BRIGHAM AND WOMEN'S HOSPITAL

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Endocrinology ADVANCES

Laura Mauri, MD, MSc, Piotr S. Sobieszczyk, MD, and Naomi D. Fisher, MD

Hypertension Research Focuses on Innovative Devices, Genetics, and Remote Monitoring to Advance Patient Care

Naomi D. Fisher, MD, Director of the Hypertension Specialty Clinic in the Division of Endocrinology, Diabetes and Hypertension, and Laura Mauri, MD, MSc, Director of Center for Clinical Biometrics in the Division of Cardiovascular Medicine, are collaborating on innovative approaches for the treatment of hypertension.

Radiance-HTN Study: Using Renal Ablation to Treat High Blood Pressure

Dr. Fisher, Dr. Mauri and Piotr S. Sobieszczyk, MD, of the Division of Cardiovascular Medicine, are currently enrolling participants for a randomized, double-blind study called the ReCor Medical Paradise System in Clinical Hypertension (Radiance-HTN) study, designed to demonstrate efficacy and safety of the Paradise Renal Denervation System in two populations of hypertensive patients.

"Many physicians think that renal nerve ablation is no longer a viable option, but treating high blood pressure with renal denervation is still very promising," said Dr. Fisher, principal investigator of the study which began in March 2016.

A total of 292 patients with a documented history of essential hypertension will receive the renal denervation procedure using The Paradise® Renal Denervation System, a minimally invasive procedure that delivers ultrasound energy to thermally ablate and disrupt the renal sympathetic nerves while sparing the renal arterial wall. A diagnostic renal angiogram will be considered the sham procedure for control participants.

The primary outcome measure of the Radiance-HTN study is the reduction of average daytime ambulatory systolic blood pressure two months following ultrasound renal denervation. The study will also track 13 additional secondary outcomes measures, including hospitalization for heart failure, acute myocar-

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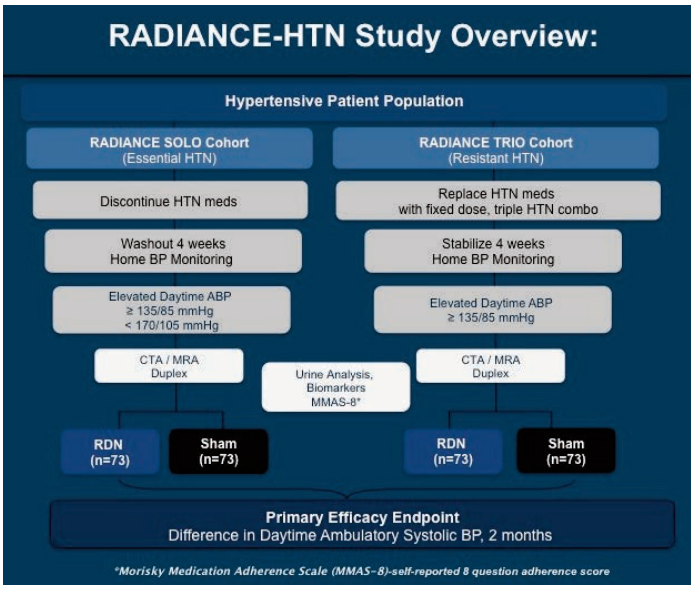
dial infarction, and renal artery or vascular complications requiring intervention.

Final data collection for the primary outcome measure – mean reduction in average daytime ambulatory systolic blood pressure – is estimated to end in August 2017, and the study completion date is scheduled for July 2020. *(For more information on Radiance-HTN, contact Dr. Fisher at nfisher@partners.org or 617-732-5666)*



Parallel randomized controlled study design now enrolling. Patients will be followed through 36 months. SOLO – Essential hypertension on 2 or fewer drugs at baseline; TRIO – Treatment resistant hypertension on 3 or more drugs at baseline changed to single pill triple drug combo for study; CTA/MRA – Prerandomization anatomic screening with CT or MR angiography; RDN – renal denervation with ultrasound catheter; Sham – renal angiogram.

HyperPATH Study: Personalized Treatment for Hypertension

Dr. Fisher is also collaborating with researcher Gordon Williams, MD, within the Division of Endocrinology, Diabetes and Hypertension, on a translational research study called the Hypertension Pathotype (HyperPATH), which aims to identify the genetic underpinnings of hormonal factors that lead to hypertension.

The study focuses on evaluating hormones that affect vascular contractility and sodium balance. The major areas of focus are the renin angiotensin aldosterone system (RAAS), kallikrein, cortisol, adducin, the beta-2 adrenergic receptor and ion transport systems.

"We want to understand the genetic factors that contribute to a patient's hypertension," explained Dr. Fisher. "High blood pressure could be the result of having too many risk genes or not enough protective genes." *(For more information on HyperPATH, contact Dr. Williams at gwilliams@partners.org or 617-525-7288)*

BP-Connect Program: Remote Blood Pressure Monitoring Program

Dr. Fisher is also enrolling patients in the BP-Connect Program, an initiative designed to promote patients' self-management of their hypertension.

"The program engages patients daily through a remote telemonitoring platform, where they can record their blood pressure measurements and report symptoms. Their care providers can view the uploaded data, thereby ensuring continuum of care, even outside of hospital settings," said Dr. Fisher.

The 230 enrolled participants were given a kit containing a blood pressure cuff and a device that transfers blood pressure data to a central database at BWH. Patients measure their blood pressures one to two times daily for three months and data are available electronically to both patients and providers.

The BP-Connect Program aims to lower blood pressure below <140 mm Hg systolic or <90 mm Hg diastolic over the three-month intervention period. The program began enrolling patients in early 2016 and will continue through 2017. *(For more information on BP-Connect, contact Dr. Fisher at nfisher@partners.org or 617-732-5666)*

BP-HOP Pilot Study: Remote Management of Uncontrolled Hypertension

Dr. Fisher is the clinical lead of the Brigham Protocol-based Hypertension Optimization Program (BP-HOP) pilot study, leading a collaborative team including primary care, cardiology, and nephrology. The study, which launches in January, aims to manage hypertension through a remote, algorithm-driven treatment plan.

The study will enroll up to 800 patients with uncontrolled hypertension, and will use patient coaches, navigators, and pharmacists to implement a comprehensive hypertension treatment algorithm, designed by experts in hypertensive management. Much of the contact with patients will be remote to allow more frequent and rapid cycling of blood pressure assessments and treatment changes. *(For more information on this study, contact Dr. Fisher at nfisher@partners.org or 617-732-5666)*

Naomi D. Fisher, MD
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Endocrinologists and Geneticists Collaborate to Treat Hereditary Endocrine Syndromes

The Endocrine Genetics Program, within the Division of Endocrinology, Diabetes and Hypertension at Brigham and Women's Hospital, sees approximately 120 patients a year with a range of genetic syndromes that display endocrine features.

This highly specialized program provides diagnostic evaluations and management of hereditary endocrine conditions for patients and their family members. The endocrinologist and genetic counselor team employs genetic tests, such as karyotype/microarray, single gene sequencing, gene panels, whole exome and whole genome sequencing, among others.

Specialists in the Program evaluate patients with the rare and sometimes fatal metabolic bone disease, hypophosphatasia, in addition to multiple endocrine neoplasia (MEN) syndromes, familial isolated pituitary adenomas (FIPA), Cowden syndrome, Albright hereditary osteodystophy, maturity onset diabetes of the young (MODY), congenital adrenal hyperplasia, pheochromocytoma and paraganglioma predisposition syndromes, and many others.

"We are one of the few programs in the country to have this level of integration of a genetics program within an endocrine division," said Dr. Barlev-Ehrenberg. "With some exceptions, endocrinologists do not routinely think about hereditary syndromes in their evaluations. One of our goals has been providing both formal and informal consultations and trainings to our endocrine faculty, which has greatly increased awareness of indications for referral."

Genetic Testing for Hypophosphatasia

The presentation of hypophosphatasia can be highly variable, family members may have had subtle symptoms for years. "We will invite patients and their family members into the clinic for a comprehensive evaluation. We discuss hypophosphatasia, run clinical and genetic tests, counsel the family on the process of genetic testing and interpretation of results, and help them manage the disease," said Adi Barlev-Ehrenberg, MD, MS, Director of the Endocrine Genetics Program.

The Program currently sees multiple families with juvenile onset and adult onset hypophosphatasia, which has led the specialists to take a particular interest in understanding and managing this disease. She said, "We are learning just how broad the range of symptoms can be, and this is leading us towards an increase in diagnosis."

Nikkola Carmichael, CGC, and Adi Barlev-Ehrenberg, MD, MS, Director, Endocrine Genetics Program, collaborate to treat patients and their families who have hereditary endocrine conditions.

The Program screens for hypophosphatasia by testing for low levels of alkaline phosphatase, as the syndrome is caused by mutations in the ALPL gene, which leads to insufficient alkaline phosphatase and the accumulation of substrates, including inorganic pyrophosphate, which inhibit formation of hydroxyapatite from inorganic phosphate and calcium.

These metabolic changes lead to varying degrees of rickets, which in severe form can include hypercalcemia, nephrocalcinosis, and respiratory failure due to abnormal rib formation. In adults, symptoms can manifest very differently, with atypical bone pain and fragility fractures. In 2015, the FDA approved asfotase alfa, an enzyme replacement therapy (ERT) for the treatment of patients with perinatal, infantile, and juvenile-onset hypophosphatasia. This has allowed the Program to offer targeted treatment to those who are more severely affected.

Diseases that Elude Diagnosis Advance to Research Phase

When clinical testing cannot confirm a diagnosis, Dr. Barlev-Ehrenberg involves Division of Genetics researchers. "The patient may have an undiscovered disorder, so we work with our research team to determine if the patient and family qualify for whole genome sequencing on a research basis," she said.

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Access to our Endocrinology Services

Our Physician Liaison Ellen Steward can provide direct assistance with patient referrals and consultations. Ellen can be reached at (617) 582-4733 or esteward@partners.org.

ENDOCRINOLOGY RESEARCH UPDATE

Patients with Non-functional Adrenal Tumors May Be at Increased Risk for Diabetes

Researchers from Brigham and Women's Hospital have found that adrenal tumors may increase a person's risk of developing type 2 diabetes. The study was published in the October issue of *Annals of Internal Medicine.*

Benign adrenal tumors may secrete hormones such as cortisol that increase the risk of developing cardiovascular and metabolic diseases. Benign adrenal tumors that are evaluated and considered to secrete no cortisol or miniscule levels of cortisol are considered "non-functional" and are left untreated. Using data from the medical records of 1479 patients, including 242 with non-functional adrenal tumors and 1237 without any adrenal tumor, Anand Vaidya, MD, MMSc, and colleagues assessed the risk of developing cardiometabolic diseases over time between these two groups.

"When we analyzed our results, we were quite surprised," Dr. Vaidya said. "Our results indicated that patients with non-functional adrenal tumors developed diabetes twice as often as patients without any adrenal tumors. This suggests that even adrenal tumors we deem to have no health risks are in fact associated with an increased risk of developing diabetes."

These findings suggest that non-functional adrenal tumors may be independent risk factors for developing diabetes and that patients with these tumors should be evaluated for diabetes more vigilantly.

Dr. Vaidya and his colleagues also analyzed a third category of patients: those with adrenal tumors that secreted small amounts of cortisol, termed subclinical hypercortisolism. They found that this category of patients had the highest risk of developing type 2 diabetes, illuminating a trend in the relationship between cortisol secretion, even in small amounts, and the risk of developing type 2 diabetes.

The next step for the research team is to determine the most effective method to address adrenal tumors that are currently considered non-functional. Future studies to evaluate whether surgical or pharmacological treatments could reduce the risk of diabetes are being considered.

"Our results imply that once you have an adrenal tumor, regardless of its functionality, you should consider recognizing it as a potential risk factor for diabetes," Dr. Vaidya said.

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Endocrinologists and Geneticists Collaborate to Treat Hereditary Endocrine Syndromes... continued from page 3

The Endocrine Genetics Program also works closely with genetics investigators with the Undiagnosed Disease Network (UDN), an NIH-funded program with seven clinical sites nationwide, including the consortium of Brigham and Women's Hospital (BWH), Massachusetts General Hospital (MGH), and Boston Children's Hospital (BCH). Experts at these hospitals evaluate and treat patients who suffer from diseases and symptoms that have eluded diagnosis.

Within the UDN, a patient will consult with a team that provides comprehensive clinical evaluation, cutting-edge genetic and genomic analysis, environmental exposure analysis, proteomics, metabolomics, systems biology and network medicine analysis.

"Genetics is constantly developing and our knowledge is rapidly expanding, but a great deal of genetic testing is already clinically available. Applying a collaborative approach allows us to both optimize clinical care and promote advances in research," said Dr. Barlev-Ehrenberg.

Adi Barlev-Ehrenberg, MD, MS,
Director, Endocrine Genetics Program,
Division of Endocrinology, Diabetes, and Hypertension