

## ORIGINAL ARTICLE

# Health-related quality of life in persons with apparent treatment-resistant hypertension on at least four antihypertensives

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Little is known about the impact of treatment-resistant hypertension (TRH) on health-related quality of life (HrQoL). We aimed to compare HrQoL measures in adults with apparent TRH (aTRH) and non-resistant hypertension among nationally representative US Medical Expenditure Panel Survey data pooled from 2000 to 2011. Cohorts compared were adults with aTRH ( $\geq 2$  unique fills from  $\geq 4$  antihypertensive classes during a year) versus non-resistant hypertension (those with hypertension not meeting the aTRH definition). Key outcomes were cohort differences in SF-12v2 physical component summary (PCS) and mental component summary (MCS) scores and disease-state utility using the SF-6D. Of 57 150 adults with hypertension, 2501 (4.4%) met criteria for aTRH. Persons with aTRH, compared with non-resistant hypertension, were older (mean, 68 vs 61 years), had a higher BMI (30.9 vs 29.7 kg m<sup>-2</sup>) and were more likely to be Black (20% vs 14%), but less likely to be female (46% vs 54%). Persons with aTRH, compared with non-resistant hypertension, had lower mean PCS scores (35.8 vs 43.2;  $P < 0.0001$ ), and utility (0.68 vs 0.74;  $P < 0.0001$ ), but similar MCS scores (49.1 vs 50.4). In multivariable-adjusted analyses, aTRH was associated with a 2.37 (95% CI 1.71 to 3.02) lower PCS score and 0.02 (95% CI 0.01 to 0.03) lower utility, compared with non-resistant hypertension. In conclusion, aTRH was associated with substantially lower HrQoL in physical functioning and health utility, but not in mental functioning, compared with non-resistant hypertension. The multivariable-adjusted reduction in physical functioning was similar in magnitude to previous observations comparing hypertension with no hypertension.

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## INTRODUCTION

Hypertension affects an estimated 1 billion adults worldwide and is the leading risk factor for major adverse cardiovascular events and death.<sup>1,2</sup> Up to 16 million Americans are thought to have treatment-resistant hypertension (TRH), typically defined as uncontrolled blood pressure (BP) on  $\geq 3$  antihypertensive drugs, or the use of  $\geq 4$  drugs regardless of BP control (or more simply, requiring  $\geq 4$  antihypertensive drugs to achieve BP control).<sup>3</sup> Moreover, the prevalence of TRH has more than doubled, from ~9% in 1988–1994 to 21% in 2005–2008 according to data from the National Health and Nutrition Examination Survey (NHANES).<sup>3</sup> Importantly, emerging evidence demonstrates that TRH is associated with a substantially increased risk of major adverse outcomes, including stroke, myocardial infarction, end-stage renal disease, cardiovascular mortality and all-cause mortality, compared with non-resistant hypertension.<sup>4–11</sup>

Studies have demonstrated a small but significant decrement in health-related quality of life (HrQoL) associated with hypertension relative to no hypertension.<sup>12</sup> Yet, almost nothing is known of HrQoL in the high-risk group of patients with TRH. This lack of humanistic outcome data in patients with TRH constitutes a major gap in the literature,<sup>13</sup> and is consistent with the relative dearth of humanistic outcomes research in cardiovascular disorders more generally.<sup>14</sup> Accordingly, we aimed to compare HrQoL measures between patients with apparent TRH (aTRH) versus those with

non-resistant hypertension in a nationally representative US adult population. The term aTRH was used to encompass those with true TRH and those with pseudoresistant hypertension since this clinically meaningful phenotype clearly identifies a subpopulation with elevated risk for adverse outcomes. We hypothesized that, compared with non-resistant hypertension, aTRH would be associated with incrementally lower HrQoL.

## MATERIALS AND METHODS

We analyzed publically available anonymous data from the US Medical Expenditure Panel Survey (MEPS), a multiyear, large-scale panel database that tracks individual health-care use and socioeconomic characteristics in a series of cross-sectional panels. The sampling frame for the MEPS Household Component is drawn from respondents to the National Health Interview Survey, which provides a nationally representative sample of the US civilian non-institutionalized population. Pooling MEPS data from 2000 to 2011 allowed for aTRH and non-resistant hypertension cohorts of robust sample size sufficient for making US national estimates. Participants in MEPS were included in this analysis if they were aged  $\geq 18$  years and had at least one diagnosis code for hypertension at any time during the interview year (either from survey responses or provider records). Participants with hypertension were then categorized into two mutually exclusive groups: (1) aTRH, those with  $\geq 2$  unique prescription fills from  $\geq 4$  different antihypertensive classes during a single panel; or, (2) non-resistant hypertension, all other included persons with diagnosed

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**Table 1.** Baseline demographic and socioeconomic characteristics

Characteristic	Non-Resistant Hypertension (n = 54 649)	Apparent TRH (n = 2501)	P-value
Female	54.4%	46.3%	< 0.001
Age, years	61.0 ± 0.2	67.8 ± 0.4	< 0.001
Race/ethnicity			
White	80.3%	75.4%	< 0.001
Black	14.4%	20.1%	< 0.001
American Indian	0.76%	0.77%	0.99
Other	4.6%	3.7%	0.1
Hispanic	8.6%	6.1%	< 0.001
Educational attainment			
No degree	18.9%	24.4%	< 0.001
High school	51.2%	51.5%	0.85
Bachelor	21.8%	17.8%	0.001
Master/doctorate	8.1%	6.3%	0.015
Income			
Poor	11.0%	12.6%	0.03
Near poor	5.0%	6.6%	0.009
Low income	14.6%	19.0%	< 0.001
Middle income	30.3%	30.4%	0.91
High income	39.2%	31.4%	< 0.001
BMI, kg m <sup>-2</sup>	29.7 ± 0.06	30.9 ± 0.2	< 0.001
Co-morbidity burden total <sup>a</sup>	3.5 ± 0.02	5.0 ± 0.08	< 0.001
Smoker	16.1%	13.5%	0.012

Abbreviations: BMI, body mass index; TRH, treatment-resistant hypertension. Data represent % or mean ± s.e.m. <sup>a</sup>Co-morbidity burden represents the total number of chronic conditions for each individual, calculated according to Clinical Classification Categories codes.

hypertension. The cohort definition for aTRH was based on antihypertensive medication use but not BP since BP data were not available in MEPS. Antihypertensive classes included angiotensin-converting enzyme (ACE) inhibitors; angiotensin II inhibitors; renin inhibitors; aldosterone receptor antagonists; diuretics; vasodilators; calcium channel blockers;  $\beta$ -adrenergic blockers;  $\alpha$ -adrenergic antihypertensives; and single-pill fixed-dose combination antihypertensives. To account for possible misclassification, we also performed a sensitivity analysis excluding all patients taking exactly three antihypertensive drugs from the non-resistant hypertension group.

Two leading HrQoL measures were used for humanistic outcome assessment: Short Form 12 version 2 (SF-12v2) and Short-Form Six-Dimension Utility Index (SF-6D).<sup>15,16</sup> Data from the SF-12v2 were disaggregated into a Physical Component Summary (PCS) score and Mental Component Summary (MCS) score. The PCS and MCS scores are each linearly transformed into norm-based scores with a mean of 50 and s.d. of 10. A one-half s.d. deviation from the norm (that is, five points from mean) is interpreted as a clinically meaningful reduction in HrQoL.<sup>17</sup> The SF-6D health utility is a preference-based score derived from SF-12v2 scores, and is used to estimate a preference-based single index measure of health utility.<sup>16</sup> The health utility can be used to calculate quality-adjusted life years that are used in cost-effectiveness analyses.

Descriptive comparisons between groups were performed with independent *t*-tests for continuous variables and  $\chi^2$  for categorical variables. For dependent variables, unadjusted means and s.e. values were compared using the adjusted Wald *F* test. Linear regression models were fit for the three outcome variables (SF-12v2 PCS, MCS, SF-6D). Independent variables for these models included aTRH, age, gender, geographic region, race, ethnicity, socioeconomic status, level of education, smoking status, BMI category (underweight (BMI < 18.5 kg m<sup>-2</sup>), normal (BMI 18.5–24.9 kg m<sup>-2</sup>), overweight (BMI 25–29.9 kg m<sup>-2</sup>), obese (BMI ≥ 30 kg m<sup>-2</sup>)), presence of relevant comorbidities (diabetes, acute myocardial infarction, chronic heart failure, stroke or chronic kidney disease), overall comorbidity burden and insurance status as collected in MEPS. As a sensitivity analysis, a Tobit regression model was fit for SF-6D

**Table 2.** Frequency of antihypertensive class used according to hypertension status

Antihypertensive class	Non-resistant hypertension (n = 54 649)	Apparent TRH (n = 2501)
ACE inhibitors	15 860 (29.02%)	1613 (64.49%)
Diuretics	12 087 (22.12%)	2022 (80.85%)
Calcium channel blockers	9705 (17.76%)	1814 (72.53%)
$\beta$ -blockers	14 786 (27.06%)	2132 (85.25%)
Angiotensin receptor blockers	5473 (10.01%)	790 (31.59%)
Antiadrenergic agents, peripherally acting	2084 (3.81%)	626 (25.03%)
Antiadrenergic agents, centrally acting	991 (1.81%)	590 (23.59%)
Vasodilators	178 (0.33%)	261 (10.44%)
Renin inhibitors	66 (0.12%)	31 (1.24%)
Aldosterone receptor antagonists	3 (0.01%)	9 (0.36%)
Antihypertensive combinations	12 283 (22.48%)	738 (29.51%)

Abbreviations: ACE, angiotensin converting enzyme; TRH, treatment-resistant hypertension.

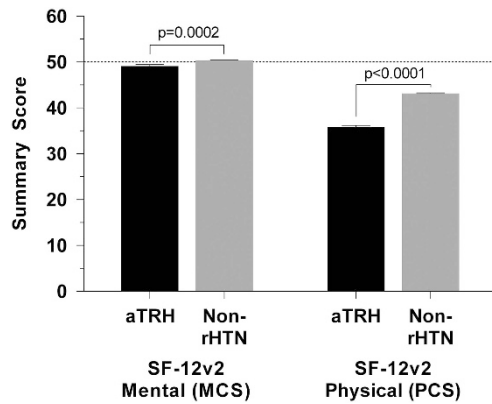
with the same candidate variables to address censoring. A *P*-value < 0.05 was considered statistically significant. Weighted data were analyzed using STATA version 11 (StataCorp LP, College Station, TX, USA).

## RESULTS

We identified a cohort of 57 150 adults with hypertension in MEPS, of which 2501 (4.4%) met inclusion criteria for aTRH. Patient characteristics are summarized in Table 1. Persons with aTRH, compared with non-resistant hypertension, were significantly older (mean age, 67.8 vs 61.0 years) and more likely to be Black (20% vs 14%), but less likely to be female (46% vs 54%) or Hispanic (6% vs 9%). In addition, those with aTRH had a significantly greater comorbidity burden (mean number of chronic conditions, 5.0 vs 3.5) and a higher mean BMI (30.9 vs 29.7 kg m<sup>-2</sup>).

Antihypertensive use by cohort is summarized in Table 2. As expected, frequency of use of each antihypertensive class was higher for the aTRH cohort compared to the non-resistant hypertension cohort. The three most common antihypertensive classes in those with aTRH were  $\beta$ -blockers (85%), diuretics (81%) and calcium channel blockers (73%). In those with non-resistant hypertension, the most frequently used classes were ACE-inhibitors (29%),  $\beta$ -blockers (27%) and diuretics (22%). Fixed-dose antihypertensive combination pills were reported in 30% of those with aTRH and 22% of those with non-resistant hypertension. Fewer than 1% of persons in either group used aldosterone antagonists.

Regarding HrQoL, average PCS and MCS scores, by cohort, are summarized in Figure 1. We observed a statistically significant (given the large sample size) but not clinically meaningful difference in mean MCS score for persons with aTRH (mean ± s.e., 49.1 ± 0.3) versus those with non-resistant hypertension (50.4 ± 0.08). Neither score represented a clinically meaningful difference from national norms (that is, 50). In contrast, PCS scores were significantly reduced in both groups: those with aTRH had a mean PCS score of 35.8 ± 0.4, compared with 43.2 ± 0.1 for those with non-resistant hypertension, for a between-group difference of 7.3 (*P* < 0.0001). Interestingly, an inverse relationship was observed between mean PCS score and number of antihypertensive medications, such that greater antihypertensive use was linked to lower mean PCS score (Figure 2, top panel). In the multivariable model, aTRH was associated with a net



**Figure 1.** Unadjusted mean SF-12v2 mental component summary (MCS) and physical component summary (PCS) score, comparing apparent treatment-resistant hypertension and non-resistant hypertension. Data are presented as mean SF-12v2 mental and physical component summary scores; error bars represent standard error of the mean. The hashed line represents the normed score of 50 for the SF-12v2 component summary scores. aTRH, apparent treatment-resistant hypertension; non-rHTN, non-resistant hypertension.

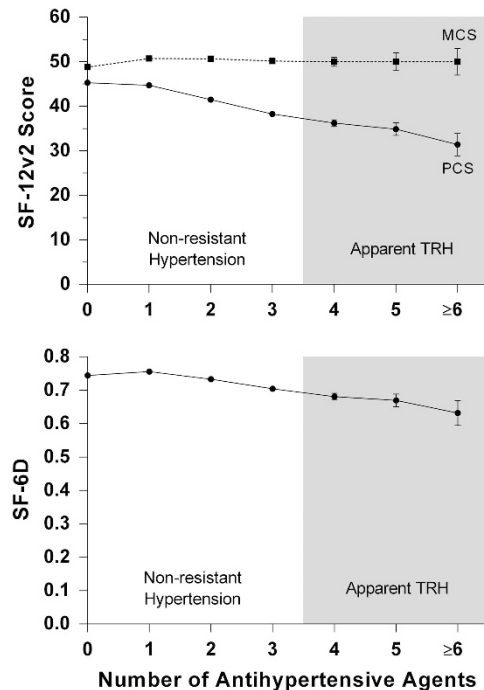
difference of  $-2.37$  (95% CI  $-3.02$  to  $-1.71$ ;  $P < 0.0001$ ) for the PCS score and  $-0.12$  (95% CI  $-0.73$  to  $0.49$ ;  $P = 0.69$ ) for the MCS score. The full models for MCS and PCS scores are reported in Table 3. Independent predictors of lower PCS score included aTRH, increasing age, female sex, geographic region (South or West), BMI  $< 18.5$  or  $\geq 30 \text{ kg m}^{-2}$ , lower education level, lower income level, smoking, specific co-morbidities and total comorbidity burden; these variables accounted for 32% of the variance in PCS score. The sensitivity analysis, excluding persons with exactly three antihypertensive drugs from the non-resistant hypertension group revealed remarkably similar results (data not shown).

Unadjusted mean utility (SF-6D) was lower for persons with aTRH (mean  $\pm$  s.e.,  $0.68 \pm 0.005$ ) compared with those with non-resistant hypertension ( $0.74 \pm 0.001$ ), for a mean difference of  $0.06$  ( $P < 0.0001$ ). As with PCS score, an inverse relationship was observed between mean SF-6D score and number of antihypertensive medications (Figure 2, bottom panel). After multivariable adjustment, SF-6D score was  $0.02$  (95% CI  $0.01$ – $0.03$ ;  $P < 0.0001$ ) lower for persons with aTRH compared with those with non-resistant hypertension (Table 3). Sensitivity analyses using Tobit regression revealed no appreciable difference in these findings (data not shown). Likewise, the sensitivity analysis excluding all patients with three antihypertensive drugs from the non-resistant hypertension group showed no appreciable differences (data not shown).

## DISCUSSION

Treatment-resistant hypertension represents a challenging and increasingly common subset of hypertension. Although TRH has been associated with a greater risk of important adverse sequelae compared with non-resistant hypertension or no hypertension, scarce data exist on associations of TRH with humanistic outcomes like HrQoL. We compared measures of HrQoL for cohorts with aTRH versus non-resistant hypertension, using nationally representative MEPS data from 2000 through 2011. We observed a clinically significant decrement in physical HrQoL and health utility for patients with aTRH, but no similar decrement in mental HrQoL. These findings begin to address an important gap on humanistic outcomes research.<sup>13,14</sup>

We observed a meaningful reduction in physical HrQoL among those with aTRH relative to the healthy norm (50) and relative to persons with non-resistant hypertension (mean, 43). Existing



**Figure 2.** Relationship between number of antihypertensive medications used and SF-12v2 mean component summary scores (top panel) and health utility as assessed by SF-6D score (bottom panel). MCS, mental component summary; PCS, physical component summary; TRH, treatment-resistant hypertension.

evidence has shown lower physical HrQoL in persons with any hypertension compared with those without hypertension. A recent meta-analysis of 20 studies found that hypertension was associated with a modest decrement on HrQoL across all subdomains, including PCS ( $-2.43$ ; 95% CI  $-4.77$  to  $-0.08$ ) and MCS ( $-1.68$ ; 95% CI  $-2.14$  to  $-1.23$ ) scores.<sup>12</sup> The difference in PCS score observed in that meta-analysis is similar to the adjusted mean difference we observed ( $-2.37$ ), suggesting that aTRH may be associated with a similar incremental adverse effect on HrQoL as that seen with hypertension over no hypertension.

Although the mechanism by which TRH may decrease HrQoL is unknown, three plausible pathways might be considered independently or concurrently. First, numerous studies have observed the relatively frequent coexistence of aTRH and other vascular diseases (for example, diabetes, heart failure, CKD);<sup>3,7,10</sup> these comorbidities are known to have a detrimental effect on HrQoL.<sup>6,7,10,18–20</sup> However, our finding of an attenuated but significant PCS score after adjustment for these comorbidities suggests that the link between reduced HrQoL and aTRH may be only partially explained by the greater prevalence of these conditions in persons with aTRH. Second, studies suggest that reductions in HrQoL among persons with hypertension are attributable to awareness of hypertension, rather than elevated BP, *per se*.<sup>21–23</sup> Although health-care providers are unlikely to convey to patients an explicit diagnosis of TRH, a similar effect may be at play whereby patients with aTRH have greater awareness of their difficult-to-control hypertension due to advancing medication regimens to control BP. This mechanism is consistent with observations that HrQoL measures are low in persons with high medication use and who consider themselves ill.<sup>24,25</sup> Third, among patients with hypertension, HrQoL appears to be lower in those taking at least one antihypertensive medication compared with patients taking no antihypertensive medications, regardless of actual BP.<sup>21</sup> Health-related quality of life decreases as

**Table 3.** Independent predictors of SF-12v2 physical and mental component summary scores and health utility

Parameter	Physical score (SF-12v2 PCS)		Mental score (SF-12v2 MCS)		Health utility (SF-6D)	
	$\beta$	P-value	$\beta$	P-value	$\beta$	P-value
aTRH (vs no aTRH)	-2.37	< 0.0001	-0.12	0.69	-0.019	< 0.0001
Age, years (reference: 18–34)						
35–49	-2.44	< 0.0001	0.58	0.1	-0.015	0.002
50–64	-4.45	< 0.0001	2.55	< 0.0001	-0.015	< 0.0001
65–79	-5	< 0.0001	6.07	< 0.0001	0.013	0.004
$\geq 80$	-8.42	< 0.0001	6.2	< 0.0001	-0.017	0.001
Female (vs male)	-0.77	< 0.0001	-0.48	< 0.0001	-0.014	< 0.0001
Race (reference: White)						
Black	0.005	0.98	-0.08	0.63	0.002	0.34
American Indian	-1.6	0.035	0.21	0.74	-0.003	0.75
Other	0.049	0.86	-0.86	0.001	-0.007	0.056
Hispanic (vs non-Hispanic)	0.82	< 0.0001	-1.42	< 0.0001	-0.008	0.006
Region (reference: Northeast)						
Midwest	-0.4	0.054	0.59	0.003	0.0005	0.86
South	-1.36	< 0.0001	0.17	0.33	-0.008	0.001
West	-1.08	< 0.0001	0.06	0.75	-0.01	< 0.0001
BMI, kg m <sup>-2</sup> (reference: 18.5–24.9)						
< 18.5	-3.81	< 0.0001	-2.31	< 0.0001	-0.042	< 0.0001
25–30	-0.29	0.078	0.52	< 0.0001	0.002	0.33
$\geq 30$	-2.84	< 0.0001	0.26	0.085	-0.02	< 0.0001
Education level (reference: no degree)						
High school	1.36	< 0.0001	1.46	< 0.0001	0.017	< 0.0001
Bachelors	2.81	< 0.0001	2.02	< 0.0001	0.027	< 0.0001
Masters/doctorate	3.81	< 0.0001	1.87	< 0.0001	0.033	< 0.0001
Socioeconomic level (reference: Poor)						
Near poor	0.89	0.003	1.33	< 0.0001	0.019	< 0.0001
Low income	1.59	< 0.0001	1.6	< 0.0001	0.027	< 0.0001
Middle income	3.07	< 0.0001	2.82	< 0.0001	0.05	< 0.0001
High income	4.43	< 0.0001	3.9	< 0.0001	0.07	< 0.0001
Insurance (reference: Private insurance)						
Public insurance	-2.92	< 0.0001	-2.25	< 0.0001	-0.041	< 0.0001
Uninsured	-1.42	< 0.0001	-1.97	< 0.0001	-0.032	< 0.0001
Smoker	-1.44	< 0.0001	-2.44	< 0.0001	-0.034	< 0.0001
Comorbidities						
Diabetes	-2.35	< 0.0001	-0.63	< 0.0001	-0.019	< 0.0001
Acute MI	-1.57	< 0.0001	-0.59	0.052	-0.013	0.001
CHF	-5.19	< 0.0001	-1.94	< 0.0001	-0.047	< 0.0001
Stroke						
ICD-9 434.XX	-2.15	0.13	-5.57	0.001	-0.068	< 0.0001
ICD-9 436.XX	-3.92	< 0.0001	-2.8	< 0.0001	-0.05	< 0.0001
CKD	-5.67	0.003	1.94	0.19	-0.015	0.48
Co-morbidity burden	-1.92	< 0.0001	-1.21	< 0.0001	-0.027	< 0.0001

Abbreviations: aTRH, apparent treatment-resistant hypertension; BMI, body mass index; MCS, mental component summary; PCS, physical component summary; SF-12v2, Short Form 12 version 2; SF-6D, Short-Form Six-Dimension Utility Index.  $\beta$  represents the direction and magnitude of the association between the parameter and the respective dependent variable (that is, SF-12v2 MCS, PCS or SF-6D). A negative sign indicates association with lower values in the dependent variable (that is, lower values in HrQoL or health utility).

patients progress from diagnosed but untreated hypertension, to treated but uncontrolled hypertension, to treated and controlled hypertension.<sup>21</sup> Thus, any gain in BP control might come at a cost of lower HrQoL that may be associated with more aggressive antihypertensive regimens. Indeed, this mechanism is consistent with the relationship we observed between decreasing mean PCS score and increasing number of antihypertensive medications (Figure 2).

We did not find a significant decrement in HrQoL in the mental health domain, as measured by SF-12v2 MCS score, for aTRH versus non-resistant hypertension. Our findings seem to contrast

those of a recent small uncontrolled cohort study of renal denervation by Lambert and colleagues, in which significantly lower MCS scores were observed in patients with uncontrolled TRH, as compared with age-, sex-, and BMI-matched patients with controlled non-resistant hypertension or no hypertension.<sup>26</sup> The difference in findings between that study and ours may be attributed to our use of a nationally representative panel of US adults with hypertension and aTRH being defined on the basis of using  $\geq 4$  antihypertensives in a panel period (regardless of whether BP was controlled). In contrast, Lambert and colleagues assessed 62 patients with uncontrolled TRH who had been



referred for renal denervation therapy only after BP control had been unachievable at specialized hypertension clinics. Consequently, this patient group is unlikely to be representative of the larger population of patients with aTRH in the United States. Moreover, the mean clinic BP reduction of 16/6 mm Hg 3 months after renal denervation was accompanied by an increase in mean MCS score from ~48 to 52 and no change in medication use.<sup>26</sup> Previous studies have found that systolic BP predicts variance in subjective well-being;<sup>27</sup> thus, achievement of BP control in some of these patients may account for the mean MCS score increase. In contrast, given the results of the SYMPPLICITY HTN-3 trial that suggest renal denervation is no more effective than a sham procedure in this patient population,<sup>28</sup> the increase in mental functioning may reflect a placebo effect.

Finally, we observed a significant decrement in health utility, as measured by SF-6D, among persons with aTRH (0.68) relative to those with non-resistant hypertension (0.74), for a mean SF-6D difference of 0.06 in unadjusted analyses. An SF-6D utility of 0.74 for those with non-resistant hypertension is generally consistent with that observed in patients with hypertension (compared to no hypertension) in a previous large study of Medicare beneficiaries.<sup>29</sup> In addition, this difference was nearly twice that of the SF-6D score generally considered as a minimum clinically important difference (~0.03) in health status change, although this minimum difference may be less applicable when comparing groups in cross-sectional analyses such as this.<sup>30</sup> More importantly, this difference remained, though attenuated, after adjusting for covariates known to influence preference-based utilities.<sup>31,32</sup> The adjusted difference (that is, that attributable to aTRH versus non-resistant hypertension) observed in the present study (–0.02) is similar to that attributable to hypertension generally (–0.013) and angina/CAD (–0.017).<sup>29</sup> Thus, our findings suggest that aTRH is associated with a nontrivial decrease in health utility compared with non-resistant hypertension alone. To our knowledge, this is the first report quantifying health utility associated with any measure of aTRH, so these findings will need replication. Future studies with aTRH health utilities will have special importance because of the growing emphasis on preventive and treatment strategies for TRH that are cost-effective, affordable and sustainable by health systems.

This study has noteworthy limitations. First, MEPS data do not contain BP data; thus, patients with TRH defined by uncontrolled BP on three antihypertensives (that is, according to the American Heart Association definition<sup>20</sup>) were misclassified as having non-resistant hypertension in this study. Although this group likely represents a minority of those with TRH,<sup>33</sup> we cannot exclude the possibility that this misclassification may have influenced our results. However, this misclassification would likely work against a difference between groups by reducing physical functioning and utility scores in the non-resistant hypertension group. Moreover, any influence caused by this misclassification is likely small given that we observed an approximately linear relationship between increasing number of antihypertensive medications used and both lower physical functioning and lower health utility. Indeed, in sensitivity analyses excluding any person with three antihypertensive drugs from the non-resistant hypertension group, we observed remarkably similar findings compared with the primary analysis. Second, medication adherence data are not present in MEPS. Although non-adherence is thought to be fairly common in persons with aTRH, previous studies have shown that nonadherence to antihypertensive medications may be associated with greater HrQoL that would again bias our findings towards no difference between aTRH and non-resistant hypertension. Future studies will need to better quantify the degree of nonadherence among patients with aTRH and to examine the influence of treatment adherence on the association between aTRH and reduced HrQoL and health utility. A final noteworthy point is that MEPS is a series of cross-sectional panels and not longitudinal

cohorts; thus, these results should not be construed as proof of aTRH being a cause (or lack thereof) of reduced HrQoL and health utility. In part with this, HrQoL are annualized, which is a limitation inherent to MEPS.

Our findings address a gap in patient-reported and humanistic outcomes research in patients with hypertension. In particular, this report is the first, to our knowledge, to measure HrQoL and health utility for patients with aTRH in a nationally representative US population. Additional research is needed to elucidate the determinants of HrQoL in persons with aTRH, and to quantify change in HrQoL parameters and health utility associated with effective treatment of this condition.

#### What is known about this topic?

- Health-related quality of life (HrQoL) is lower in those with hypertension compared with those without hypertension and greater treatment intensity may portend greater decrements in HrQoL.
- Previous limited research suggests that treatment-resistant hypertension, a high-risk hypertension phenotype, is associated with increased anxiety and stress, and possibly decreased mental HrQoL.

#### What this study adds?

- Among a nationally representative sample of US adults from the Medical Expenditure Panel Survey, TRH was associated with decreased physical HrQoL and health utility, compared with non-resistant hypertension; both measures were inversely related to number of antihypertensives taken.
- Mental HrQoL was not substantially reduced in patients with apparent TRH or non-resistant hypertension.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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