as differences in standards of care and methodologic expertise in the conduct of clinical trials.

The most anomalous finding in the TOPCAT trial is the low event rate in the hospitalization stratum, which reduced the potential for a benefit of spironolactone therapy in this subgroup. In previous trials, a history of hospitalization for heart failure has been predictive of high event rates, even in heart failure with a preserved ejection fraction. In the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE), the overall rate of death from cardiovascular causes or hospitalization for heart failure (a composite outcome similar to that in the TOPCAT trial) was 6.84 per 100 patient-years; it was 10.47 per 100 patient-years among patients with a hospitalization for heart failure in the previous 6 months, as compared with 4.38 per 100 patient-years among those without such a hospitalization with a history of hospitalization for heart failure in the previous 6 months, as compared with 4.38 per 100 patient-years among those without such a hospitalization (with data derived from Fig. 2 of the article). The wording of the hospitalization inclusion criterion in the TOPCAT trial, which differed from that in previous trials, may therefore have been important. Indeed, we wonder whether some of the patients in the hospitalization stratum actually had heart failure with a preserved ejection fraction, not least because this is a diagnosis that is not straightforward and that relies on the ruling out of other potential causes of dyspnea and edema.

These observations suggest that investigators in future trials should specify more precisely what they mean by hospitalization for heart failure and may wish to verify the details of such admissions, at least in a proportion of cases, as well as monitor event rates according to inclusion stratum and region during follow-up. The TOPCAT trial also underscores the importance of natriuretic peptide levels as a predictor of adverse outcomes in heart failure and their value as an inclusion and quality criterion in clinical trials, nowhere more so than in heart failure with a preserved ejection fraction, which remains difficult to define.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); and Duke University Medical Center, Durham, NC (C.O.).

1. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol 2012; 60:2349-56.
2. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-69. [Erratum, Eur J Heart Fail 2013;15:361-2.]

DOI: 10.1056/NEJMe1401231
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Renal Denervation for Resistant Hypertension?
Franz H. Messerli, M.D., and Sripal Bangalore, M.D.

Ever since Schlaich et al. first reported on a patient with a blood pressure of 161/107 mm Hg (despite treatment with seven different antihypertensive drugs) that decreased to 127/81 mm Hg after renal denervation, the medical community has been enamored with this procedure. Resistant hypertension evolved into a fashionable diagnosis, and the number of publications pertaining to it grew rapidly. Medical-device companies fancied renal denervation as the next big innovation and as a blockbuster therapy for millions of patients. A press release from the American Heart Association even touted renal denervation as a potential “cure” for mild hypertension.
als such as the SYMPLICITY HTN-1\(^4\) and HTN-2\(^5\) studies showed impressive decreases in blood pressure, seemingly attesting to the efficacy and safety of renal denervation. Three-year follow-up of the SYMPLICITY HTN-1 study revealed a decrease in blood pressure of 32/14 mm Hg.\(^6\) These unprecedented results seemed to surpass what was achievable with drug therapy and continued to fan the flames of renal denervation.

The SYMPLICITY HTN-3 study, a blinded, sham-controlled study now reported in the Journal by Bhatt et al.,\(^7\) brings the renal-denervation train to a grinding halt. After 6 months, office systolic blood pressure decreased from baseline to a similar extent in the renal-denervation and sham-procedure groups (P<0.001 for both comparisons of the change from baseline); the difference in the change in blood pressure between the two groups was a paltry −2.39 mm Hg (Table 1). In addition, a prespecified difference in 24-hour ambulatory systolic pressure of only 2 mm Hg was not met. Thus, in the SYMPLICITY HTN-3 study, renal denervation had no significant effect on office or 24-hour ambulatory systolic blood pressure, findings that contradict most published data on renal denervation, although a recent trial even suggested inferiority of renal denervation, as compared with adjusted drug treatment.\(^8\)

At first blush, the most likely explanation for the findings of the SYMPLICITY HTN-3 study is the inclusion of a sham-control group. In clinical trials testing interventional procedures and medical devices, sham procedures are seminal, analogous to the use of a placebo in pharmaceutical trials. However, for ethical reasons sham procedures are frowned upon\(^9\); neither the SYMPLICITY HTN-1 study nor the HTN-2 study had a sham-control cohort. For this reason, placebo effects may well explain all or most of the blood-pressure differences noted in the first two trials. Lack

### Table 1. Selected Findings of the SYMPLICITY HTN-2 and HTN-3 Studies.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SYMPLICITY HTN-2</th>
<th>SYMPLICITY HTN-3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renal Denervation</td>
<td>No Renal Denervation</td>
</tr>
<tr>
<td>No. of patients</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>No. of antihypertensive medications at baseline</td>
<td>5.2±1.5</td>
<td>5.3±1.8</td>
</tr>
<tr>
<td>Aldosterone antagonist at baseline (% of patients)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Office systolic blood pressure at baseline (mm Hg)</td>
<td>178±18</td>
<td>178±16</td>
</tr>
<tr>
<td>Heart rate at baseline (beats/min)</td>
<td>75±15</td>
<td>71±15</td>
</tr>
<tr>
<td>Absolute change in office systolic blood pressure at 6 mo (mm Hg)</td>
<td>−32±23</td>
<td>1±21</td>
</tr>
<tr>
<td>Change relative to control group</td>
<td>−33</td>
<td>−2.4</td>
</tr>
<tr>
<td>Change in office systolic blood pressure at 6 mo (mm Hg)</td>
<td>−20±17</td>
<td>2±21</td>
</tr>
<tr>
<td>Change relative to control group</td>
<td>−22</td>
<td>−1.3</td>
</tr>
<tr>
<td>Change in 24-hr ambulatory systolic blood pressure at 6 mo (mm Hg)</td>
<td>−11±15</td>
<td>−3±19</td>
</tr>
<tr>
<td>Change relative to control group</td>
<td>−8</td>
<td>−1.96</td>
</tr>
<tr>
<td>Decrease in dose or no. of medications</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Increase in dose or no. of medications</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. NR denotes not reported.
† In the SYMPLICITY HTN-2 study, data were available for 32 patients who underwent renal denervation and 40 patients who did not.
‡ In the SYMPLICITY HTN-2 study, data were available for 20 patients who underwent renal denervation and 25 patients who did not.
of efficacy could also be caused by incomplete or ineffective denervation. No reliable markers of renal denervation are available, and questions remain as to what exactly the procedure accomplishes. Nevertheless, the ablation catheter used in the SYMPLICITY HTN-3 study was no different from that used in the SYMPLICITY HTN-1 and HTN-2 studies.

A decrease in systolic blood pressure was observed in both the renal-denervation group and the control group, a finding that is in marked contrast to the findings in previous trials. At 6 months, the decrease in office systolic blood pressure from baseline in the renal-denervation group in the SYMPLICITY HTN-3 study was about half that observed in the corresponding group in the SYMPLICITY HTN-2 study, despite the fact that baseline blood pressures were similar in the two studies. This is puzzling, because the degree of reduction in blood pressure is related to pretreatment blood-pressure levels (unpublished data). In addition, there was a larger decrease in blood pressure in the control group of the SYMPLICITY HTN-3 study, as compared with the meager decrease in the SYMPLICITY HTN-2 study. Is it conceivable that greater exposure to spironolactone in the SYMPLICITY HTN-3 study facilitated this decrease (and possibly contributed to a neutral outcome)?

Could we have predicted the outcome of the SYMPLICITY HTN-3 study? The standard deviations of the change in office systolic blood pressure from baseline in both study groups in both trials were remarkably similar, indicating a wide variation in response. In fact, in the SYMPLICITY HTN-2 study, the change in blood pressure from baseline in 95% of patients was between −78 mm Hg and 14 mm Hg in the renal-denervation group and between −43 mm Hg and 41 mm Hg in the control group. The mean blood-pressure reduction in the SYMPLICITY HTN-3 study is well within this range for both study groups. The wide variability in response to renal denervation begs the question of whether this procedure could be more efficacious in selected patients with increased sympathetic drive only, such as those with heart failure. Regardless of this conjecture, the SYMPLICITY HTN-3 study certainly has raised the bar.

To be enrolled in a study, patients need to fulfill predefined blood-pressure criteria on a particular day. Patients whose blood pressure is above their usual average will preferentially be enrolled. Thus, subsequent blood-pressure measurements are prone to be lower regardless of whether there was an intervention. This phenomenon, although unlikely to fully explain the differences in blood-pressure decrease among various studies, occurs only when inclusion criteria require a certain blood-pressure level. It should not be confused with regression to the mean or a placebo effect, both of which could also have contributed to the uneven blood-pressure response in the SYMPLICITY trials. Indeed, regression to the mean was probably responsible for a less extreme decrease in office systolic blood pressure in the renal-denervation group and a more impressive decrease in the control group, as compared with changes observed in prior studies.

Exuberance about renal denervation has been widespread, as is illustrated by these statements: “The potential of renal denervation is enormous” and it “may be used not only to treat hypertension, but also . . . diseases that are characterized by high sympathetic activity such as diabetes and hyperinsulinemia, heart failure, arrhythmias, and chronic kidney disease.” These words, thoroughly referenced, tout the benefits of renal denervation in these metabolic or cardiovascular disorders. In contrast, the conclusions of the SYMPLICITY HTN-3 study by one of the same authors now 6 months later soberly state that “a significant effect on systolic blood pressure was not observed. Further evaluation in rigorously designed clinical trials will be necessary . . . to confirm previously reported benefits of renal denervation in patients with resistant hypertension.” Should this statement indeed hold true, we will have to come to grips with two facts: the SYMPLICITY studies merely document the natural history of resistant hypertension in clinical trials, and the time has come to turn the page on renal denervation for hypertension but by all means, let’s not close the book.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Division of Cardiology, Mount Sinai Roosevelt Hospital, Icahn School of Medicine (F.H.M.), and the Leon H. Charney Division of Cardiology, New York University School of Medicine (S.B.) — both in New York.

This article was published on March 29, 2014, at NEJM.org.

Fibrinolysis of Pulmonary Emboli — Steer Closer to Scylla

C. Gregory Elliott, M.D.

According to Homer, Odysseus was forced to choose whether to steer his ship closer to Scylla, a six-headed sea monster, or Charybdis, a ship-swallowing whirlpool. Odysseus steered closer to Scylla, risking the loss of a few sailors, rather than risking an entire ship and crew.

Much like Odysseus, the physician treating a patient with acute pulmonary embolism occasionally must navigate treacherous waters. The risk of fatal thromboembolism stands on one side, and the risk of fatal bleeding lies just opposite. Unlike Odysseus, the physician has empirical evidence to guide decisions, but tragic outcomes occur sometimes, no matter how carefully the physician navigates.

Acute pulmonary embolism is a common disorder with a wide clinical spectrum. Current estimates suggest that physicians diagnose pulmonary embolism in more than 200,000 patients annually in the United States.¹ Anticoagulant agents provide effective and safe treatment for the majority of patients with acute pulmonary embolism.² However, in a subgroup of patients with pulmonary emboli, the risk of death is increased despite anticoagulant treatment. Therefore, current practice embraces risk stratification of patients with pulmonary embolism, so that higher-risk therapies are offered to patients with the greatest chance of benefit.³

Not surprisingly, physicians have long recognized that hypotension or cardiac arrest predicts high early mortality (>15%) associated with acute pulmonary embolism.⁴ Authors of evidence-based guidelines suggest that such patients undergo systemic fibrinolysis when a high risk of bleeding is not present.² The absence of hemodynamic decompensation identifies patients who are unlikely to die from pulmonary embolism if they receive anticoagulant therapy promptly. The size of the emboli does not predict risk. In this regard, the terms massive and submassive pulmonary embolism can mislead physicians.

Controversy remains over the role of fibrinolysis among normotensive patients with an intermediate risk of death after acute pulmonary embolism. Investigators have suggested that right ventricular dysfunction detected with echocardiography, myocardial injury defined by elevated biomarker levels, and the absence of hypotension characterize this intermediate-risk group.⁵ The increased risk of fatal bleeding conferred by fibrinolysis and uncertainty about the risk of death among patients with right ventricular dysfunction and myocardial injury have fueled debates about the treatment of such patients.⁶,⁷

In this issue of the Journal, Meyer et al. report the main results of the Pulmonary Embolism Thrombolysis (PEITHO) trial.⁸ In the PEITHO trial, investigators at 76 centers randomly assigned 1006 patients who had acute pulmonary embolism and right ventricular dysfunction, as well as a positive cardiac troponin test, to initial treatment with anticoagulants and fibrinolysis or with anticoagulants and placebo. The primary end point of death or hemodynamic decompensation within 7 days after randomization oc-