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Peripheral Vascular Disease in 2021

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It seems fitting in this year of isolation and pandemic to open the Compendium on Peripheral Vascular Diseases with the voices of patients. Gertrude Campbell was a pioneer as the first black Postmaster in Starkville, Mississippi, but when she developed pain in her legs it was attributed to her diabetes and not recognized as PAD until she had advanced disease requiring amputation. Ultimately she lost both her legs and became a spokesperson for patients with peripheral artery disease (PAD). When I met her, she spoke eloquently about advancing the science for vascular disease and awareness in the medical and patient community. In an interview with an aspiring physician-scientist many years later, he expressed his interest in studying venous thrombosis to understand why it occurred to him at a young age and during the COVID-19 pandemic.

We have had the distinct honor of working together to create an update in the rapidly evolving field of vascular disease science and management. Nick Leeper and I met each other more than a decade ago at the yearly meetings of the NHLBI-funded fellows in Vascular Medicine and have been inspired by so many of the founders of this field that served as our inspiration including John Cooke, Joseph Vita, Mark Creager, Emile Mohler, Mary McDermott, Alan Hirsch, and so many others. We want to pay special tribute this year to Dr. William Hiatt who transformed the science of PAD from early work investigating exercise and skeletal muscle metabolism to his establishment of international multicenter randomized clinical trials of PAD patients. His kindness, thoughtfulness, dedication to patients, and love of the mountains echo throughout the pieces in this Compendium.

The first set of articles is focused on PAD and start with an update of the genetic basis of PAD by Drs. Klarin, Tsao, and Damrauer[1] that highlights recent work identifying inflammatory and thrombotic pathways distinct to PAD risk. In their discussion of the

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Dr. Hamburg has consulting relations with Merck, NovoNordisk and Sanifit and has equity interest in Acceleron Pharma. Dr. Leeper recently had consulting relations with Janssen Pharmaceuticals.

epidemiology of PAD, Drs. Aday and Matsushita[2] move from traditional risk factors to identifying novel biomarkers of PAD risk and the importance of vascular disease in multiple territories (termed polyvascular disease) in risk prediction. In an exciting new area of PAD science, Drs. Flores, Demsas, Leeper, and Ross[3] detail how 'big data', machine learning and artificial intelligence can serve to overcome the challenges in underdetection and undertreatment of PAD. Using sophisticated computing combined with the electronic medical record may be the future of identifying patients with PAD, risk stratifying and delivering optimal medical therapy in an equitable fashion to a greater number of patients.

The next set of PAD-focused topics covers the impact of disease management approaches. Drs. McDermott, Dayanidhi, Kosman, Saini, Slyz, Leeuwenburgt, Hartnell, Sufit, and Ferrucci[4] review the impact of chronic ischemia on the phenotype of the leg skeletal muscle including alterations in mitochondrial metabolism and the multitude of restorative mechanisms with walking exercise therapies. The past five years have seen a dramatic increase in clinical trial evidence supporting medical therapies to reduce cardiovascular and limb events in patients with PAD. Drs. Bonaca, Hamburg, and Creager's[5] discussion includes the evolving field of diabetes therapies in patients with atherosclerosis and the key new findings supporting the clinical utility of dual pathway antithrombotic therapies. Even with optimal medical therapy, many patients with PAD require revascularization through surgical or endovascular approaches; a discussion by Drs. Beckman, Schneider, and Conte[6] includes an elegant overview of the barriers to therapies that need further research such as microvascular disease, calcification, restenosis, and thrombosis. There remain persistent gaps in the treatments of patients with PAD are even more marked in Black Americans, underlying the increasingly recognized epidemic of nontraumatic amputations. Drs. Hacker, White Solaru, and Hamburg[7] give an overview of the available information regarding racial and ethnic disparities across the detection, management, and outcomes of patients with PAD, including the fact that even contemporary trials of PAD patients have been almost exclusively comprised of non-Hispanic white patients, emphasizing the need for new strategies to promote equity in clinical trial enrollment and optimal care delivery. To improve the care of PAD, new treatments are still needed across the entire spectrum of disease. Drs. Alsaigh, DiBartolo, Mulangala, Figtree, and Leeper[8] describe a platform for translational science in PAD employing multi-omics in clinical cohorts combined with pre-clinical models including iPSC, organoids, and animal models of ischemia, wound healing, and plaque vulnerability. Finally, Drs. Annex and Cooke[9] look to the future of promoting growth of blood vessels to treat advanced PAD with both cell-based and pharmacologic approaches.

The next set of articles covers particular areas of interest in arterial disease and beyond. Recent evidence is starting to undercover the biology of fibromuscular dysplasia and spontaneous coronary artery dissection, as reviewed by Drs. Kim, Saw, Kadian-Dodov, Wood, and Ganesh[10]. Large clinical cohorts from registries have described the important overlap of these two conditions, particularly in women, and point to new potential pathways to treat these patients with few current medical options. Advances in cancer therapies have generated the new field of cardio-oncology, including the critical impact on the vasculature. Drs. Fleming, Xiao, Jackson, Beckman, Barac, and Moslehi[11] review the intersection of vascular disease and cancer treatment with a focus on new information regarding the

vascular effects of Bruton's tyrosine kinase inhibitors that include hypertension and bleeding. There has been much interest in acute venous thrombosis during the COVID-19 pandemic, but there is also a high burden of chronic venous disease that are poorly understood and lack medical therapies, as discussed by Drs. Baylis, Smith, Klarin, and Fukaya[12], who cover exciting new information from genetics that may transform future therapies. Dr. Stanley Rockson[13] masterfully describes the science of lymphedema, covering both clinical management and the science of lymphatics. The final article from Drs. Colling, Tourdot, and Kanthi[14] covers the emerging evidence linking inflammation and thrombosis, which has been at the forefront of the minds of those caring for patients with COVID-19-related thrombosis, but also holds opportunities for prevention and treatment of venous thrombosis in general.

This amazing collection of Reviews highlights how much evidence is emerging from experimental and clinical research to advance our understanding of vascular disease in a meaningful fashion for our patients. We are intensely grateful to all of the contributors to this Compendium, who demonstrate their passion and dedication to discovery, and to their patients.

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