Hypertensive Target-Organ Damage in the Very Elderly

Cianán O’Sullivan, Joe Duggan, Simon Lyons, John Thornton, Michael Lee, Eoin O’Brien

Abstract—In people aged >80 years, the so-called very elderly, there is uncertainty about the relation between hypertension and cardiovascular morbidity. The aims of this study were to investigate whether hypertension in people aged >80 years is associated with target-organ damage, over and above the effects of age, and to determine whether ambulatory blood pressure monitoring (ABPM) could improve on conventional blood pressure monitoring (CBPM) in predicting target-organ damage. Investigations included echocardiographic measurement of left ventricular mass index (LVMI), brain magnetic resonance imaging assessment of periventricular hyperintensity (PVH), urinary albumin-creatinine ratio (ACR), aortic pulse wave velocity (PWV), and 24-hour ABPM. Forty-three subjects, at a mean age 84.3 years, were studied, 22 normotensive (NT) and 21 hypertensive (HT). CBP was 184/89 and 145/76 mm Hg in the HT and NT groups, respectively. In men, LVMI was significantly greater in HT subjects, 157±37 vs 123±15 g/m² in NT subjects (P<0.05). In women, LVMI was similar in both groups. Urinary ACR was greater in HT than in NT subjects (log ACR, 1.21±0.50 vs 0.95±0.23; P<0.05). Cerebral PVH grade was higher in the HT subjects (2.6±0.8 vs 2.2±0.9), although this difference was not significant. Aortic PWV did not differ between the 2 groups. ABPM was positively associated with urinary ACR and cerebral PVH, independent of its correlation with CBPM. In advanced old age, HT is associated with evidence of target-organ damage. ABPM can improve on CBPM in predicting very elderly subjects with HT target-organ damage. (Hypertension. 2003;42:130-135.)

Key Words: elderly ■ blood pressure monitoring, ambulatory ■ hypertrophy, left ventricular ■ cerebrovascular disorders ■ albuminuria ■ vascular resistance

The positive association between blood pressure and cardiovascular complications is well established in middle-aged and older adults.1 In people aged >80 years, the so-called very elderly, there is uncertainty about the relation between hypertension (HT) and cardiovascular morbidity and mortality.2–5 There is also uncertainty about the benefits of antihypertensive treatment in the very elderly, because firm conclusions cannot be drawn from clinical trial data to date.6–10 For example, treatment appears to be less effective in very elderly people with isolated systolic hypertension.10 It is possible that people who survive to 80 years and older, a select group, might be somewhat tolerant of high blood pressure. The presence of target-organ damage in very elderly HT subjects would not be consistent with the notion that HT is a benign condition in this age group. Previously published data on HT target-organ damage in elderly people relate to younger subjects, usually aged 60 to 75 years. Formal target-organ assessment has not previously been conducted in the very elderly. Furthermore, HT research in this population is complicated by the difficulty in distinguishing the changes in organ systems due to HT from those of normal ageing.

Left ventricular mass increases with age and with increased blood pressure.11,12 In the very elderly, it is unknown whether HT adds to the existing age-related increase in left ventricular mass. Increased urinary albumin excretion is associated with damage in other organs and with adverse prognosis in HT subjects.13 The relation between HT and urinary albumin in the very elderly is unknown. Cerebral white-matter changes observed on brain imaging in elderly subjects are associated with age, HT, and other indicators of vascular disease.14 The relation between HT and cerebral white-matter change is confounded by the strong association between white-matter changes and age,15 and again, this issue has not been specifically investigated in the very elderly. Increased arterial stiffness is associated with HT, atherosclerosis, diabetes, and other cardiovascular risk factors.16 Age is one of the most important determinants of arterial stiffness.16 Whether HT is associated with vascular stiffening additional to that of ageing in people aged >80 years is not known.

There is evidence that the correlation between target-organ damage and blood pressure is better for ambulatory blood pressure monitoring (ABPM) than is conventional blood pressure measurement (CBPM),17 and ABPM provides more accurate prognostic information on the risk of HT.18,19 There have been no previous studies correlating ABPM with target-organ damage in the very elderly. The aims of the present study were therefore to investigate whether HT in people aged 80 and older is associated with target-organ damage,
over and above the changes related to ageing. The separate organ systems studied were cardiac, cerebral, renal, and arterial. In addition, we sought to establish whether ABPM could improve on CBPM in predicting very elderly subjects with HT target-organ damage.

Methods

Subjects
The study protocol was approved by the Beaumont Hospital Research Ethics Committee. Subjects were 80 years or older, healthy, community dwelling, and independent in self-care and were able to provide informed consent. They were recruited from an outpatient clinic, a general practice, and an existing database of healthy, elderly subjects. Subjects were included if there was no history of cardiovascular disease (other than HT), stroke, diabetes, or other major illness and if they had normal cognitive function (Folstein Mini-Mental State Examination score ≥24/30). Further assessment to exclude illness included physical examination, full blood count, erythrocyte sedimentation rate, biochemistry profile, and ECG. Results of these investigations were required to be within normal limits, except left ventricular hypertrophy (LVH) on the ECG, which was permitted. Subjects were classified by CBPM. Screening blood pressure was the mean of 4 seated measurements, 2 readings on 2 occasions at least 2 weeks apart.

The HT group was defined as those with a screening systolic blood pressure (SBP) ≥160 mm Hg and/or a diastolic blood pressure (DBP) ≥90 mm Hg. Treated HT subjects (n=10) discontinued treatment at least 2 weeks before study entry. The normotensive (NT) group consisted of those with a screening SBP <160 mm Hg and a DBP <90 mm Hg.

Procedures
Subjects came to the study center (Blood Pressure Unit) in the morning between 9 and 11 AM.

Conventional Blood Pressure
After 5 to 20 minutes of rest, 2 seated blood pressure measurements were taken with a mercury sphygmomanometer at least 2 minutes apart. Two blood pressure measurements were similarly recorded the following morning. The mean of these 4 readings and the 4 screening readings was the CBP used in the analysis.

Cardiac Assessment
M-mode echocardiography was performed, and left ventricular mass index (LVMI) was calculated. Accurate measurement of LVMI was not possible in 2 subjects. Sokolow-Lyon voltage criteria for LVH on the ECG were applied.

Renal Assessment
Two consecutive early morning urine samples were collected. One HT subject was excluded from the analysis because of proteinuria and trace hematuria on the standard dipstick. Laboratory measurements of urinary creatinine (Jaffa reaction) and urinary albumin (immunoturbidity method) were performed. The albumin-creatinine ratio (ACR) was expressed as micrograms albumin per milligram creatinine. The mean of the 2 ACR measurements was used in the analysis.

Cerebral Assessment
Axial T1- and T2-weighted magnetic resonance imaging of the brain was performed on all subjects. Abnormalities in the periventricular signal on T2-weighted images were evaluated with the method of Shimada et al. In brief, periventricular hyperintensity (PVH) was graded 1 to IV, grade I being no abnormality or minimal periventricular signal hyperintensity and grade IV being multiple, confluent areas of hyperintensity. The neuroradiologist interpreting the scans was unaware of the subjects’ clinical details.

Pulse Wave Velocity
Aortic pulse wave velocity (PWV) was measured with a Complior device (Colson), with 2 transducers placed simultaneously over the carotid artery in the neck and the femoral artery in the groin. The average PWV for 7 to 10 cardiac cycles was calculated. Accurate PWV measurement was not possible in 1 subject.

Twenty-Four-Hour ABPM
The SpaceLabs 90207 device was used according to a standard protocol. Daytime was defined as 9 AM to 9 PM and nighttime as 10 PM to 6 AM. A minimum of 16 daytime and 6 nighttime readings was required for inclusion in the study. The mean±SD number of blood pressure readings during daytime, nighttime, and total were 21±2.6, 10±0.5, and 47±3.8, respectively. One ABPM was repeated because of insufficient nocturnal recordings.

Statistical Analysis
Data were analyzed with the SPSS statistics package (SPSS Inc). Accurate pretest sample-size calculations were hindered by the lack of available data on target-organ assessment in this age group. This was a preliminary study based on an estimated sample size of at least 20 subjects per group. Raw urinary ACR data were skewed but were normal when logarithmically transformed. Although gender did influence LVMI, male and female subjects were analyzed separately for cardiac results. The interaction between gender and blood pressure status was not significant for any of the other target-organ variables, and data for both genders were otherwise combined. The unique component of ABP that is independent of CBP was calculated. This was residual blood pressure, derived from the regression equation of 24-hour blood pressure on the CBP. A value of P<0.05 was considered significant for all tests.

Results

Subject Characteristics
A total of 43 subjects were included, 22 NT and 21 HT. Ten of the HT subjects were taking antihypertensive drugs, and these were discontinued for a median of 18 days before assessment. Age and gender distribution was similar in both groups. Subject characteristics and blood pressure levels are shown in Table 1. Substantial blood pressure differences were evident. There were no significant differences in body size or blood results between HT and NT subjects of the same gender. Cognitive performance was the same in both groups; the mean Folstein score was 28/30. There was good overall correlation between CBP and daytime blood pressure: r=0.81 (P<0.001) and r=0.74 (P<0.001) for SBP and DBP, respectively.

Left Ventricular Size
Cardiac assessment is presented in Table 2. LVH as assessed by ECG was present in 6 of 21 HT and 1 of 22 NT subjects (P<0.05). The difference was confined to male subjects. When ECG voltages were analyzed as a continuous variable, the differences between male HT and NT subjects just failed to reach significance (P=0.08). In men, HT subjects had a significantly greater LVMI than did NT subjects, 157±37 versus 123±15 g/m² (P<0.05). In women, there was no difference in left ventricular mass, as estimated by ECG or as measured by echocardiography between the HT and NT subjects.

Urinary Albumin Excretion
There were no differences in plasma indices of renal function between the 2 groups. Gender or body size did not influence
TABLE 1. Subject Characteristics and Blood Pressure Levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NT</th>
<th>HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (M/F)</td>
<td>22 (10/12)</td>
<td>21 (12/9)</td>
</tr>
<tr>
<td>Age, y</td>
<td>84.8±3.1</td>
<td>83.7±2.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.1±3.2</td>
<td>24.1±2.0</td>
</tr>
<tr>
<td>MMSE, 0–30</td>
<td>28.1±1.1</td>
<td>28.1±1.8</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.2±1.2</td>
<td>13.1±1.1</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>89±27</td>
<td>98±33</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>39.8±3.1</td>
<td>41.0±2.5</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Con SBP</td>
<td>144.6±10.2</td>
<td>184.3±12.2</td>
</tr>
<tr>
<td>Con DBP</td>
<td>75.6±6.1</td>
<td>89.1±6.0</td>
</tr>
<tr>
<td>Day SBP</td>
<td>137.1±12.1</td>
<td>161.5±15.3</td>
</tr>
<tr>
<td>Day DBP</td>
<td>74.4±9.7</td>
<td>87.4±9.1</td>
</tr>
<tr>
<td>Night SBP</td>
<td>120.0±15.9</td>
<td>147.6±22.2</td>
</tr>
<tr>
<td>Night DBP</td>
<td>61.5±8.3</td>
<td>75.8±12.9</td>
</tr>
<tr>
<td>24-Hour SBP</td>
<td>132.8±13.2</td>
<td>159.0±17.9</td>
</tr>
<tr>
<td>24-Hour DBP</td>
<td>71.7±10.3</td>
<td>84.2±10.4</td>
</tr>
<tr>
<td>SBP difference</td>
<td>7.5±11.1</td>
<td>22.8±9.8</td>
</tr>
<tr>
<td>DBP difference</td>
<td>1.2±8.7</td>
<td>1.6±5.6</td>
</tr>
<tr>
<td>Night/day SBP*</td>
<td>0.88±0.08</td>
<td>0.91±0.08</td>
</tr>
<tr>
<td>Night/day DBP*</td>
<td>0.83±0.08</td>
<td>0.87±0.11</td>
</tr>
</tbody>
</table>

Values are mean±SD. BMI indicates body mass index; MMSE, Folstein Mini-Mental State Exam (higher score, better performance); Con, conventional; difference=conventional–daytime BP difference. *Unitless measure.

The urinary ACR. The urinary ACR was significantly greater in the HT subjects compared with the NT subjects: log ACR 1.21±0.50 versus 0.95±0.23 (P<0.05). There was a continuous, positive relation between log ACR and blood pressure, both conventional and ambulatory (Table 3).

TABLE 2. Left Ventricular (LV) Dimensions

<table>
<thead>
<tr>
<th>LV Measurement</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT</td>
<td>HT</td>
</tr>
<tr>
<td>ECG, n</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>LVH on ECG, n</td>
<td>0</td>
<td>5*</td>
</tr>
<tr>
<td>V1 and V5, mm</td>
<td>22.3±7.1</td>
<td>30.2±11.5†</td>
</tr>
<tr>
<td>V1 and V6, mm</td>
<td>18.9±6.5</td>
<td>26.3±11.2</td>
</tr>
<tr>
<td>Echo, n</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>LV diast diam, mm</td>
<td>47.8±3.3</td>
<td>52.9±8.1</td>
</tr>
<tr>
<td>IV septum, mm</td>
<td>10.7±1.1</td>
<td>11.4±2.5</td>
</tr>
<tr>
<td>LV post wall, mm</td>
<td>10.5±1.2</td>
<td>11.1±2.6</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>214.5±28.2</td>
<td>275.6±64.3*</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>122.8±15.0</td>
<td>156.8±37.2*</td>
</tr>
</tbody>
</table>

Values are mean±SD. V1 and V5/6 indicates ECG voltages S wave V1 plus R wave V5/6; LVH on ECG, ECG voltages >35 mm; echo, echocardiography; diast diam, diastolic diameter; IV, interventricular; and post, posterior wall. *P<0.05 vs NT males; †P=0.08 vs NT males.

The urinary ACR. The urinary ACR was significantly greater in the HT subjects compared with the NT subjects: log ACR 1.21±0.50 versus 0.95±0.23 (P<0.05). There was a continuous, positive relation between log ACR and blood pressure, both conventional and ambulatory (Table 3).

Cerebral White-Matter Changes

Brain magnetic resonance imaging scanning was completed in all subjects. Gender or body size did not influence PVH grade. Mean PVH grade was higher in the HT group, but the difference was not significant: 2.6±0.8 versus 2.2±0.9 (P=0.16). A trend of increasing PVH grade with increasing SBP was evident when subjects were divided into quartiles of SBP (Figure). Differences in PVH grade between subjects grouped by quartiles of SBP were significant for day SBP (P<0.05; Figure) and approached statistical significance for conventional SBP (P=0.08), nighttime SBP (P=0.07), and 24-hour SBP (P=0.1). For each SBP variable, PVH grade was significantly higher (P<0.05) in subjects in the highest quartile of SBP compared with subjects in the lowest quartile of SBP. This was the case for conventional SBP and ambulatory SBP. Conversely, blood pressure levels increased uniformly across the 4 grades of PVH. Differences in mean SBP across the 4 grades of PVH were statistically significant for daytime SBP, nighttime SBP, and 24-hour SBP (P=0.05 for all) but not conventional SBP (data not shown).

PVH grade was positively and significantly associated with CBP, daytime SBP, nighttime blood pressure, and 24-hour blood pressure. Correlation coefficients between PVH and
blood pressure are shown in Table 3; the strongest correlation was with 24-hour SBP (r=0.49, P<0.01).

**Pulse Wave Velocity**
Aortic PWV ranged from 9.6 to 29.6 m/s. Gender, body mass index, or other subject characteristics did not influence PWV. There was, however, no relation between aortic PWV and blood pressure, neither conventional nor ambulatory. Consequently, there was no difference in PWV between the HT and NT group. Differences in left ventricular mass between HT and NT men in our study, an additive effect of HT on left ventricular mass was still detected. It has been reported that ABP is better correlated with left ventricular mass than is CBP. In the present study, men of mean age 69 years who were free of clinical cardiovascular disease had a mean LVMI of 109 g/m,2,31 lower than in the present study. However, NT men in the present study were significantly older and also had higher blood pressures than the Framingham subjects. Despite the increased left ventricular mass in the NT men in our study, an additive effect of HT on left ventricular mass was still detected. It has been reported that ABP is better correlated with left ventricular mass than is CBP. In the present study, however, ABPM did not improve on CBPM in predicting increased left ventricular mass. Fagard et al reported that the mean of repeated CBPM had as close a correlation with left ventricular mass as did ABPM. CBPM in our study was the mean of 8 measurements on 4 occasions, and this might explain our findings. Despite this, however, ABPM did improve on casual blood pressure in predicting renal and cerebral target-organ damage.

**Ambulatory Blood Pressure**
Correlation analysis was conducted to investigate which blood pressure variables, CBP or ABP, demonstrated the closest association with target-organ assessment. Results are shown in Table 3. In the case of left ventricular mass, the correlations with ABP were either nonsignificant or weaker than for CBP. The correlations between PVH grade and urinary ACR and ABP were significant and slightly stronger than for CBP; 24-hour blood pressure tended to have the closest association with target-organ assessment. Results are shown in Table 3; the strongest correlation was with 24-hour SBP (r=0.49, P<0.01).

**Discussion**
The very elderly represent the fastest-growing segment of the population, and conducting research in this age group is challenging for both subjects and investigators. This is the first study to comprehensively examine the relation between blood pressure and HT target-organ damage in people aged 80 and older and to examine the role of ABP. We found that HT in this age group was associated with cerebral white-matter ischemic changes, elevated urinary albumin excretion, and in men, LVH. In addition, ABPM had advantages over CBPM in predicting target-organ injury in the very elderly.

A threshold value of SBP <160 mm Hg was chosen for the NT group. This higher threshold value was chosen because at the time the study was designed, it was thought that a threshold value of 160 mm Hg better reflected clinical practice in the very elderly. Furthermore, a current randomized, controlled trial, specifically investigating antihypertensive treatment in the very elderly, is using the same blood pressure criteria as in the present study.26

Experience from a previous study involving very elderly subjects indicated that healthy subjects in this age group commonly had conventional SBP levels >140 mm Hg.27 Indeed, SBP levels <140 mm Hg in the very elderly have been associated with frailty and illness rather than “healthy ageing.”4-28 Recruitment of an age-matched control group required recognition of the age-associated rise in SBP and setting a higher threshold for NT. There was a clear and significant difference in blood pressure between the groups in the present study. Subjects in both groups were free of clinical cardiovascular disease and were age matched. Therefore, other than blood pressure, the cardiovascular risk profile was similar in both groups, and differences in target-organ damage can be attributed to differences in blood pressure.

The inclusion of subjects who were HT, by current criteria, in the NT group might have reduced the chances of detecting differences between the 2 groups. Therefore, the significant differences in target-organ damage, despite the higher threshold value, underline the association between high blood pressure and target-organ damage. This potential bias might, however, have accounted for the absence of difference in cardiac target-organ damage in women.

Ageing is associated with alterations in left ventricular geometry, concentric remodeling, and increased left ventricular mass.29,30 This occurs in both HT and NT subjects with age.31 Left ventricular mass has been found to increase with age independently of blood pressure.32 In the Framingham study, men of mean age 69 years who were free of clinical cardiovascular disease had a mean LVMI of 109 g/m2,31 lower than in the present study. However, NT men in the present study were significantly older and also had higher blood pressures than the Framingham subjects. Despite the increased left ventricular mass in the NT men in our study, an additive effect of HT on left ventricular mass was still detected. It has been reported that ABP is better correlated with left ventricular mass than is CBP.28-35 In the present study, however, ABPM did not improve on CBPM in predicting increased left ventricular mass. Fagard et al reported that the mean of repeated CBPM had as close a correlation with left ventricular mass as did ABPM. CBPM in our study was the mean of 8 measurements on 4 occasions, and this might explain our findings. Despite this, however, ABPM did improve on casual blood pressure in predicting renal and cerebral target-organ damage.

The absence of an association between HT and LVH in very elderly women in our study might be due to small sample size. Alternatively, it could indicate that HT affects cardiac structure differently in men and women in this age group. Differences in left ventricular mass between HT and NT women could be more difficult to detect because of a high prevalence of LVH in elderly women, both NT and HT. The Framingham study reported a 34% prevalence of LVH in elderly women of mean age 69 years who were considered to
be free of clinical cardiovascular disease. The mean LVMI for both HT and NT women in our study was >110 g/m², the cutoff for LVH in females in the Framingham study. This figure is, however, derived from a much younger population who also had lower blood pressure levels than did the subjects in the present study.

In nondiabetic, HT subjects, microalbuminuria is an indicator of glomerular vascular injury or dysfunction. In HT subjects, its presence is associated with higher urinary albumin concentrations, and the association was strongest for ABP, particularly nocturnal blood pressure. Our finding is consistent with those of other studies, which have reported that a nocturnal blood pressure elevation is particularly associated with urinary albumin excretion and other indicators of HT target-organ damage. The renal and cerebral findings in the present study suggest that elevation of basal or resting blood pressure, as represented by nocturnal blood pressure, is especially harmful.

PVH on brain magnetic resonance imaging scans represents white-matter ischemia, and PVH is associated with age, cerebrovascular disease, and HT. Cognitive impairments ranging from subtle neuropsychologic deficits to clinical dementia are also associated with white-matter changes. Shimada and colleagues in Japan found an association between HT and severity of PVH in healthy, younger elderly subjects, of mean age 70 years, with no history of cerebrovascular disease. In the present study, subjects were of equal age in both groups, were free of clinical cardiovascular disease, and had normal cognitive function. Therefore, the positive association between PVH and increasing blood pressure that was apparent was not influenced by the common confounding factors. In keeping with previous reports, we also found that ABP had a stronger correlation with PVH than did CBP. Our findings are consistent with the concept that HT is responsible for subclinical or latent cerebrovascular disease in healthy, very elderly people, because we found a positive association between PVH and increasing blood pressure.

The ability of large arteries to “cushion” the pulsatile flow of ventricular ejection and convert this to laminar flow, arterial compliance, diminishes with age as arteries stiffen. PWV serves as a clinically useful index of arterial stiffness; velocity is greater in stiffer arteries. A positive association between PWV and cardiovascular damage has been reported in both cross-sectional and prospective studies. Age and blood pressure are 2 of the most important determinants of arterial stiffness and PWV. One might have expected therefore to find greater PWV in the HT subjects in the present study. A possible explanation for the absence of a difference is that after the passage of 80 years and more, the process of age-related arterial change, calcification and loss of elastic tissue in the medial layer, has advanced to such an extent that the additional effect of HT on large-artery distensibility is small. The mean values of PWV in the present study are well in excess of those reported in healthy, elderly subjects of younger age and similar to those reported among hospitalized, very elderly subjects of similar age. In the very elderly, therefore, age-related change might be the dominant influence on large-artery compliance.

Our study does have some limitations; in particular, the sample size was relatively small, and this might have made it more difficult to detect differences between groups. Considering that there was a significant, positive correlation between CBP and PVH grade, it is possible that a larger sample size would have resulted in a significant difference in PVH grade between the 2 groups. Although gender does influence left ventricular mass independent of body size and, therefore, cardiac data were analyzed separately by gender, published data do not suggest that the other indices of target-organ damage are significantly influenced by gender. Of the HT subjects who were taking treatment, some discontinued treatment for a minimum of only 2 weeks, which is less than the usual drug cessation period of 4 weeks. This might have made it more difficult to detect differences between HT and NT subjects. Although the subjects were screened to exclude disease, in this age group it is difficult to categorically exclude occult disease, which might have influenced results.

**Perspectives**

We have demonstrated that in advanced old age, HT is associated with evidence of target-organ damage in multiple organ systems, including renal, cerebral, and in men, cardiac. ABP is independently associated with indicators of cerebral and renal target-organ damage in this age group and might therefore be a useful instrument in identifying HT patients with greater severity of cardiovascular damage and increased risk. Although the benefits of antihypertensive treatment have not been established in people aged >80 years, our findings suggest that there is no upper age limit beyond which HT ceases to cause target-organ damage.

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**References**

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