.
15. Kapoor K, et al. Patients with Very High Triglycerides and Treatment with Omega-3s. American College of Cardiology. February 2, 2016. Accessed May 8, 2019.
16. Backes, James, et al. "The clinical relevance of omega-3 fatty acids in the management of hypertriglyceridemia." *Lipids in Health and Disease* 15.1 (2016): 118.
17. Ballantyne, Christie M., et al. "Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study)." *The American Journal of Cardiology* 110.7 (2012): 984-992.
18. Bays, Harold E., et al. "Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial)." *The American Journal of Cardiology* 108.5 (2011): 682-690.
19. Abbasi, Jennifer. "Another nail in the coffin for fish oil supplements." *JAMA* 319.18 (2018): 1851-1852.
20. Aung, Theingi, et al. "Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals." *JAMA Cardiology* 3.3 (2018): 225-234.
21. Yokoyama, Mitsuhiro, et al. "Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis." *The Lancet* 369.9567 (2007): 1090-1098.
22. ASCEND Study Collaborative Group. "Effects of n− 3 fatty acid supplements in diabetes mellitus." *New England Journal of Medicine* 379 (2018): 1540-1550.
23. Orringer, Carl E. "Icosapent ethyl: where will it fit into guideline-based medical therapy for high risk atherosclerotic cardiovascular disease?" *Trends in Cardiovascular Medicine* (2019).
24. American Diabetes Association. "American Diabetes Association® issues critical updates to the 2019 standards of medical care in diabetes." March 27, 2019, available at http://www.diabetes.org/newsroom/press-releases/2019/ada-issues-critical-updates-to-2019-standards-of-care.html, accessed August 6, 2019.

The Utility of Genetic Testing in Cardiometabolic Health

A conversation with Elizabeth M. McNally, MD, PhD, Professor of Medicine (Cardiology), Biochemistry and Molecular Genetics, and Director of the Center for Genetic Medicine at Northwestern University Feinberg School of Medicine in Chicago, IL



Genetic testing is one of the cornerstones of personalized medicine, and while this approach has made significant strides in other therapeutic areas, such as cancer, the utility and applicability of genetic testing in cardiometabolic disease remains a novel area of investigation. However, there are certain high-risk familial cardiometabolic conditions where genetic testing is currently a viable approach to care, and in several other areas of cardiometabolic medicine this approach is gaining momentum. We discussed the current state of genetic testing for cardiometabolic health and much more with Elizabeth McNally, MD, PhD.

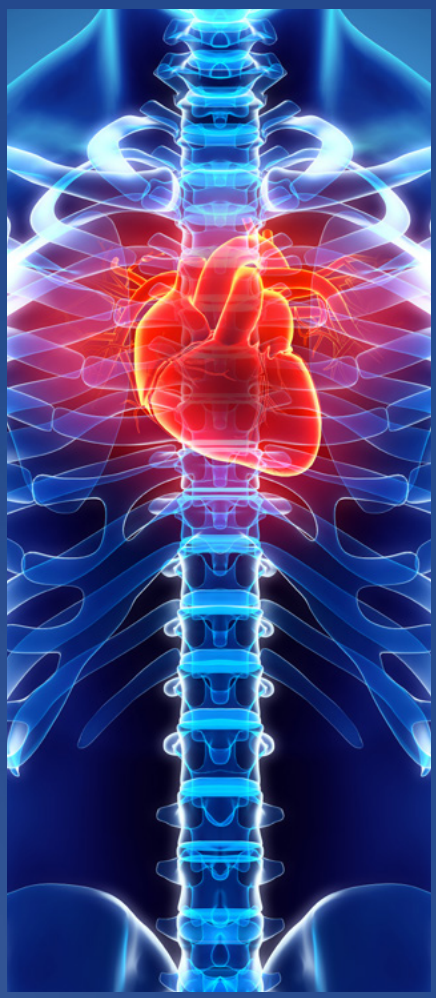
CARDIOMETABOLIC CHRONICLE: ***When we talk about genetic testing in cardiometabolic disease, it definitely encompasses several therapeutic areas, but what are some of the disease states that we have a good understanding about the role of genetics as a driver of disease development and progression?***

DR. MCNALLY: There are at least two broad approaches to genetics right now, one is known as genetic risk score or polygenic risk scores and the second involves sequencing genes. Polygenic risk scores gather information from genome-wide association studies and association studies to estimate the risk of cardiovascular disease. This type of testing might help predict risk for coronary artery disease, metabolic syndrome, diabetes and atrial fibrillation, and the field is working towards implementing this type of testing into clinical practices. In the second approach, we sequence a small panel of genes, maybe 50-150 genes, and then predict risk of disease, including that of genetic cardiomyopathy and heart failure in the patient. Gene sequencing helps us to sub-classify types of cardiomyopathy, heart failure and in particular who is at risk for developing specific types of complications, for instance, arrhythmia risks. These are really two completely different types of genetic testing. Genetic risk scores can be done on anybody and at any age to help them predict their lifetime risk of developing coronary artery disease or other cardiovascular conditions, while the second approach is more specific genetic testing for individuals who have a personal or family history of cardiomyopathy or heart failure to help them whether they have the same risk as their family members.

CARDIOMETABOLIC CHRONICLE: ***In addition to family history, what other factors should clinicians look for to determine whether a patient would benefit from genetic testing?***

DR. MCNALLY: There a few areas where we are doing panels of genes regularly. In our center, any person under the age of 60 with non-ischemic dilated cardiomyopathy will usually have gene sequencing, given that the success of this testing is now up to around 30-50%. Usually these patients are worried about the occurrence of these diseases in their family members, hence in those cases, these tests help them to not only identify what their diagnosis is, and sometimes how to manage it better, but also this information is quite powerful to predict the chances of risk for their family members.

We also offer genetic testing in different types of inherited aortic disease, in younger individuals who have thoracic aneurysms, certain types of arrhythmia syndromes, and neuromuscular disease. It's especially important for neuromuscular diseases like myotonic dystrophy and related disorders that have cardiac complications predicted by their gene mutation status. Many times, we see patients who often have cardiometabolic presentations, also have involvement of their skeletal muscles, and often that diagnosis is missed because we're not trained to think beyond our own discipline. So sometimes when patients have a little bit of muscle weakness, then that can actually be a very meaningful symptom and can lead to a diagnosis. So, there are a bunch of areas in which we're doing testing having to do with people under a certain age, usually under the age of 60 and presenting with unusual symptoms.



CARDIOMETABOLIC CHRONICLE: ***Crossing over into the lipid space and cardiovascular risk, there have been a few developments with genetic testing in this area as well.***

DR. MCNALLY: Indeed. Familial hypercholesterolemia (FH) is a condition that has very clear genetic incidence but is generally underdiagnosed and probably treated later in life that it should be because of underdiagnosis. There hasn't been as much use of genetic testing for FH, probably because of clinicians' attitudes which focuses on treating people with statins without knowing their genetic background. Here, I would suggest that it is actually really useful to know who carries genetic mutations that predispose to familial hypercholesterolemia. Within families with dominant FH, 50% of the people will not carry the risk, so we would really want to tailor our therapies towards those who need it. In principle, based on genetic screening, we could identify people very early in life who should benefit from being on statins. Gene panels for FH are expanding and include genes beyond just the LDL receptor. Hence, this testing useful for the diagnosis as well as their proper management of patients with FH.

CARDIOMETABOLIC CHRONICLE: ***Are there disparities in genetic testing and how can we get past them?***

DR. MCNALLY: That is a really great question. A lot of genetics has been done on people of European or Caucasian ancestry. One of the biggest studies that is yielding a lot of genetic information right now is UK biobank. However, this biobank has data almost exclusively from people with white or Caucasian background. So, the disparity arises in the use of genetic risk scores, as they are very useful in Caucasians or people of white European descent, but their utility beyond this population remains to be evaluated. Hence, one of the big questions is, how do we apply those better to more diverse populations?

If we look at the population in the United States, we have a very mixed and diverse population particularly among younger people, and this is where we'd ideally like to apply some of this genetic risk scores to identify diseases early in life, so we can make changes in lifestyle and medications for appropriate disease management. Therefore, we have to figure out how to make these risk scores and genetic testing work for people from an incredibly diverse population. We're working very hard on that problem.

CARDIOMETABOLIC CHRONICLE: ***Are there challenges in interpreting the information that comes from genetic testing and what it may mean for patient care?***

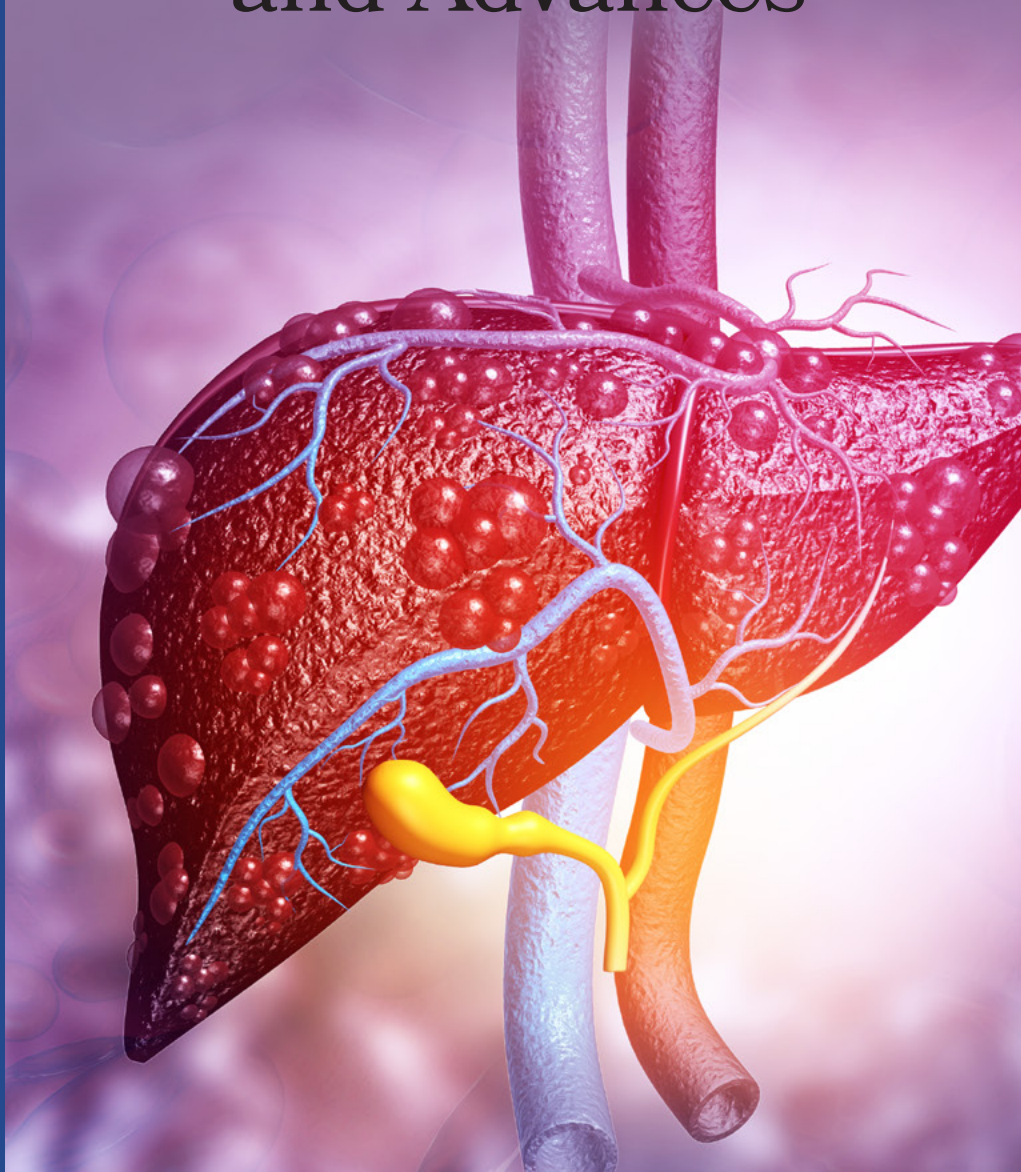
DR. MCNALLY: Typically, three types of answers can be attained with genetic testing. Genetic testing results are interpreted as pathogenic or likely-pathogenic mutations. Sometimes the result is benign, and this type of genetic result is not included on the test report. But then we have a middle area, a gray zone, which we call 'variants of uncertain significance'. We can see this type of result in anyone, but those from non-Caucasian backgrounds have an increased chance of getting this type of result. I think it's important for clinicians who might be working with a variant of uncertain significance result, to work a little bit harder with that patient and that family to try to interpret that result in a better way. That often includes getting clinical information from family members to figure out who else has that disease and then making sure that they get tested. It is also really important to work with a genetic counselor to determine whether that variant is actually pathogenic or non-pathogenic. So, when interpreting a variant, you may have to work a little harder to get to a conclusion.

Additionally, the availability of large databases, including large publicly-accessible data, contain genetic testing results. This type of information really helps in the interpretation of these results. In the last few years, the large genetic testing companies have generally made all their data available through these databases. That has helped us to improve the quality of the interpretation across all populations.

CARDIOMETABOLIC CHRONICLE: *In the future, how do you envision the role of genetic testing and even polygenic risk scores in the care for patients with the cardiometabolic disease?*

DR. MCNALLY: I think we'll probably see some increase in genetic risk scores and polygenic risk scores. Cost is much less of a barrier, with high throughput technologies reducing costs. I think in some settings what we will see is a blending of the tests with gene panels integrated with polygenic risk scores. If we imagine a world where the cost of testing is $50-100, many people would choose this. Of course, it depends what you get for that price, but ancestry testing has already shown us that people are interested in this information. One could envision doing this type of testing fairly early in life, of course on a voluntary basis, and knowing some degree of lifetime risk of different diseases. We have seen that having this genetic information has empowered a lot of patients and their family members to personally manage their daily lifestyles, for instance, including exercise and suitable diet as part of their chronic disease management. The data can be incredibly empowering for people and I think that's what we will see going forward.

NASH Clinical Trials: An Outlook On Challenges and Advances



Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome (MetS) and defined as the accumulation of fat in the liver in patients who do not consume significant amounts of alcohol.[1] NAFLD encompasses a wide spectrum of conditions, from simple fat accumulation (fatty liver) to steatohepatitis (NASH) with or without fibrosis up to the stage of cirrhosis.[1] Features of MetS are highly prevalent in patients with NAFLD and the risk of developing NAFLD increases with the number of components of MetS. As a consequence, the increasing prevalence of MetS and NAFLD go hand in hand, and NAFLD is strongly associated with insulin resistance, type 2 diabetes, central adiposity, dyslipidemia, and hypertension.[1,2]

NAFLD affects an estimated 20-30% of people in the United States and is the leading cause of chronic liver disease in the Western World.[2, 3] NASH, the most aggressive form of the disease, when accumulation of liver fat is accompanied by cellular injury and inflammation, is estimated to affect 2-5% of Americans; however, the actual prevalence of NASH may be considerably higher due to the challenge of identifying patients with the disease, which remains largely symptomless until well advanced.[3-5] The disease can progress to fibrosis, cirrhosis, and/or hepatocellular carcinoma (HCC)[2,4] making these the second leading cause of liver transplants in the United States and poised to become the leading cause of transplants by 2020.[6] Several clinician specialties are involved in the management of this disease, and the role of the endocrinologists, diabetologists, and primary care clinicians is crucial in the early recognition, diagnosis, and overall management of NAFLD and NASH.[7]

Despite these impacts, NASH frequently goes undiagnosed.[5, 8-11] In addition, its management is challenging since there are no current FDA-approved agents for this condition. However, many agents are being evaluated in clinical trials for the treatment of NASH. To explore some of the challenges and considerations with NASH clinical trials, we spoke with **Andrew Roche, PhD**, Senior Director, Scientific Affairs at ICON, one of the largest international clinical research organizations with expertise in running NASH studies.

Cardiometabolic Chronicle: Currently, a big part of the problem with NASH is delayed diagnosis or underdiagnosis. How is this affecting NASH clinical trials?

Dr. Roche: Without a doubt, diagnosis remains a challenge on multiple levels, including obtaining and assessing the liver biopsy, which remains the gold standard for diagnosing and staging of NASH[12]. It's also believed that a high proportion of NASH patients are undiagnosed because the disease is largely symptomless or causes non-specific symptoms until well advanced. Also, patients and their physicians may prefer to sidestep diagnosis, knowing that the recommended treatment for most patients, improved diet and more exercise, is anyway within their grasp.

From a clinical trials perspective, studies from phase 2b and on need to have a liver biopsy per the FDA guidance.[12] Prior to phase 2b, other less invasive assessments can be performed (e.g., imaging), although the different clinical accuracies of the respective processes can be expected to lead to differences in the characteristics of the populations studied pre and post phase 2b. The risk of performing a liver biopsy is a hurdle for enrollment in many studies. Increasing awareness about the implications and complications of NASH is important, but at this time, NASH is still an underappreciated disease for which many people do not want to get tested. This is compounded by the current absence of approved therapies and thus the enticements to encourage patients to undergo a liver biopsy are currently comparatively limited. It is expected that this will be partially alleviated by providing a better understanding of the exciting new therapies for NASH that are currently in development

Another challenge that impacts site engagement and, consequently, enrollment rates is the analysis of the liver biopsy and the differences in assessments performed by the local pathologist and the central specialist pathologist. A diagnosis of NASH by a local pathologist may lead to the conclusion that the patient is suitable to be enrolled in the trial. However, it is not uncommon that the central specialist pathologist deem the patient to be unsuitable for the study when the NAFLD Activity Score (NAS)[13] criteria are used to assess suitability of the subject against the enrollment criteria of the clinical study protocol. The NAS scoring system is designed to allow for assessment of changes with therapy during the course of a clinical trial and is not commonly utilized at local level. Such situations of discordance can demotivate sites if they are unable to enroll subjects who, they feel, are appropriate for the study. Improving communication between the local pathologist, investigator and the central pathologists is crucial to ensure understanding of the role of the central pathologist, i.e., to ensure uniformity of the study population and the consistency of assessment throughout the study.

It is also important to note that a liver biopsy will not represent the whole liver and it is critical to obtain as sizeable a specimen as possible. The impact of sampling quantity and variability can significantly affect the assessment, e.g., *Ratizu et al*.[14] illustrated how often a diagnosis can be missed if you have too little specimen. In 24% and 35% of cases hepatocyte ballooning and bridging fibrosis, respectively, were missed as a result of insufficient sample.

Cardiometabolic Chronicle: What is being done to better identify patients and overcome challenges associated with liver biopsies?

Dr. Roche: Several groups are trying to address this by creating clinical diagnostic tools, including imaging solutions, that are less invasive and of comparable clinical accuracy thus eliminating the need for liver biopsy. While there are promising candidates on the horizon such a tool does not yet exist. As such, liver biopsies for phase 2b trials and up are still required as these remain to be the gold standard method of NASH diagnosis.[12]

Other strategies include use of non-invasive tools to pre-screen subjects to better predict those that are least likely to be suitable for the enrollment requirements of a clinical study and therefore should not proceed to a biopsy. There are a number of imaging tools and laboratory biomarkers that have a strong ability to predict steatosis and fibrosis, e.g., ultrasound in the case of the former and the Fibrosis-4 (FIB-4) score[15] in the case of the latter. The European Medicines Agency (EMA) has approved the ELF test for assessment of fibrosis. Both are based on multiple blood-borne biomarkers and work very well in identifying subjects who have cirrhosis (F4) and those who have no fibrosis (F0) but are not optimal for differentiating between intermediate stages of fibrosis e.g. F2 vs F3. While strong options exist to identify levels of steatosis and fibrosis, the same is currently not true for biomarkers that can accurately distinguish, with high accuracy, presence of NASH from absence. Some biomarkers, like cytokeratin-18 (CK-18) fragments, have reported levels of clinical accuracy of up to 80% which, while promising, is still not ideal. Noninvasive NASH biomarkers are an area of continued focus for the industry and an area of considerable unmet need.

Cardiometabolic Chronicle: What are the important NASH endpoints that are being evaluated in clinical trials?

Dr. Roche: The current prevailing opinion is that a NASH therapy must demonstrate ability to prevent a liver transplantation in order to ensure reimbursement. As such, a key component that a candidate drug must address is fibrosis. NASH also includes other manifestations in addition to fibrosis, such as steatosis, inflammation, and ballooning, but ultimately it is fibrosis that determines the need for a liver transplant.

This focus on recruiting NASH patients with moderate fibrosis (F2-F3) creates one of the key challenges of NASH studies - enrolling subjects at a suitable rate, 25-45% of NAFLD patients typically have no fibrosis, approximately 30% have fibrosis stage F1, 5-10% have cirrhosis (F4), leaving only ~25% with fibrosis stage F2 to F3.

Cardiometabolic Chronicle: Based on your experience with NASH trials, is there any outreach to other physician specialties that are in the forefront the NASH epidemic to better identify patients who can be candidates for these trials?

Dr. Roche: This is a very important point. Historically, NASH clinical trials have been supported primarily by hepatologists or gastroenterologists. However, the field needs to involve those physicians who see the majority of diagnosed and undiagnosed NASH patients, i.e., primary care physicians and endocrinologists. This can be achieved by increasing general awareness of NASH amongst these physicians and their patients. ICON is working to expand our network of NASH qualified clinicians and sites by helping them link up with specialists with the appropriate skills and equipment (e.g., MR imaging, radiologist for biopsies and Fibroscan to measure liver stiffness) as a means of optimizing enrollment.

References:

1. Chalasani, Naga, et al. "The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases." *Hepatology* 67.1 (2018): 328-357.
2. Stefan, Norbert, Hans-Ulrich Häring, and Kenneth Cusi. "Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies." *The Lancet Diabetes & Endocrinology* (2018)
3. Vernon, G., A. Baranova, and Z. M. Younossi. "Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults." *Alimentary Pharmacology & Therapeutics* 34.3 (2011): 274-285.
4. Oseini, Abdul M., and Arun J. Sanyal. "Therapies in non-alcoholic steatohepatitis (NASH)." *Liver International* 37 (2017): 97-103.
5. Polanco-Briceno, Susan, et al. "Awareness of nonalcoholic steatohepatitis and associated practice patterns of primary care physicians and specialists." *BMC Research Notes* 9.1 (2016): 157.
6. Bellentani, Stefano. "The epidemiology of non-alcoholic fatty liver disease." *Liver International* 37 (2017): 81-84.
7. Sumida, Yoshio, and Masashi Yoneda. "Current and future pharmacological therapies for NAFLD/NASH." *Journal of Gastroenterology* 53.3 (2018): 362-376.
8. Bertot, Luis C., et al. "Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma." *Hepatology Communications* 1.1 (2017): 53-60.
9. Rinella, Mary E., et al. "Practice patterns in NAFLD and NASH: real life differs from published guidelines." *Therapeutic Advances in Gastroenterology* 9.1 (2016): 4-12.
10. Said, Adnan, et al. "Primary care practitioners survey of non-alcoholic fatty liver disease." *Annals of Hepatology* 12.5 (2013): 758-765.
11. Wieland, Amanda C., et al. "Identifying practice gaps to optimize medical care for patients with nonalcoholic fatty liver disease." *Digestive Diseases and Sciences* 58.10 (2013): 2809-2816.
12. U.S. Food and Drug Administration. "Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment – guidance for industry." December 2018, available at https://www.fda.gov/media/119044/download, accessed August 2, 2019.
13. Kleiner, David E., et al. "Design and validation of a histological scoring system for nonalcoholic fatty liver disease." *Hepatology* 41.6 (2005): 1313-1321.
14. Ratziu, Vlad, et al. "Sampling variability of liver biopsy in nonalcoholic fatty liver disease." *Gastroenterology* 128.7 (2005): 1898-1906.
15. Younossi, Zobair M., et al. "Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis." *Hepatology* 68.1 (2018): 349-360.

THE SPECTRUM OF CARDIOVASCULAR PREVENTION:

Obesity Paradox, Physical Activity, Sedentary Behaviors and Emerging Therapeutics in Type 2 Diabetes Mellitus

A conversation with **Salvatore Carbone, PhD, Assistant Professor at the Department of Kinesiology & Health Sciences, College of Humanities & Sciences** at the Virginia Commonwealth University in Richmond, VA.

CARDIOMETABOLIC CHRONICLE: ***An interesting concept that has been proposed is the "obesity paradox," a view that obesity confers some sort of protection for adverse CV events. Can you comment on what is the basis for this and whether it is a real phenomenon?***

DR. CARBONE: First I'd like to point out that obesity is a major risk factor for cardiometabolic disease. There are significant data which show that if you have obesity, you have a high risk of developing coronary heart disease, heart failure, type 2 diabetes mellitus (T2DM) or risk factors such as hypertension and dyslipidemia.[1]

Several reports from epidemiologic studies, however, have demonstrated that once you have established cardiovascular disease, particularly coronary heart disease or heart failure, obesity can exert some degree of protection.[2,3] This association is more pronounced for those with class I obesity (body mass index [BMI] between 30-35 kg/m2), which tend to have a better prognosis compared to normal weight (BMI of 18.5 – 25 kg/m2) and underweight individuals (BMI<18.5 kg/m2), but this benefit is less pronounced in patients with class II or severe obesity (when BMI is between 35-39.9 kg/m2, or ≥40 kg/m2). Early studies demonstrated that in ambulatory patients with advanced heart failure, overweight and obesity was not a risk factor for increased mortality, but rather it was associated with a trend towards improved survival compared to underweight or normal weight individuals.[4] More recently, at least at the epidemiologic level, the obesity paradox has been confirmed in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), but also in those with coronary heart disease.[5,6] So, it seems that once cardiovascular disease is present, then obesity may offer some degree of protection.

Now with that being said, I want to make sure that we don't pass the wrong message that obesity is a good thing, because if these individuals didn't become obese in the first place, it could have likely prevented the development of cardiovascular disease. So, we still need to make all the effort we can to prevent obesity.[7] But I think that one important point that has come out of these studies and a paradigm change in how we think about patients compared to 15-20 years ago, is that we should pay greater attention to heart failure patients with a normal BMI and clearly in those underweight, perhaps more than heart failure patients with class I obesity, since the former have a higher all-cause and cardiovascular mortality risk.

I believe that the obesity paradox is a real phenomenon, but we still don't clearly understand the underlying mechanisms responsible for it, nor do we have data from

large multicenter randomized controlled trials looking at targeting obesity in the setting of heart failure or other established cardiovascular disease, so we can't say this with certainty. One hypothesis we have proposed as a group is that patients with obesity in addition to having excess body fat, typically also have excess lean mass, which is a surrogate for skeletal muscle mass.[8] And we know that high lean mass is associated with improved prognosis in some cardiovascular conditions, including heart failure. So, it is plausible to think that patients with obesity may do better because they have that excess lean mass. We recently published a review article in *Current Problems in Cardiology* discussing the role of lean mass and different body composition phenotypes (sarcopenia, sarcopenic obesity and cachexia) in determining cardiorespiratory fitness and overall prognosis in heart failure, where we make a strong distinction between the use of BMI and body composition compartments such as lean mass.[9] For example, heart failure patients with excess body fat (i.e., obesity) but a low amount of lean mass (also called sarcopenic obesity) are the ones who actually do worse and have the most impaired cardiorespiratory fitness, even if they have class I obesity, so it is important to make that distinction.

CARDIOMETABOLIC CHRONICLE: ***Could some of the obesity paradox then be attributed to heavily relying on BMI to evaluate obesity?***

DR. CARBONE: At a population level, BMI remains a very good marker of adiposity and it still remains a strong predictor for the development of cardiometabolic disease.[10] However, in some conditions BMI is just not enough. Patients with heart failure for instance, have continuous changes in fluid status, which is unfortunately part of the pathophysiology of the disease which ultimately leads to increased risk for hospitalizations, and using BMI may often misclassify a patient as overweight or obese. Those are the setting in which I strongly believe we should really start looking at body composition, quality of the weight, how much of weight is fat, how much is fluid, and how much is muscle mass, rather than just focusing on total body weight and calculated BMI. To do this, however, you need some relatively sophisticated tools that not everybody has available in their practice, including devices to measure body composition, like bioelectrical impedance analysis (BIA), which is frequently being used in research and more recently also in clinical practice. Other tools involve dual-energy X-ray absorptiometry (DEXA), which is mostly used in research to estimate total body composition and segmental body composition (i.e., appendicular lean mass), and more sophisticated tools like magnetic resonance imaging (MRI) or computed tomography (CT) scans.

However, there are also very cheap and practical ways to assess adiposity, particularly its distribution, in addition to BMI. For example, in our clinical practice here in Richmond, we always do an assessment of waist circumference in addition to BMI and BIA when available. Measuring waist circumference is very easy to do and is a good assessment of visceral adiposity, which is considered to be a strong cardiometabolic risk factor. So, in addition to just keeping track of changes in BMI, we also always keep track of the changes in waist circumference. For example, if you have an individual with a BMI of 23 kg/m2 and without any cardiovascular disease, but with a waist circumference of 104 cm (cut-off for men is <102 cm and for women <88cm), that individual would be considered to have an increased cardiometabolic risk despite having a normal BMI and no other apparent red flags. Overall, BMI is a decent tool, but we can do better, and there are definitely other practical tools that we can use.

CARDIOMETABOLIC CHRONICLE: ***In your research, you have also looked at physical activity and cardiovascular health. What levels of exercise intensity or duration are beneficial?***

DR. CARBONE: The new physical activity guidelines were published in 2018, an update after 10 years from the prior guidelines.[11] They recommend that the ideal amount of physical activity for adults is 150 - 300 minutes a week of moderate-intensity, or 75-150 minutes a week of vigorous-intensity aerobic physical activity per week, or a combination of both. A good way to practically think about this to define moderate-intensity is an activity that involves fast walking (a pace of 3-4 mph), which is what we typically recommend to our patients. In addition to aerobic physical activity, the recommendation is also to add some kind of strength exercise two days a week, and although this seems to be a relatively easy goal to meet, it is very scary to think that only 30% of people actually meet the physical activity guidelines. Compared to the 2008 guidelines, where only exercises or activities that last at

least 10 minutes could count towards the 150 minute/week goal, in the 2018 guidelines, any kind of moderate to vigorous physical activity can count toward the weekly goal, regardless of duration. This is important because now we can consider any kind of physical activity we do throughout the day to count towards the goal.

The levels of physical activity recommended in the guidelines have been associated with significant improvements in cardiometabolic health, including reduction in cardiovascular disease, overall mortality, improved mental health, sleep quality, as well as prevention of weight gain, obesity and T2DM. So, we should definitely do a better job in promoting physical activity[12] and make sure that our patients actually meet these guidelines.

CARDIOMETABOLIC CHRONICLE: ***What about the impacts of prolonged sedentary activity or sedentary behavior, in other words, are you at higher risk if you exercise regularly but spend most of the day sitting?***

DR. CARBONE: A study recently published in the Journal of the American College of Cardiology looked at the effect of physical activity and sedentary behaviors in a very large number of patients,[13] and we have reviewed this topic in a recent review published on Circulation Research.[14] What they found is that if you meet the guideline recommendations for physical activity, unless you are sitting for more than 8 hours a day, the sedentary behavior does not affect your cardiovascular risk, suggesting that physical activity is somewhat counteracting the damages induced by sedentary behavior. If you are not physically active, however, or doing less than the recommended physical activity levels, then the amount of sedentary behavior really matters, in fact, the more you sit the higher is your risk to develop cardiovascular disease in a dose-dependent manner. Thus, especially in individuals with low physical activity, sedentary behavior should be addressed and highly discouraged as a potential approach to improve cardiovascular health. Another important part that the study addressed is that replacing 1 hr of sitting with 1 hr of moderate-to-vigorous physical activity can reduce cardiovascular disease risk by 20% , with this risk being reduced by over 60% when replaced with vigorous physical activity.

Another interesting study recently published in JAMA Internal Medicine looked at the number of steps associated with lower mortality rates in a large population of older women.[15] The authors found that women who walked 4400 steps/day had a lower mortality risk compared to those who walked 2,700 steps/day over a follow-up period of 4.3 years, with no mortality benefit in women that walked more than 7500 steps/day. We tend to recommend to walk at least 10,000 steps a day in clinical practice, but in this study, and at least in the investigated population, they found that when you go above 7500 steps there wasn't really a reduction of all-cause mortality.

The good news is that even if you sit for very long or do not walk 10,000 steps a day, if you increase the amount of daily physical activity, including the number of daily steps, you can still significantly reduce your cardiovascular risk. This is something that all clinical providers should address in their visits with patients, in fact, asking questions to trying to quantify daily physical activity and sedentary behaviors and ultimately trying to address them, could result in improved overall cardiovascular and metabolic health.

CARDIOMETABOLIC CHRONICLE: ***To what extent are lifestyle factors, like physical activity and nutrition, addressed during a routine visit?***

DR. CARBONE: Frequently, clinical providers, including primary care physicians, cardiologists, endocrinologists, physician assistants, nurse practitioners and pharmacists tend to dedicate very little time to addressing lifestyle factors. But with a myriad of issues to think about, including optimizing medications, addressing patient compliance, potential recent admissions, and more, clinicians are extremely busy and simply do not have time. It is for this reason that the 2019 ACC/AHA guidelines for primary CVD prevention[16] encourage referrals of patients to clinicians and professionals that specialize in lifestyle medicine and can adequately address nutrition and physical activity, such as dietitians, whose role to improve cardiovascular health is too often underestimated. I still think, however, that in absence of a nutrition expert, providers can do a better job in doing a brief lifestyle assessment, for instance, asking some crucial questions about daily physical activity or diet, which could make a difference in our patients' health. Definitely, increasing the number of hours dedicated to nutrition during medical school would help achieving such goal.

CARDIOMETABOLIC CHRONICLE: ***There seems to be tremendous excitement in cardiology about diabetes drugs, like sodium-glucose co-transporter (SGLT)-2 inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RA). What is their role in addressing CVD risk?***

DR. CARBONE: I think we live in a very exciting time right now for those who work in diabetes and cardiovascular disease. We have to consider that until a few years ago, all we were doing in terms of treating diabetes was to improve glycemic control, which improves microvascular complications, like neuropathy, nephropathy, and retinopathy, as data from the UKPDS study suggested.[17] Glycemic improvement alone, however, has not been associated with improved risk of macrovascular diabetes complications, such as myocardial infarction, stroke and heart failure. This was a huge gap, because most patients with T2DM die from cardiovascular disease, and until recently, we had no means of preventing adverse cardiovascular events in these patients. Cardiovascular outcomes trials with SGLT-2 inhibitors have shown a strong effect in preventing major cardiovascular events (i.e., empagliflozin[18] and canagliflozin[19]), and particularly heart failure and renal events in patients with T2DM (i.e., empagliflozin, canagliflozin and dapagliflozin[20]), even in patients with T2DM-related nephropathy (i.e., canagliflozin[21]) that affects a large portion of patients with T2DM, further increasing their cardiovascular risk. Furthermore, these effects seem to be independent of glycemic control, although we still don't fully understand the mechanisms involved. Due to these remarkable results, SGLT-2 inhibitors are being evaluated in clinical trials for heart failure patients even without T2DM.

GLP-1 RAs such as liraglutide[22], semaglutide[23] and albiglutide[24] have shown a strong signal in prevention of atherosclerotic cardiovascular disease as well as renal events in patients with T2DM, although not all agents in this class have shown uniformity in this aspect. Based on these results, updated diabetes guidelines recommend that in T2DM patients with atherosclerotic cardiovascular disease, we should use GLP-1 RAs, and in T2DM patients with heart failure or chronic kidney disease, we should use an SGLT-2 inhibitor after first-line therapy with lifestyle and metformin.[25] The type of agent that we ultimately choose to address cardiovascular risk in patients with T2DM also depends on the patients' characteristics and comorbidities; for example, most GLP-1 RAs have very favorable metabolic effects by promoting significant weight loss, which is clearly desirable in obesity, while SGLT-2 inhibitors exert a much stronger effects on blood pressure. So, if a patient is concerned about their weight or blood pressure, treatment needs to be individualized accordingly.[26] Finally, when one of these agents is not sufficient to achieve glycemic goals, a combination of GLP1-RAs and SGLT-2 inhibitors should also be considered.

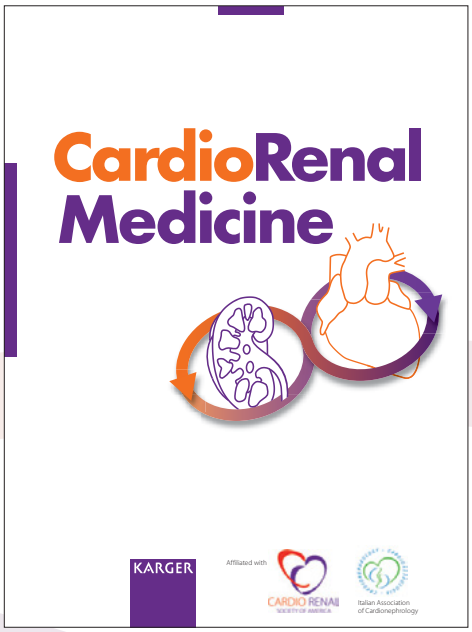
References:

1. Ortega, Francisco B., Carl J. Lavie, and Steven N. Blair. "Obesity and cardiovascular disease." Circulation Research 118.11 (2016): 1752-1770.
2. Carbone, Salvatore, et al. "Obesity paradox in cardiovascular disease: where do we stand?." Vascular Health and Risk Management 15 (2019): 89 - 100.
3. Carbone, Salvatore, Carl J. Lavie, and Ross Arena. "Obesity and heart failure: focus on the obesity paradox." Mayo Clinic Proceedings 92.2 (2017): 266 – 279.
4. Horwich, Tamara B., et al. "The relationship between obesity and mortality in patients with heart failure." Journal of the American College of Cardiology 38.3 (2001): 789-795.
5. Padwal, R., et al. "The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data." International Journal of Obesity 38.8 (2014): 1110 - 1114.
6. Romero-Corral, Abel, et al. "Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies." The Lancet 368.9536

(2006): 666-678.
7. Lavie, Carl J., et al. "Healthy weight and obesity prevention: JACC Health Promotion Series." Journal of the American College of Cardiology 72.13 (2018): 1506 - 1531.
8. Carbone, Salvatore, et al. "Obesity, body composition and cardiorespiratory fitness in heart failure with preserved ejection fraction." Future Cardiology 13.5 (2017): 451-463.
9. Carbone, Salvatore, et al. "Lean mass abnormalities in heart failure: the role of sarcopenia, sarcopenic obesity and cachexia." Current Problems in Cardiology (2019).
10. Ortega, Francisco B., et al. "Body mass index, the most widely used but also widely criticized index: would a criterion standard measure of total body fat be a better predictor of cardiovascular disease mortality?." Mayo Clinic Proceedings. 91.4 (2016): 443 - 455.
11. Piercy, Katrina L., and Richard P. Troiano. "Physical activity guidelines for Americans from the US Department of Health and Human Services: cardiovascular benefits and recommendations." Circulation: Cardiovascular Quality and Outcomes 11.11 (2018): e005263, also available at https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf
12. Fletcher, Gerald F., et al. "Promoting physical activity and exercise: JACC health promotion series." Journal of the American College of Cardiology 72.14 (2018): 1622-1639.
13. Stamatakis, Emmanuel, et al. "Sitting time, physical activity, and risk of mortality in adults." Journal of the American College of Cardiology 73.16 (2019): 2062-2072.
14. Lavie, Carl J., et al. "Sedentary behavior, exercise, and cardiovascular health." Circulation Research 124.5 (2019): 799-815.
15. Lee, I-Min, et al. "Association of Step Volume and Intensity With All-Cause Mortality in Older Women." JAMA Internal Medicine (2019).
16. Arnett, Donna K., et al. "2019 ACC/AHA guideline on the primary prevention of cardiovascular disease." Journal of the American College of Cardiology (2019): 26029.
17. UK Prospective Diabetes Study (UKPDS) Group. "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)." The Lancet 352.9131 (1998): 837-853.
18. Zinman, Bernard, et al. "Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes." New England Journal of Medicine 373.22 (2015): 2117-2128.
19. Neal, Bruce, et al. "Canagliflozin and cardiovascular and renal events in type 2 diabetes." New England Journal of Medicine 377.7 (2017): 644-657.
20. Wiviott, Stephen D., et al. "Dapagliflozin and cardiovascular outcomes in type 2 diabetes." New England Journal of Medicine 380.4 (2019): 347-357.
21. Perkovic, Vlado, et al. "Canagliflozin and renal outcomes in type 2 diabetes and nephropathy." New England Journal of Medicine 380.24 (2019): 2295-2306.
22. Marso, Steven P., et al. "Liraglutide and cardiovascular outcomes in type 2 diabetes." New England Journal of Medicine 375.4 (2016): 311-322.
23. Marso, Steven P., et al. "Semaglutide and cardiovascular outcomes in patients with type 2 diabetes." New England Journal of Medicine 375.19 (2016): 1834-1844.
24. Hernandez, Adrian F., et al. "Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial." The Lancet 392.10157 (2018): 1519-1529.
25. American Diabetes Association. "9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2019." Diabetes Care 42.Supplement 1 (2019): S90-S102.
26. Carbone, Salvatore, et al. "Glucose-lowering therapies for cardiovascular risk reduction in type 2 diabetes mellitus: State-of-the-Art Review." Mayo Clinic Proceedings 93.18 (2018): 1629 – 1647.

Metabolic abnormalities, heart and kidney disease

CardioRenal Medicine



CardioRenal Medicine explores the mechanisms by which obesity and other metabolic abnormalities promote the pathogenesis and progression of heart and kidney disease (cardiorenal metabolic syndrome). It provides an interdisciplinary platform for the advancement of research and clinical practice, focussing on translational issues.
The journal addresses a multidisciplinary audience consisting of nephrologists, cardiologists, nutritionists, endocrinologists, physiologists and general internists.

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Dr. Virani's research portfolio aims to understand several domains in the delivery of high-quality primary and secondary cardiovascular disease preventive care. Dr. Virani has been a recipient of the Scott Grundy Award for Excellence in Lipids Metabolism Research from the American Heart Association (AHA) and the Jeremiah Stamler Distinguished Young Investigator Research Award. Dr. Virani serves as the Chair for the Prevention of Cardiovascular Disease Section of the American College of Cardiology (ACC) and Chair for the AHA's Cardiovascular Disease Statistics Committee. He has been involved in several guideline writing committees, including the 2018 AHA/ACC multi-society cholesterol guidelines and the 2019 ACC/AHA primary CVD prevention guideline. Dr. Virani has authored or co-authored over 300 peer-reviewed publications related to various preventive therapies including cholesterol, blood pressure control and aspirin therapy, published in several high-impact journals such as Circulation, European Heart Journal, JAMA Internal Medicine, JAMA Cardiology, and Journal of the American College of Cardiology

What inspired you to become a physician?
Growing up in outside of the US, career choices were very few, you could either become an engineer or a doctor. I always had a great interest in biology and deeply enjoyed the subject. Also, I enjoy interacting with people, and what better way to interact with people and touch their lives than being a physician. Furthermore, as a researcher and an educator I can do a lot of meaningful work together with other fellow researchers, colleagues, and mentees. There are very few professions where you can be involved in patient care, do research, teach, and at the same time make a good living, and these are great reasons to be a physician.

Who has had the greatest influence on your career?
I would say my parents and early teachers because I am the product of a family that moved through two countries. My family is originally from India, and they moved to Bangladesh because of financial constraints. Then war broke out and they had to move to Pakistan, so you can imagine it was a struggle for my family. My parents always told me something that they had learned over the years: you can lose everything, but as long as you have a sound mind, you're still going to retain all the abilities that you have acquired through good education. Where I come from, education is not a right, but a privilege, and my parents, who unfortunately were not able to get very good education, sacrificed a lot and gave me all the possible resources they could so I could get a good education. Their sacrifices served as my biggest inspiration. I would also mention the mentors throughout my professional career. These individuals have given their time, expertise, and advice without expecting anything in return.

What has been the greatest challenge during your professional career?
I think if I were to say the biggest challenge I have is how to prioritize things and then work on a few tasks and not try to do too many at once. I think for me personally, that has been the biggest challenge and then how to keep a balance between medicine and life outside of it.

What area of research in cardiometabolic health interests you most now and why?
In the cardiometabolic space, most of my work has been in lipids, and I look at it from a little bit of different perspective rather than the therapeutic side of things. I obviously am quite involved in the therapeutic side, being part of the guidelines on how therapeutics should be used when it comes to lipids. But the other side of it where our team makes a contribution, is looking at it from a healthcare systems perspective using big data, as to what is the impact of new therapies and how are we doing in terms of delivering therapies that we know work in our patients. Being a cardiologist at the VA has been great because VA has one of the strongest informatics platforms in terms of a healthcare system. The availability of big data, being able to work with great teams, and having had the opportunity to be mentored by some of the best in the field greatly facilitates this approach. This is an important area of focus for me, how can big data guide and inform us in terms of where we are, what we know and where we can go with the new therapeutics that are being developed.

What do you think is going to be the next big thing in your field over the next decade?
At the patient level, I think medicine is going to get more and more precise and personalized based on a patient's characteristics, and here I don't mean just genetics. Factors like where patients live, how do they interact with the medical community, in addition to their genetic makeup, will be important. How can you precisely use medications in one person or the other? That is a very exciting area. We've been talking about it for decades now, but I think we're definitely in a much better position to apply this today and in the near future.

At the healthcare systems level, the conversation is going to be about what can systems do to assist clinicians in delivering care that is guideline directed. So what cognitive support can be given so that healthcare systems can survive through electronic medical records (EMR), because EMR has become very detailed, and how can we simplify it to the point where it is not a deterrent but actually something that creates more opportunities for clinicians to better take care of patients. This includes providing point-of-care support, solutions and tools that that can guide clinicians to better know the patient in front of them, and how to optimize care in this patient in the best possible way.

Lastly, I think, and I hope, that there will be a lot of work that will happen in the next decade or so in terms of clinicians' understanding of how patients interact with social media and what are the implications of it, since we know that a lot of patients use social media, and so do a lot of clinicians. How can we optimize that to the point that the information that each of these stakeholders receives is reliable and something that helps in the therapeutic plan versus creating controversies that may not be really driven by actual data?

What do you consider your greatest achievement?
I think of opportunities and achievements the same way since they both add value to our lives and help us improve. I would choose three. One is being part of some of the practice guidelines where you get the opportunity to work with real giants in the field and learn from them. Second is the ability to be mentored by some great mentors and then being able to mentor our fellows in training and junior faculty. Third and perhaps most important, being able to use what I have learned here in US to make a very small dent to improve the quality of life for communities in low-middle income countries. Those are some of the biggest rewards I've had thus far in my academic career.

What are your hobbies outside of medicine?
I do a fair amount of reading on a variety of topics. Reading that can help explain why we as human beings do what we do, and that's one area that I'm very interested in. I definitely like to watch sports. I do watch basketball and football, but I am definitely a cricket fan, and I try to follow cricket very closely as much as I can.

I also do quite a bit of community work both in my local community and as a medical volunteer in other countries, and I do that on a very regular basis. For me it is important to volunteer my time and make sure that I give it back to the community where I've gotten so much from.

What is your motto or philosophy?
I don't have a mantra per se, but I think that we're all very fortunate to be living in a country where anything and everything is possible. Living in the United States, we all have the possibility to achieve what we want to do, because opportunities will be there if we are willing to work hard and ask the right questions. So, I always remind myself whether I'm asking the right questions, is this really what I want in life, and if the answer is yes, I'll try very hard to achieve it and do it on a consistent basis. I personally believe that although creativity and innovation are important, a lot of what we are able to achieve and contribute to is actually dependent on doing the right things that we know work and doing them on a consistent basis.

Denial? Or Doctorly Deference?

By Carolyn Thomas

Recently, the *British Medical Journal (BMJ)* ran a compelling opinion piece[1] from Boston physician Dr. Abraar Karan on why some patients just don't seem to understand what their doctors are telling them. Here's how he opens his essay:

"***'Why am I here?'*** *Mrs. S looked up at me for the first time since I had entered the room and begun speaking to her. I had spent the past five minutes talking about the need for her to start new medications for her heart failure. She had nodded along for most of the conversation, but I wondered if she had heard, or more importantly understood, anything I had been saying. She had had three admissions for worsening heart failure in the past few months. And yet she looked at me and said,* ***'Do I have heart problems? No one ever told me!'***".

Dr. Karan, who is an internal medicine resident at the Brigham and Women's Hospital/ Harvard Medical School, and author of the book *"Protecting the Health of the Poor: Social Movements in the South"*,[2] felt understandably discouraged and disappointed by her puzzling response to his important explanations. Was her apparent confusion because no other doctor had **explained the diagnosis** to her? Or that the explanations had been too complicated or **jargon-heavy** for her to comprehend? Or was this a symptom of her **low health literacy**? (Health literacy is simply the capacity we have to obtain, process and understand basic health information and services needed to make good health decisions for ourselves).[3] Dr. Karan also asked himself, "*Have we as a medical system collectively failed to communicate effectively?*" but he eventually began to wonder if perhaps none of these issues was the sole culprit all by itself.

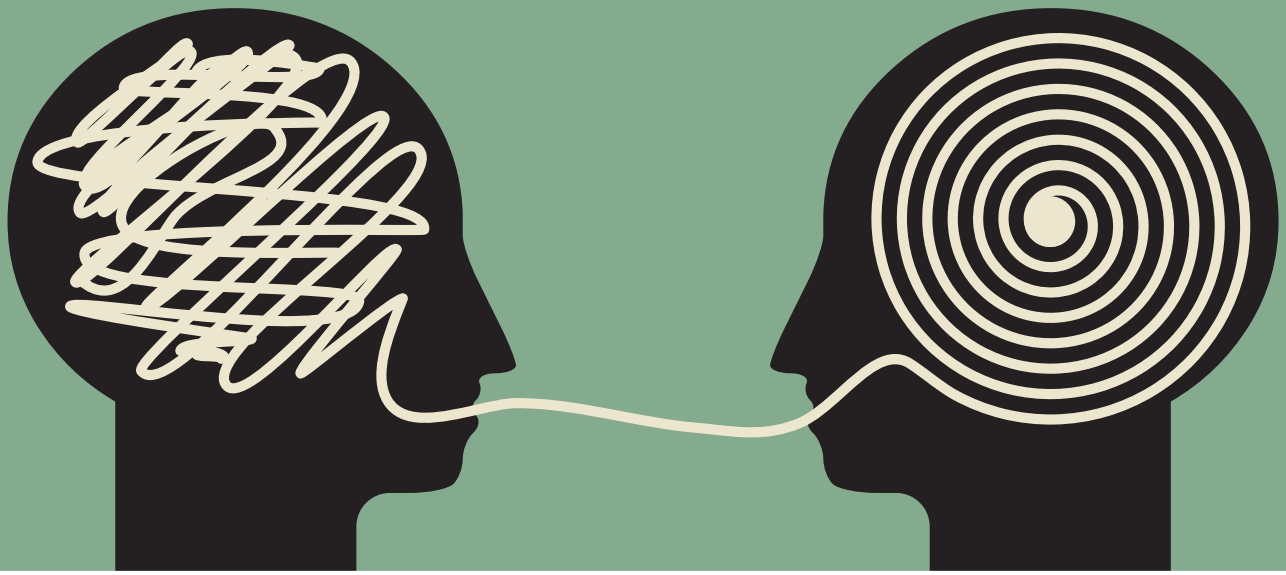
Maybe this wasn't just about a doctor's ability to communicate the facts of a medical condition. When he discussed this troubling case with his colleagues, some mentioned to him that "*communication is only one part of the equation*". One experienced doctor suggested the possibility that Dr. Karan's patient was **in denial**.

"What if I had missed an important consideration – that Mrs. S just wasn't quite ready to accept her diagnosis? Denial is a complex coping mechanism – a universal emotion that almost anyone reading this has dealt with – and which may play a much larger part in people's ability to understand their own illness than we appreciate."

Was she aware, he wondered, that she was possibly nearing the last year or two of her life (repeat heart failure admissions do, in fact, predict mortality[4])?
"I then wondered – maybe it was not a failure to explain on the part of her medical teams, but her own difficulty with acceptance that she was quite sick."

And even if she were not in denial, was his patient perhaps just **too overwhelmed by this distressing news** to properly process what it meant?

"I fear that we don't always take the time, or are even adequately trained, to figure out what patients do and don't understand, what they do and do not accept, and what



they are and are not able to cope with in that moment. In one study5, nearly 40% of hospitalized patients had no understanding regarding their plan of care for the day – and only 32% remembered the name of even one of their doctors (60%, however, could name their nurses)."

My own response to Dr. Karan's observations was mixed. Everything he wrote made sense to me. And for 10 years, I've been grappling with this same question of why doctor-patient communication seems so fraught with potential misunderstanding, including my essays on the dangers of heart patients in denial, and women's treatment-seeking-delay behaviors during heart attack. But something also seemed to be missing, and in my subsequent reader response to the BMJ, I described the missing bit as *"the inherent hierarchy in medicine that supports this communication gap"*.

Here's what I wrote:
"While growing up in my family during the 1950s, I observed how deferential my parents, especially my mother, always were towards our longtime family physician, and of course towards any specialist that physician may have ever referred them to over the years.

"My mother, who was whip-smart but had little formal education, believed that whatever doctors were telling her was right, that any recommendation was the best one, that doctors wouldn't be prescribing anything unless she really needed it. And that was good enough for her.
"She was also highly aware of a doctor's very valuable time, and thus reluctant to waste it by asking him to repeat what he'd just said, or to clarify complicated instructions, and most important, extremely reluctant to appear stupid in front of him if she had to admit she hadn't understood what he was talking about.

"I'm pretty sure she had smiled and nodded throughout each medical visit no matter what the doctor said, and very likely even answered "No, Doctor!" when asked if she had any further questions or concerns. For decades, her family physician likely felt confident after each visit with Mom that all had gone well, and that he had appropriately explained what each test result, medical decision or upcoming procedure was all about."

I also shared a story I've told many times because it knocked me over when it happened during one of my Heart-Smart Women presentations:

"I was reminded of my own mother recently when an elegantly-dressed older woman in one of my audiences raised a beautifully manicured hand during the Q&A and asked me: 'Carolyn, my doctor says I have a 'heart rhythm' problem. What does that mean?'
"I wondered at the time how this articulate, intelligent woman had managed to leave her doctor's office without knowing anything about her diagnosis. The likely reason: she was very much like my own mother...."

But this apparent inability to understand the doctor is not unique to elderly women. When a cardiologist was called into the Emergency Department during my previously misdiagnosed heart attack and said to me the words **"You have significant heart disease,"** I could see his lips moving and I could hear sounds coming out of his mouth. But I honestly could not comprehend one word he said after that fateful pronouncement. I may have been nodding as if I understood. And I think I may have signed something, too. . .

As Dr. Karan's conclusion suggests, neither he nor any physician can ever be completely reassured that even a smiling, nodding patient understands anything that's being said. He blames what he calls the "undiagnosed disconnect between what doctors think their patients understand and what they actually understand", and he further urges that **integrating medical communication as a formal practice of study into medical school** curricula would be an important start:

"Mrs. S said to me that no one had ever told her she had heart issues, and I tried my best to explain further. Yet I couldn't be entirely sure that she understood, accepted, or even truly wanted me to be explaining this to her in that moment in time. She looked at me, smiled, nodded, and offered a polite, 'Thank you.' But in a few weeks or months' time, will she ask her next doctor the same question, and might they also wonder, as I did, where her previous doctors went wrong?
"As much as we must ask how much our patients understand about their illness, we must also ask ourselves how much we understand about our patients. Patients do not always remember what we say, but they will always remember the way we made them feel.
"We need to do better at knowing what to say, how to say it, and when to say it if we want communication to truly work."

This story is printed with permission from the blog Heart Sisters, created and run by Carolyn Thomas (for more information, please visit https://myheartsisters.org/). Carolyn is a patient and an advocate for women with heart disease, and in addition to her successful blog, she also recently authored the book "A Woman's Guide to Living with Heart Disease" (Johns Hopkins University Press, 2017).

References:

1. Karan, Abrar. "Making sure patients understand and that doctors do too." The British Medical Journal Opinion, May 23, 2019. Available at https://blogs.bmj.com/bmj/2019/05/23/abraar-karan-making-sure-patients-understand-and-that-doctors-do-too/, accessed August 1, 2019.
2. Karan, Abraar, and Geeta Sodhi, eds. "Protecting the health of the poor: social movements in the south." Zed Books Ltd., 2015.
3. National Network Libraries of Medicine. "Health literacy – definition." Available at https://nnlm.gov/initiatives/topics/health-literacy, accessed August 1, 2019.
4. Lin, Andrew H., et al. "Repeat hospitalizations predict mortality in patients with heart failure." Military Medicine 182.9-10 (2017): e1932-e1937.
5. O'Leary, Kevin J., et al. "Hospitalized patients' understanding of their plan of care." Mayo Clinic Proceedings. 85.1 (2010): 47-52.

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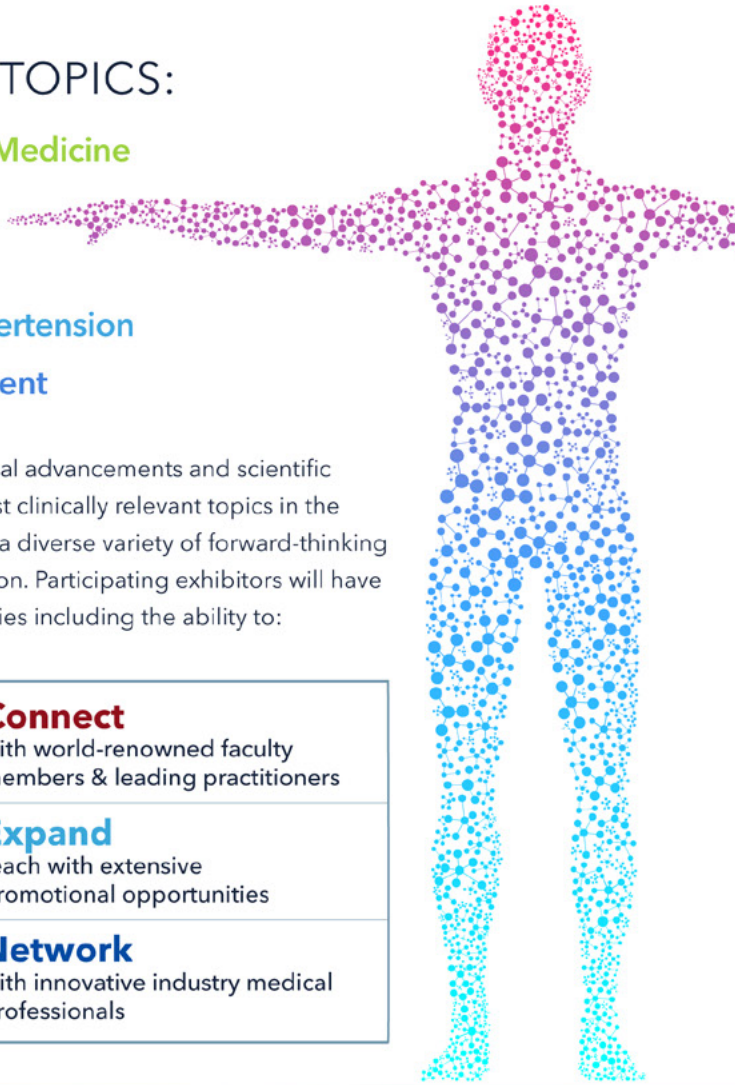

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