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Quality of Life in Treatment-Resistant Hypertension

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Abstract Treatment-resistant hypertension (TRH) is an increasingly common and clinically challenging hypertension phenotype associated with adverse impact on cardiovascular events and death. Recent evidence, although limited, suggests that TRH may also adversely affect health-related quality of life (HrQoL) and other patient-reported outcomes. However, the precise mechanisms for this link remain unknown. A number of recent studies focusing on both the general hypertensive population and those with TRH suggest that patient awareness of difficult-to-control blood pressure, chronically elevated blood pressure levels, and the use of aggressive medication regimens with attendant cumulative adverse effects may play significant roles. This review summarizes the existing literature on HrQoL in persons with TRH, highlights literature from the general hypertensive population with relevance to TRH, and discusses important remaining questions regarding HrQoL in persons with TRH.

Keywords Quality of life · Resistant hypertension · Hypertension · Patient-reported outcome

This article is part of the Topical Collection on *Resistant Hypertension*

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Introduction

Chronically elevated blood pressure was first linked to excess mortality over a century ago [1]. Since that time, myriad epidemiologic studies and clinical trials have further quantified the association between elevated blood pressure (BP) and increased risk of cardiovascular morbidity and mortality as well as the impact of BP reduction on these outcomes [2]. As a consequence of these studies and the proliferation of evidence-based treatment guidelines, rates of hypertension awareness, treatment, and to a lesser extent, control have been steadily increasing worldwide [3–6]. With these gains, a substantial number of cardiovascular events and death have been prevented [7]. However, as noted recently by the Institute of Medicine, patient-centered care goes beyond just improving survival and reducing morbidity to attending to patients' physical and emotional needs, and maintaining or improving their quality of life [8]. Thus, as patients with hypertension have begun to live longer with less disability, patient-reported outcomes, such as quality of life, have become important assessment components in the chronic—often life long—management of this condition.

Despite the ubiquity of this disease, relatively few studies have assessed quality of life in relation to hypertension and its treatment, similar to the relative dearth of studies regarding quality of life in cardiovascular disorders more generally [9]. Even more concerning, very little is known of these humanistic outcomes in patients with particularly challenging hypertension phenotypes, such as treatment-resistant hypertension (TRH) [10]. Of the estimated one billion adults with hypertension worldwide [11], perhaps as many as 10 to 12 % are classified as having TRH [12], which is usually defined as uncontrolled BP on ≥3 antihypertensive agents or use of ≥4 agents regardless of BP control (or, more simply, requiring ≥4 antihypertensive agents to achieve BP control) [13]. This

phenotype has come under increased scrutiny in recent years and has been consistently linked with a greater risk for adverse cardiovascular outcomes and mortality compared with nonresistant hypertension [14–19].

Given the well-known challenges of managing TRH—for both patients and clinicians—this lack of humanistic outcome data represents a significant gap in the literature. In this article, we highlight literature from the general hypertension population with relevance to TRH and its treatment and summarize the existing literature assessing health-related quality of life (HrQoL) in patients with TRH. We also address some of the remaining questions regarding HrQoL in patients with TRH.

Quality of Life in Hypertension

Studies to date have shown somewhat mixed results with regard to HrQoL in patients with hypertension compared to no hypertension, likely in part because of significant heterogeneity between studies with regard to sampling criteria, comparison groups, and assessment tools. For example, a number of cross-sectional population-based studies have demonstrated lower HrQoL in patients with hypertension [20–26], whereas others have shown a more mixed effect or no substantial difference in HrQoL measures between those with and without hypertension [27, 28]. A 2011 meta-analysis by Trevisol and colleagues, limited to 20 studies that used the Short-Form 36- or 12-item (SF-36 or SF-12) Health Survey for HrQoL assessment, demonstrated small but significant decrements in patients with hypertension compared to those without hypertension [29]. These decrements were observed across all eight domains of the SF-36 and SF-12 (i.e., physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health), as well as in both the physical and mental component summary scores, suggesting that having hypertension does adversely impact HrQoL.

The precise mechanisms by which hypertension might lower HrQoL remain a subject of debate. As with other chronic diseases, reduced HrQoL in persons with hypertension may be related to a multitude of factors, including knowledge of the disease, elevated BP and accompanying symptoms, and treatment of the disease (e.g., pharmacologically related adverse events, difficulty affording medications, frustrations with frequent monitoring), among others. Almost certainly, adverse impacts of hypertension on HrQoL result from a confluence of these myriad factors.

Previous work has demonstrated that awareness of hypertension is associated with reduced HrQoL, even after taking into account BP differences between aware and unaware hypertensive patients [20, 30•, 31–34]. This "labeling" effect seems particularly relevant early after diagnosis and may be associated with patient perceptions of adverse consequences of hypertension or forthcoming recommendations for treatment and lifestyle modification. Consistent with this, the labeling effect may attenuate over time [35], possibly because relatively stable patients who do not require more aggressive therapy begin to cope more easily with the disease and treatment. Interestingly, labeling patients with high-normal BP as "prehypertensive" does not appear to have any such effect [36], presumably because most patients with high-normal BP do not receive immediate treatment. While most patients with TRH are not likely to receive an explicit diagnosis of "resistant hypertension," it seems plausible that awareness of difficult-to-control BP and advancing medication regimens may adversely impact HrQoL [37]. As in the more general hypertensive population, the relative contribution of awareness of difficult-to-treat hypertension, to reduced HrQoL, probably wanes as BP and treatment regimens stabilize, although to our knowledge, this question remains unanswered.

Among persons with hypertension, BP levels also have been empirically linked with reduced HrQoL or subjective well-being [38, 39••]. Not surprisingly, patients with BP levels at either extreme (e.g., significant hypotension or stage 2 hypertension) seem to have the lowest HrQoL, probably related to a higher likelihood of symptoms at these BP extremes. One particularly interesting study examined BP levels associated with "optimal HrQoL" among nearly 11,500 white Europeans with hypertension [39••]. In this study, a systolic BP of ~125 and diastolic BP of ~75–80 were associated with the smallest decrement in HrQoL (i.e., the "most optimal" HrQoL) related to physical functioning; as BP increased significantly, so too did decrements in HrQoL. On the other hand, mental functioning seemed to vary little by BP level except in those aged ≥65 years, where the optimal BP for mental functioning was again ~120–125 mmHg systolic and 70–80 mmHg diastolic. Most pertinent to this discussion, the investigators found that those patients taking ≥4 antihypertensive agents (i.e., those with TRH) had significantly lower physical and mental functioning compared to patients taking 1–3 antihypertensive drugs (Fig. 1, blue lines). Furthermore, this inverse relationship between number of antihypertensive drugs and HrQoL persisted in multivariate models controlling for "BP control" (i.e., BP<140/90 mmHg). Additionally, they found that a BP of ~130/70 mmHg was associated with the greatest physical functioning among patients with TRH. Curiously, the systolic BP value that optimized HrQoL in those with TRH was 15 mmHg higher than the systolic BP value that optimized HrQoL in patients taking only one antihypertensive (~115 mmHg), in other words, as the number of antihypertensive agents taken increases, so does the BP level associated with optimal HrQoL.

The level of hypertension treatment also appears to significantly affect HrQoL. In a recent study by Trevisol and colleagues in Brazil, HrQoL was assessed using the SF-12 in 1858 patients taking part in the Syndrome of Obesity and Risk Factors for Cardiovascular Disease (SOFT) trial [30]. Not

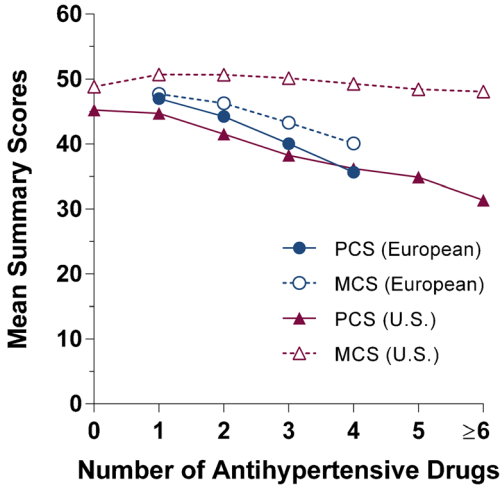

Fig. 1 Health-related quality of life by number of antihypertensive medications prescribed in European patients and US patients. Data for European patients are extrapolated from Zygmuntowicz et al. [39••], whereas those for US patients are from Carris et al. [40••]. *MCS* mental component summary, *PCS* physical component summary

surprisingly, those with hypertension (34 % of the study population) had modestly lower HrQoL scores than normotensive patients. However, one of the most interesting findings from this study was that participants with untreated, uncontrolled hypertension had higher HrQoL than those with treated but uncontrolled hypertension, and both of these groups had higher HrQoL than patients who were treated and controlled. These differences were relatively modest but suggest two important messages: (1) Any treatment of hypertension may be associated with reduced HrQoL, and (2) more aggressive treatment of hypertension (i.e., to achieve goal BPs) may be associated with further reductions in HrQoL. The latter message has special relevance to those with TRH because it suggests that more aggressive therapy, such as that used in patients with TRH (by definition), may actually worsen HrQoL. Indeed, our work (discussed in more detail below) and others' [39••] support this supposition. Furthermore, data from several clinical trials also suggest that treatment-to-goal strategies, typically using stepped therapy, only minimally improve, or perhaps even worsen HrQoL [41–43]. However, questions remain regarding what role the interaction between aggressiveness of treatment and BP level has on HrQoL. Put another way, it remains unclear whether, and to what degree, the relationship between more aggressive antihypertensive therapy and reduced HrQoL is attenuated by achievement of satisfactory BP levels.

The relationship between more advanced medication regimens and lower HrQoL is almost certainly also influenced by the specific treatments used in any given patient. Unfortunately, existing literature is mixed as to whether specific antihypertensive agents or classes differentially affect HrQoL in persons with hypertension. Some studies have noted differences between classes or even within classes [44–46], while others have reported no difference between classes [47, 48]. Of most concern in patients with TRH are β-blockers and diuretics: Both are commonly employed in patients with TRH [40••, 49, 50], and diuretics are often considered a prerequisite for classification as TRH [13]. A number of reports suggest that treatment with these particular classes is associated with reduced general well-being or smaller improvements in HrQoL relative to other classes [45, 46, 51, 52]. Perhaps not coincidentally, these classes, especially diuretics, also have some of the highest discontinuation rates and lowest persistence rates among all mainstream antihypertensive classes [53–58], ostensibly due to drug-related adverse effects. Thus, greater use of antihypertensive medications, especially those that are associated with a greater incidence of real or perceived adverse events, may contribute to decrements in HrQoL in patients with TRH.

Patient-Reported Outcomes in Treatment-Resistant Hypertension

Health-Related Quality of Life

Lambert and colleagues assessed HrQoL, using the SF-36, in a small subset of patients taking part in a larger study of renal denervation therapy in Australia [59•]. Included patients (n= 62) were those with uncontrolled TRH (according to the American Heart Association guidelines [13]) who had been referred for renal denervation therapy only after BP control had been unachievable at specialized hypertension clinics (and, presumably, at primary care clinics before that). Most of these patients (65 %) were men, with a mean age of ~62 years, BMI of ~32 kg/m^2, and systolic and diastolic BPs of 166 and 88 mmHg, respectively, and using a mean of 4.8 antihypertensive medications. At baseline, those with uncontrolled TRH reportedly had significantly (at $p<0.005$) lower mental component summary (MCS) scores (mean± SEM, 47.6±1.1) compared to age-, sex-, and BMI-matched controls with controlled hypertension or without hypertension, although baseline point estimates for MCS scores in the latter two (control) groups were not explicitly reported. However, despite these apparent differences between groups, the MCS scores in those with uncontrolled TRH appear to be of questionable clinical significance. The component summary scores for the SF-12 and SF-36 tools are normed to a population-specific mean score of 50 and standard deviation (SD) of 10 points (based on US general population data); typically, a decrement of one half SD (i.e., 5 points) is considered the minimum clinically important difference in HrQoL [60]. Thus, the difference between the MCS score observed in those with uncontrolled TRH (47.6) and the normed mean of the Short Form tools (50) may not be clinically important. In contrast, the mean physical component summary (PCS) score

appeared to be substantially reduced in those with uncontrolled TRH at baseline (~43) relative to the normed mean of 50 [59•]. However, the authors reported no significant difference (at $p<0.005$) between PCS scores in those with uncontrolled TRH versus controlled nonresistant hypertension or no hypertension (~46 to 47). Among those with uncontrolled TRH, lower PCS score was associated with female sex, increasing age, BMI, and systolic BP (R^2=45 % including all of these variables). Interestingly, the number of antihypertensive agents reported by patients was not associated with PCS score.

In a remarkably similar study, Lenski and colleagues assessed HrQoL, using SF-12 version 2 (SF-12v2), in 119 patients with uncontrolled TRH (defined here as systolic BP≥160 mmHg on ≥three antihypertensive agents, including a diuretic) who were candidates for renal denervation [61]. The patient population was quite similar to that in the aforementioned study by Lambert (55 % men; mean age, ~62 years; mean BMI, ~30 kg/m^2; mean±SD systolic and diastolic office BP, 165±22 and 91±15 mmHg, respectively), except baseline antihypertensive use that was somewhat greater (mean, 5.7 antihypertensive drugs). In this cohort of patients with uncontrolled TRH, mean PCS score was ~38, while mean MCS score was ~48, suggesting a significant impact on physical functioning, but minimal, if any impact on mental functioning, in those with TRH relative to the general population (i.e., compared with the standardized mean of 50). The authors did not report data on matched controls, thus providing no evidence for the comparison between TRH and nonresistant hypertension [62].

The findings from these two trials suggest a significant association between TRH and lower HrQoL, particularly with regard to physical functioning. However, several factors limit the generalizability of these studies to the larger population of patients with TRH. First, both studies were small and included only patients with very difficult-to-control hypertension, as evidenced by significantly elevated BP, substantial antihypertensive use, and the need for referral from specialized hypertension centers for renal denervation therapy. Such patients are likely not reflective of the larger TRH population. Second, the investigators limited the "TRH" group to only those with *uncontrolled* BP. And, in the Lambert et al. study, the comparison group consisted of patients with *controlled* nonresistant hypertension. Thus, it is difficult to know what role the elevated BP, per se, played in the finding of lower HrQoL in patients with TRH in these renal denervation cohorts [59•, 61].

More recently, we compared HrQoL measures (using SF-12v2) in patients with apparent TRH (defined as use of ≥4 antihypertensive agents, regardless of BP) and nonresistant hypertension using data from the US Medical Expenditure Panel Survey (MEPS), which provides nationally representative estimates for noninstitutionalized US adults [40••]. Using MEPS data from 2000 to 2011, we found no clinically significant difference in MCS scores between patients with TRH and nonresistant hypertension. Interestingly, we did observe substantial decrements in PCS score among those with TRH (mean, 36) relative to persons with nonresistant hypertension (mean, 43) and the general US population (i.e., the standardized mean of 50). Figure 2 provides some context for HrQoL decrements in those with TRH, nonresistant hypertension, and several other selected conditions known to have significant impacts on HrQoL. Furthermore, our finding of reduced HrQoL in the physical realm persisted, although somewhat attenuated, in multivariable regression analyses controlling for various demographic, socioeconomic, and clinical characteristics (including other comorbidities known to adversely impact HrQoL, such as a history of stroke, diabetes, heart failure); taken together, these variables accounted for approximately one third of the variance in PCS score. Of note, the adjusted effect of TRH on physical HrQoL that we observed was quite similar in magnitude to that seen comparing patients with hypertension to those without [29]. Finally, we also observed an interesting inverse association between the number of antihypertensive drugs used and mean PCS score, but not mean MCS score which is largely in keeping with others' [39••] findings (Fig. 1).

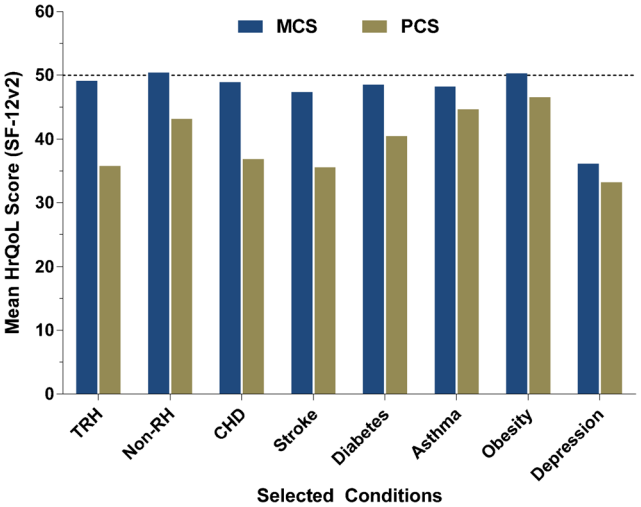

Fig. 2 Mean physical component summary (PCS) and mental component summary (MCS) scores for patients with treatment-resistant hypertension and selected other chronic conditions. Summary scores are derived from the SF-12v2 Health Survey, where the standardized score of 50 (dotted line) represents the general US population. Data for hypertension [40••], CHD [63], stroke [64], diabetes [65], asthma [66], and obesity [67] are from the national representative US Medical Expenditure Panel Survey. Data for patients with depression are from a large study of US Veterans [68]. *TRH* treatment-resistant hypertension, *non-RH* nonresistant hypertension, *CHD* coronary heart disease

Stress & Anxiety

Schmieder and colleagues surveyed 4574 persons with self-reported uncontrolled hypertension (BP≥140/90 mmHg on ≤2 antihypertensive drugs) or TRH (BP≥140/90 mmHg on ≥3 antihypertensives or use of ≥4 antihypertensives, regardless of BP control) [69••]. Respondents in this study with self-reported TRH were significantly more likely to "strongly agree" or "somewhat agree" to questions about "feel[ing] powerless to control their blood pressure," and being "often anxious about managing their blood pressure." In addition, those with TRH were significantly more likely to report that their hypertension had "a lot" or "a great deal" of impact on overall health, overall peace of mind, desire to participate in certain activities, mood, and relationships with family or friends, than those with uncontrolled nonresistant hypertension. Interestingly, nearly three quarters of patients with TRH, compared with 59 % of those with uncontrolled nonresistant hypertension, "strongly agreed" or "somewhat agreed" that their quality of life would improve if they were able to achieve BP control. These data are consistent with previously discussed studies in the general hypertensive population and suggest that BP control may be an important factor in improving HrQoL in most patients with hypertension, including those with TRH. However, the difference between the groups is somewhat surprising since, presumably, some proportion of those with TRH in this study had controlled BP. The authors did not report BP data in this study, but self-selection bias may have contributed to a larger proportion of patients with uncontrolled BP in the TRH group than has been seen in unselected populations [70]. Alternatively, these data may support a possible interaction between BP control (or lack thereof) and more aggressive antihypertensive therapy on HrQoL. Nevertheless, these results clearly suggest an increased level of stress and anxiety associated with TRH relative to those with nonresistant hypertension but uncontrolled BP; put another way, greater stress and anxiety may be ascribed to more aggressive antihypertensive regimens (i.e., use of ≥three to four agents) rather than uncontrolled BP per se. Anxiety disorders have been associated with markedly compromised HrQoL and psychosocial functioning [71]; thus, one might expect that an association between more aggressive treatment (e.g., as seen in persons with TRH) and increased anxiety, if severe enough, could lead to lower mental functioning.

Remaining Questions

To date, most research has focused on identifying whether TRH is associated with reduced HrQoL. Moving beyond that, a number of questions remain regarding HrQoL in patients with TRH. Foremost among these are identifying the influential mechanisms—and their interplay—that explain the link between TRH and reduced HrQoL, determining whether achievement of BP control actually improves HrQoL in patients with TRH, and if so, elucidating what treatment strategies (e.g., drug regimens, order of drug initiation, nonpharmacologic strategies, health systems approaches) optimize HrQoL for patients with TRH.

Possible mechanisms for the relationship between TRH and reduced HrQoL may include patient awareness of, frustration with, or frequent monitoring for difficult-to-control BP, as well as a greater likelihood of being prescribed antihypertensive regimens with greater cumulative adverse effects, as discussed previously. Treatment nonadherence, which is believed to be a major cause of "pseudoresistant hypertension," [72–75] may also be related to HrQoL, although the nature and direction of this relationship remain unclear. Studies from the general hypertensive population have demonstrated mixed associations between treatment nonadherence and HrQoL, including weak positive correlations (i.e., lower adherence associated with lower HrQoL) and weak inverse correlations (i.e., lower adherence associated with greater HrQoL) [76–80]. These findings highlight the complex relationship between treatment nonadherence (and its myriad causes) and subjective HrQoL, as well as the challenge in elucidating this relationship in individuals with varying—and often competing—reasons to be adherent or purposefully nonadherent. For example, a patient may seek to optimize HrQoL by gaining greater BP control, via dietary and medication adherence, with the goal of reducing the frequency of healthcare visits; however, greater adherence may be associated with more adverse effects (particularly with multidrug regimens), which may incline the patient towards nonadherence to optimize HrQoL. However, to our knowledge, these complex relationships between adherence and HrQoL have not been well studied in the general hypertension population or at all in those with TRH.

An alternative explanation for the finding of reduced HrQoL in persons with TRH is that it may be somewhat artifactual because persons with TRH are known to have a high frequency of comorbid conditions (e.g., diabetes, stroke, myocardial infarction, heart failure) that impact HrQoL negatively. Our work has shown that controlling for these comorbidities attenuates, but does not eliminate, the association between TRH and reduced HrQoL [40••]. Nevertheless, current statistical approaches to this question are limited in their ability to fully eliminate such potential confounding.

As previously discussed, a number of trials in the general hypertensive population have suggested minimal, if any, correlation between improved BP and improved HrQoL. Conceivably, patients with TRH, who have worse HrQoL (relative to those with nonresistant hypertension), may benefit more from BP reductions. However, such gains are likely offset by increased medication use (and corresponding adverse events and frustrations with medication regimen complexity) in most

patients. Presumably, medication regimens can be optimized to reduce the impact on HrQoL, but we are aware of no studies that have examined this issue. Indeed, few trials have assessed treatment strategies in those with TRH, and almost none have assessed HrQoL changes associated with these strategies. Furthermore, it remains unclear whether BP goal attainment through more aggressive treatment positively impacts any major outcomes in patients with TRH. We previously found no difference in the occurrence of death or major cardiovascular events (except possibly stroke), comparing those with controlled TRH to those with uncontrolled TRH, despite significant (~28/10 mmHg) differences in mean BP between the groups [14]. Similar findings have been echoed elsewhere [18]. Thus, additional work is needed to determine whether patients with TRH benefit from such aggressive therapy in terms of improved HrQoL or reduced death and disability.

Conclusion

Growing interest in TRH has led to a substantial increase in the study of this challenging hypertension phenotype in recent years [70]. The link between TRH and adverse cardiovascular consequences has been fairly well established, but emerging evidence shows that TRH is also associated with substantially reduced quality of life. Whether this link is part and parcel with the underlying processes that cause TRH or a function of more aggressive treatment is unknown. Accordingly, while the general trend among recent consensus guidelines and hypertension researchers has been to pursue relatively aggressive strategies to reduce BP, it remains unclear whether reduced HrQoL in persons with TRH is improved or exacerbated by such strategies. Moreover, little is known of the optimal treatment strategies for maintaining quality of life in persons with TRH. This lack of knowledge should serve as an important reminder to clinicians to engage patients in their care and to consider quality of life in the ongoing management of patients with TRH.

Compliance with Ethics Guidelines

Conflict of Interest Nicholas W. Carris and Steven M. Smith declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the author's.

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- •• Of major importance

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