the 87 with essential RH (35.6%) fulfilled the office systolic BP criteria (≥160 mm Hg or ≥150 mm Hg for diabetics) for RDN; 5 of these patients had out-of-office BP <135/85 mm Hg, and 2 had an eGFR <45 ml/min/1.73 m^2. Consequently, only 24 patients were eligible for RDN on both BP and eGFR criteria. Renal artery anatomy was appropriate for RDN on a computed tomography angiogram reviewed by a senior radiologist in only 15 of these 24 patients (62.5%). Therefore, only 1.5% (15 of 1,034) of all hypertensive patients or 17.2% (15 of 87) of the patients with essential RH referred to our tertiary care hypertension department were fully eligible for RDN (see Fig. 1). These proportions might even be overestimates, because: 1) spironolactone, which has proved effective for the treatment of RH (7), was prescribed to only 7 of 29 patients (24.1%); and 2) compliance with treatment was not assessed by systematic plasma or urinary drug determinations.

Our findings demonstrate that percutaneous RDN, whether for clinical trials or specific patients, is limited to a highly selected fraction of patients with RH—even in a specialist hypertension unit—and that a thorough diagnostic work-up is essential for appropriate patient selection. Moreover, the risk associated with this invasive procedure also depends on the careful selection of patients eligible for RDN as well as the experience of the radiologist/cardiologist conducting the intervention. Finally, further evaluation of this technique is still required in large, correctly designed clinical trials, with ambulatory BP as the primary endpoint.

Sébastien Savard, MD, MSc
Michael Frank, MD, MSc
Guillaume Bobrie, MD
Pierre-François Plouin, MD
Marc Sapoval, MD, PhD
***Michel Azizi, MD, PhD**

*Vascular Medicine and Hypertension Unit
Hôpital Européen Georges Pompidou
20 rue Leblanc
75015 Paris
France
E-mail: michel.azizi@egp.aphp.fr

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Please note: Drs. Frank, Bobrie, Plouin, Sapoval, and Azizi were investigators in the Symplicity HTN-2 (Renal Denervation in Patients With Uncontrolled Hypertension) trial (ARDIAN, Inc.) and are participating in the REDUCE-HTN protocol (Vessix Vascular, Inc., Laguna Hills, California). Dr. Azizi has served as a consultant for Vessix Vascular, Inc. and Cordis. Dr. Sapoval has served as a consultant for Vessix Vascular, Inc., Cordis, and St. Jude Medical and is a member of the advisory board of ReCord Medical. Dr. Savard has received financial support from la Société Québécoise d'Hypertension Artérielle, la Société Québécoise de Néphrologie, and La Faculté de Médecine de l'Université Laval (McLaughlin Scholarship Program) for his post-doctoral fellowship.

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Letters to the Editor

The Impact of Treatment on the Pathophysiologic Mechanisms Linking Coronary Heart Disease and Depression

We would like to congratulate Blumenthal et al. (1) for their interesting paper recently published in the *Journal* in which patients with coronary heart disease (CHD) and depression symptoms treated with aerobic exercise reached significantly greater reduction in depression symptoms as compared with the control group. This reduction in depression symptoms is comparable to the sertraline group (1). However, some issues should be addressed. First, in the Results section, the authors stated that sertraline and exercise had a null effect on flow-mediated dilation (FMD). Conversely, in Table 2, the sertraline group showed an improvement in FMD (+1.5%; before treatment 2.6%, after treatment 4.1%) (1). The association between the treated group and improvement in depression symptoms, the autonomic nervous system, FMD, and other markers will be assessed by a 2-sided test (2). This test provides objective information on evaluating the effects of interventions in clinical trials. This clinical trial confirms a recent randomized controlled trial that sertraline improved FMD in those CHD patients treated with 85% statins (3). The data of this study demonstrated vascular endothelial dysfunction in CHD, and depression symptoms might be improved beyond the effects of statins. Nevertheless, the authors did not comment on it in the Discussion section. Second, Blumenthal et al. (1) found that physical activity during daily life was associated with significantly less sympathetic nervous system activity as measured by the standard deviation of the normal-to-normal R-R intervals as compared with the sertraline group and the placebo group. This beneficial effect on the autonomic nervous system does not have a

notable effect on the endothelial function. This contrasts with other studies that have demonstrated that physical activity enhances FMD (4). To measure altered cardiac autonomic tone, the authors used time-domain components of heart rate variability. In the Results section, they only gave the standard deviation of the normal-to-normal R-R intervals. Did they evaluate other indices of both the parasympathetic and the sympathetic tone?

***Carmine Pizzi, MD**
Luigi Santarella, MD
Grazia Maria Costa, MD
Raffaele Bugiardini, MD

*Department of Specialistic, Diagnostic and Experimental Medicine
Padiglione 11
University di Bologna
Via Giuseppe Massarenti 9
40138 Bologna
Italy
E-mail: carmine.pizzi@unibo.it

http://dx.doi.org/10.1016/j.jacc.2012.09.012

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Reply

We thank Dr. Pizzi and colleagues for their interest in our paper (1) and agree that it is perplexing that although both active treatments (exercise and sertraline) resulted in improved depression symptoms, some of our hypothesized mechanisms of risk associated with depression did not show corresponding improvements. We had hypothesized that the active treatments would result in improved flow-mediated dilation (FMD), but as shown in Table 2 of our paper, a priori contrasts between the 2 active treatments versus placebo and between exercise versus sertraline were not statistically significant. Because several research teams, including our own, have reported previously that impaired FMD is associated with depression in cardiac patients (2), and that exercise training resulted in improved FMD (3), we were surprised by these findings; but as noted in our Discussion, we have no ready explanation for our failure to confirm these prior observations in the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) trial. Our small sample size and the apparent failure of the randomization procedure to achieve balance for baseline FMD between treatment groups may have been contributing factors. Although the sertraline group appears to show post-treatment improvements in FMD, this observation was not statistically significant. Nonetheless, we agree that in our study, the observed direction of change in FMD associated with sertraline treatment is consistent with the observations reported by Pizzi et al. (4).

In addition to standard deviation of normal-to-normal R-R intervals (SDNN), which was our primary biomarker of coronary heart disease risk and main measure of heart rate variability (HRV), the letter by Pizzi et al. (4) suggested that we consider additional time and frequency domain measures of HRV. As seen in Table 1, we found similar improvements in HRV measured from the standard deviation of the average R-R intervals over 5-min segments and from total power and ultra-low–frequency power, but not from high-frequency power. An association between physical activity and these slower variations in heart rate has been documented previously (5,6) and is consistent with greater activity levels and more frequent changes in posture in patients who underwent exercise training. We note that none of the HRV measures was significantly changed in the placebo group or the sertraline-treated group.

***James A. Blumenthal, PhD**
Andrew Sherwood, PhD
Lana L. Watkins, PhD
Alan Hinderliter, MD

*Department of Psychiatry and Behavioral Sciences
Box 3119
Duke University Medical Center
Durham, NC 27710
E-mail: blume003@mc.duke.edu

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Table 1 Time-Domain and Frequency-Domain HRV Before and After Treatment

	Exercise		Sertraline		Placebo	
	Before	After	Before	After	Before	After
Time domain HRV indices						
SDANN, ms	104 ± 32	118 ± 38*	104 ± 32	104 ± 33	107 ± 27	107 ± 31
Frequency domain HRV indices						
Total power, ln ms^2	9.3 ± 0.6	9.5 ± 0.7*	9.2 ± 0.7	9.2 ± 0.6	9.3 ± 0.5	9.4 ± 0.6
ULF power, ln ms^2	9.1 ± 0.7	9.3 ± 0.8*	9.0 ± 0.8	9.1 ± 0.7	9.1 ± 0.5	9.2 ± 0.6
HF power, ln ms^2	4.6 ± 1.1	4.8 ± 1.1	4.9 ± 1.1	4.7 ± 1.2	4.5 ± 1.2	4.4 ± 1.4

Values are mean ± SD. *A p value <0.05 reflects the contrast between values before and after treatment.
HF = high frequency; SDANN = standard deviation of the average R-R intervals over 5-min segments; ULF = ultra-low frequency.