BLOOD PRESSURE 2002; 11: 352–356

Cardiovascular Risk In White-coat and Sustained Hypertensive Patients

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Celis H, Staessen JA, Thijs L, Buntinx F, De Buyzere M, Den Hond E, Fagard RH, O'Brien ET. *Cardiovascular risk in white-coat and sustained hypertensive patients.* Blood Pressure 2002; 11: 352–356.

We compared cardiovascular outcome between patients with white-coat and sustained hypertension who had previously participated in the Ambulatory Blood Pressure Monitoring and Treatment of Hypertension (APTH) trial. Baseline characteristics, including office and ambulatory blood pressure (BP), were measured during the 2-month run-in period of the APTH trial. During follow-up, information on the occurrence of major cardiovascular events (death, myocardial infarction, stroke and heart failure), achieved office BP and treatment status was obtained. At entry, 326 patients had sustained hypertension (daytime ambulatory BP $\geq$140 mmHg systolic and/or $\geq$90 mmHg diastolic) and 93 had daytime ambulatory BP below these limits and were classified as white-coat hypertensives. During 2088 patient-years of follow-up (median follow-up 5.3 years), all major cardiovascular events ($n = 22$) occurred in the patients with sustained hypertension (rate 12.7 per 1000 patient-years, $p = 0.02$ for between-group difference). Furthermore, multiple Cox regression confirmed that after adjustment for important covariables, daytime ambulatory BP – but not office BP at entry – significantly and independently predicted cardiovascular outcome. After additional adjustment for office BP, daytime ambulatory BP still predicted the occurrence of major cardiovascular events. Although white-coat hypertension was less frequently associated with antihypertensive drug treatment during follow-up, it carried a significantly better prognosis than sustained hypertension. *Key words: ambulatory blood pressure, cardiovascular risk, office blood pressure, sustained hypertension, white-coat hypertension.*

INTRODUCTION

White-coat hypertension is usually defined as a high blood pressure (BP) on conventional measurement in the doctor's office in the presence of a normal daytime ambulatory BP [1–5]. The prevalence of white-coat hypertension depends on the thresholds to diagnose the condition and varies from 15% to over 50% of patients with mildly elevated office BP [4, 6, 7]. In view of the high prevalence of white-coat hypertension, we compared cardiovascular outcome of patients with white-coat and sustained hypertension, who had been randomized in the Ambulatory Blood Pressure Monitoring and Treatment of Hypertension Trial (APTH) [8, 9] and who were followed-up until January 31, 2001.

METHODS

The study population consisted of 419 patients whose office diastolic BP measured off treatment was 95 mmHg or more and who previously participated in the APTH trial [8–10]. In line with previous publications [11–14], we classified patients as white-coat hypertensive if their average daytime ambulatory BP was $<$140 mmHg systolic and $<$90 mmHg diastolic. Those with higher daytime BP were considered to have sustained hypertension.

The characteristics of the patients at baseline, including office and ambulatory BP were measured during the run-in period of the APTH trial [8], when the patients were on single-blind placebo treatment for 2 months. Office BP was the average of six sitting readings, three at each of two baseline visits, approximately 1 month apart. Daytime BP was the mean of all ambulatory readings between 10.00 and 20.00 h, weighted for the time interval between consecutive readings [15]. The Sokolow–Lyon index was calculated as the sum of the S wave in V1 and the tallest of either the R wave in V5 or V6.

To obtain follow-up information, we asked each patient's personal physician to return a standardized questionnaire on vital status, cause of death, incidence of major cardiovascular events, treatment status and achieved office BP levels. Major cardiovascular events included cardiovascular death, myocardial infarction, stroke and heart failure. In case an event had occurred,

 ISSN 0803-7051

Table I. *Baseline and follow-up characteristics of patient with white-coat and sustained hypertension at entry*

	Type of hypertension		
	White-coat	Sustained	*p*
Number of patients	93	326	–
Baseline characteristics			
Age (SD), years	50.3 (12.5)	53.2 (11.0)	0.04
Body mass index (SD), kg/m^2	29.6 (5.0)	28.6 (4.5)	0.05
Office BP (SD), mmHg			
Systolic	157.1 (19.1)	166.8(20.1)	≤0.001
Diastolic	100.1 (6.5)	104.4 (9.6)	≤0.001
Daytime ambulatory BP (SD), mmHg			
Systolic	131.2 (6.4)	155.1 (14.0)	≤0.001
Diastolic	81.6 (5.8)	98.4 (9.6)	≤0.001
Women, n (%)	59 (63.4%)	167 (51.2%)	0.04
Current smoker, n (%)	11 (11.8%)	66 (20.3%)	0.06
Drinking alcohol, n (%)	42 (45.2%)	175 (53.7%)	0.15
Previous antihypertensive treatment, n (%)	54 (58.1%)	233 (71.5%)	0.01
Characteristics at end of follow-up			
Office BP (SD), mmHg			
Systolic[a]	144.2 (16.3)	142.4 (17.5)	0.39
Diastolic[a]	89.6 (10.2)	87.7 (10.7)	0.13
Current antihypertensive drug intake, n (%)[b]	75 (80.6%)	298 (91.4%)	0.003

BP, blood pressure.
Sustained hypertension was defined as daytime ambulatory BP ≥140 mmHg systolic or ≥90 mmHg diastolic; all remaining patients had white-coat hypertension.
[a] In patients experiencing a major cardiovascular event this variable reflects the last known BP before the occurrence of the event.
[b] In patients experiencing a major cardiovascular event this variable reflects the last known antihypertensive treatment status before the occurrence of the event.
p, level of statistical significance for difference between groups.

the physicians provided additional clinical information and documentation [16]. In patients with more than one event, only the first event was considered in cause-specific analyses.

Database management and statistical analysis were performed using SAS version 6.12 (SAS Institute Inc, Cary, NC). We compared means and proportions using the standard *z* test and the χ^2 statistic or Fisher's exact test, respectively. Event rates were compared using Kaplan–Meier survival curves and the log-rank test. In multiple Cox regression, we allowed for sex, age, antihypertensive treatment before entry, smoking and the level of the office BP at baseline.

RESULTS

At entry (Table I), the 93 patients with white-coat hypertension had a more favourable cardiovascular risk profile than the 326 patients with sustained hypertension. Median follow-up (5.3 years, range 0.1–7.5 years) was similar in patients with white-coat and sustained hypertension. At the end of follow-up (Table I), office BP was similar in the two groups, but fewer patients with white-coat hypertension were taking antihypertensive drugs. During 2088 patient-years of follow-up, 20 patients experienced 22 major cardiovascular events (four deaths, eight myocardial infarctions, seven strokes and three cases of heart failure). All major cardiovascular events occurred in patients with sustained hypertension (rate 12.7 per 1000 patient-years, $p = 0.02$ for between group difference, Fig. 1).

Longitudinal electrocardiograms of sufficient quality were available for 107 patients (22 with white-coat hypertension and 85 with sustained hypertension). Analysis restricted to this cohort, revealed that the significant difference in Sokolow–Lyon index at baseline (white-coat vs sustained hypertension, 21.5 vs 24.3 mm, $p = 0.04$) weakened to a non-significant level during follow-up (19.2 vs 21.5 mm, $p = 0.20$), even after correction for the baseline voltages and other covariables including age, sex, body height and body weight.

To further explore the prognostic significance of office and ambulatory BPs, we performed a multiple Cox regression in which we adjusted for the differences in cardiovascular risk factors at entry (Table I). Our model allowed for sex, age, antihypertensive drug treatment before enrolment and smoking. With these adjustments applied, cardiovascular outcome was significantly and

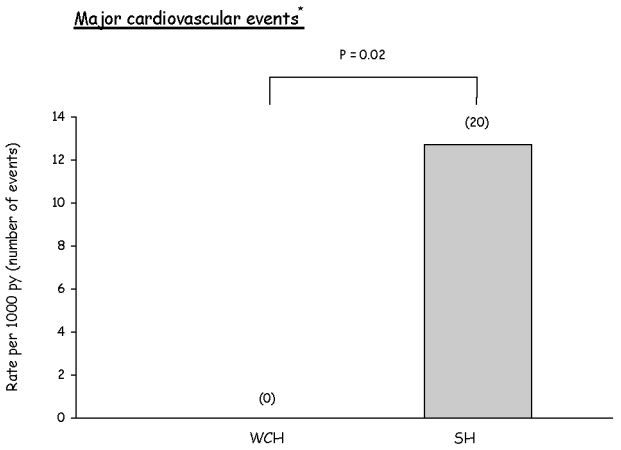

Fig. 1. Major cardiovascular events in patients with white-coat and sustained hypertension. WCH, white-coat hypertension; SH, sustained hypertension; py, patient-years. * In patients experiencing more than one cardiovascular event, only the first occurring cardiovascular event was taken into account

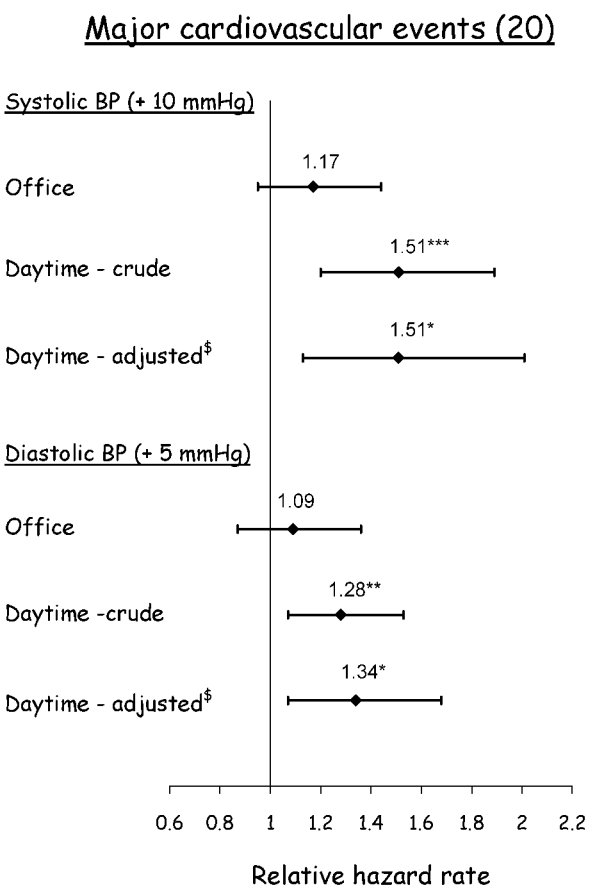

Fig. 2. Crude and adjusted relative hazard rates for systolic and diastolic blood pressure on office and ambulatory measurement at entry. BP, blood pressure; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. $ Adjusted for sex, age, smoking habits at entry, antihypertensive drug treatment before entry and the level of the office blood pressure at entry.

independently correlated with systolic and diastolic daytime BPs, but not with the corresponding office BPs. Further adjustment for the office BP confirmed the significant correlation between cardiovascular outcome and daytime ambulatory BP. The relative hazard rates associated with a 10/5 mmHg higher systolic/diastolic daytime BP were 1.51 (95% confidence interval, 1.13–2.01) and 1.34 (1.07–1.68), respectively (Fig. 2).

DISCUSSION

Follow-up of our patients previously randomized in the APTH trial ($n = 419$) [8–10] demonstrated that all major cardiovascular events occurred exclusively in patients with sustained hypertension. Multiple Cox regression, in which we adjusted for the differences in cardiovascular risk between patients with white-coat and sustained hypertension, confirmed that daytime ambulatory BP refined the prediction of major cardiovascular events over and beyond the office BP.

In the APTH trial, antihypertensive drug treatment was adjusted to attain a diastolic BP level of 80–89 mmHg on conventional or daytime ambulatory BP measurement [8–10]. For this reason and in keeping with several other publications [6, 12–14], we used daytime ambulatory BP values lower than 140 mmHg systolic and 90 mmHg diastolic to diagnose white-coat hypertension. Recent guidelines [17, 18] advocate a daytime BP level of 135/85 mmHg as the upper limit of normalcy. When we repeated our analyses using the latter thresholds, we obtained comparable results. Again, all major cardiovascular events occurred in the patients with sustained hypertension (rate of major cardiovascular events = 11.2 per 1000 patient-years), but due to the redistribution of patients form the group with white-coat hypertension ($n = 48$) to the group with sustained hypertension ($n = 371$), the p-value no longer reached the 5% level of significance.

Perloff *et al.* were the first to demonstrate that the prognostic accuracy of BP measurement was increased by ambulatory monitoring [19, 20]. They showed that the portion of the daytime ambulatory BP, which was not already explained by systolic or diastolic office BP, could discriminate high-risk from low-risk hypertensive patients [20]. Further analyses in a subgroup of untreated patients [19] confirmed that with stratification for previous cardiovascular complications and with cumulative adjustments for office BP, sex, age, electrocardiographic left ventricular hypertrophy and subsequent antihypertensive therapy, a higher systolic ambulatory BP was still a strong predictor of a worse cardiovascular

prognosis. After publication of these seminal papers, several other studies identified ambulatory BP as an independent predictor of target organ damage [21, 22] or cardiovascular risk [2, 15, 23, 24], even after controlling for the level of office BP.

Other investigators compared target organ damage and/or cardiovascular risk between patients with normotension, white-coat hypertension and sustained hypertension. Despite the use of varying criteria to define white-coat hypertension, several [2, 3, 7, 25–27], albeit not all [12, 28–30] publications suggest that on balance cardiovascular risk is comparable in patients with white-coat hypertension and normotension, especially if low cut-off values for the (daytime) ambulatory BP are applied [2, 3, 7, 26, 27]. In a follow-up of patients with hypertension and normotensive controls, Verdecchia *et al.* [2, 3, 7] defined white-coat hypertension as a daytime ambulatory BP <136/87 mmHg in men and 131/86 mmHg in women. They reported that, after adjustment for the traditional markers of cardiovascular risk, morbidity did not differ between the normotensive subjects and those with white-coat hypertension. Our study population did not include normotensive subjects. However, cardiovascular risk was negligible in our patients with white-coat hypertension and our findings support the notion that the cardiovascular risk of normotensive and white-coat hypertensive subjects may be similar [2, 3, 7, 25, 26]. Although the possibility of publication bias – making the publication of non-significant results less likely – cannot be fully excluded, our results are nevertheless in agreement with the majority of published data, indicating that patients with white-coat hypertension have a lower risk of cardiovascular complications [2, 3, 6, 7, 11, 19, 32, 33] and target organ damage [6, 11, 26, 30–32] than their counterparts with sustained hypertension. We found only two studies that did not support this hypothesis. Strandberg *et al.* [29] reported that white-coat hypertension had a worse prognosis in terms of higher total mortality than sustained hypertension. However, these results should be interpreted with caution, since the definition of white-coat hypertension was unusual and based on the difference between BP measurements performed by doctors and nurses. Muldoon and colleagues [12] conducted a matching study in which male patients were matched on the basis of race and office and ambulatory BP levels. They found that the risk of target organ damage (carotid artery atherosclerosis) was greater in patients with white-coat hypertension as compared to normotensives and similar to that of patients with persistent hypertension.

Our results are similar to a report published by Khattar and colleagues [6]. They also recruited patients with white-coat and sustained hypertension and did not enrol patients with normotension. They used continuous intra-arterial BP readings instead of intermittent non-invasive BP measurement with as diagnostic cut-off points for the 24-h ambulatory BP values <140 mmHg systolic and <90 mmHg diastolic. They reported that patients with white-coat hypertension had a lower risk (relative hazard rate 0.29, 95% confidence interval (0.10–0.91)) of experiencing a cardiovascular event than those with sustained hypertension.

In conclusion, we found that white-coat hypertension although associated with less intensive antihypertensive drug treatment during follow-up, carried a significantly better prognosis than sustained hypertension. However, whether white-coat hypertension is also associated with a higher risk of developing sustained hypertension remains to be elucidated.

ACKNOWLEDGEMENTS

The APTH follow-up study was sponsored by AstraZeneca (Brussels, Belgium). Follow-up of the APTH patients was only possible thanks to the collaboration of the patients and their physicians, the relentless help of Paul Drent (Study Coordinating Centre, Leuven, Belgium) and Claude Vincent (AstraZeneca, Brussels, Belgium). In addition, the authors gratefully acknowledge expert technical and secretarial assistance of Cindy Corijn (AstraZeneca, Brussels, Belgium), and Lutgart De Pauw, RN, Fan Heng, Yvette Toremans, Sylvia Van Hulle, RN and Renilde Wolfs (Study Coordinating Centre, Leuven, Belgium) and the support provided by Christophe Giot, MD and Guy Vandenhoven, MD (AstraZeneca, Brussels, Belgium).

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Submitted August 9, 2002 accepted September 4, 2002

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