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ORIGINAL CONTRIBUTIONS

Risk Factors Promoting Hypertensive Crises: Evidence From a Longitudinal Study

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BACKGROUND
Current knowledge about risk factors promoting hypertensive crisis originates from retrospective data. Therefore, potential risk factors of hypertensive crisis were assessed in a prospective longitudinal study.

METHODS
Eighty-nine patients of the medical outpatient unit at the University Hospital of Bern (Bern, Switzerland) with previously diagnosed hypertension participated in this study. At baseline, 33 potential risk factors were assessed. All patients were followed-up for the outcome of hypertensive crisis. Cox regression models were used to detect relationships between risk factors and hypertensive crisis (defined as acute rise of systolic blood pressure (BP) ≥200 mm Hg and/or diastolic BP ≥120 mm Hg).

RESULTS
The mean duration of follow-up was 1.6 ± 0.3 years (range 1.0–2.4 years). Four patients (4.5%) were lost to follow-up. Thirteen patients (15.3%) experienced hypertensive crisis during follow-up. Several potential risk factors were significantly associated with hypertensive crisis: female sex, higher grades of obesity, the presence of a hypertensive or coronary heart disease, the presence of a somatoform disorder, a higher number of antihypertensive drugs, and nonadherence to medication. As measured by the hazard ratio, nonadherence was the most important factor associated with hypertensive crisis (hazard ratio 5.88, 95% confidence interval 1.59–21.77, $P < 0.01$).

CONCLUSIONS
This study identified several potential risk factors of hypertensive crisis. Results of this study are consistent with the hypothesis that improvement of medical adherence in antihypertensive therapy would help to prevent hypertensive crises. However, larger studies are needed to assess potential confounding, other risk factors and the possibility of interaction between predictors.

Keywords: *blood pressure; blood pressure monitoring; ambulatory; hypertension; hypertensive crisis; medication adherence*

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Hypertensive crisis presents as an acute elevation of blood pressure (BP) mostly associated with systemic symptoms as a consequence of elevated BP.[1] It is a common problem in hypertensive patients and may cause life-threatening complications.[2–4] Therefore, the search for risk factors associated with hypertensive crises is important. Current knowledge about such risk factors originates from retrospective cross-sectional or survey studies.[3–8] In these studies, ineffective BP control as well as nonadherence with antihypertensive treatment were identified as independent risk factors for hypertensive crises. However, selection or recall bias and confounding may be inherent in retrospective studies and the findings of these studies have never been confirmed in prospective studies. One recent systematic review concluded that although poor compliance is assumed to be an important explanation for inadequate BP control, any convincing empirical evidence to support this hypothesis is currently lacking.[9] Regarding predictors of hypertensive crisis, only one prospective study was conducted so far.[10] Predictors in this study, however, were confined to BP measures derived from 24-h ambulatory BP monitoring (ABPM). We therefore conducted a prospective longitudinal study elucidating a broad spectrum of potential risk factors promoting hypertensive crises.

METHODS

Study population. For participation in this prospective longitudinal study, 112 consecutive patients aged 18 years or older in whom 24-h ABPM was performed during a predefined time-period (December 2006–August 2008) at the medical outpatient unit of the University Hospital of Bern were eligible. Patients were referred to 24-h ABPM by their treating physician at the medical outpatient unit or by a local general practitioner for the evaluation of either suspected hypertension or for the evaluation of BP during therapy. Patients with at least one of the two following a priori criteria were excluded. First,

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21 patients who did not have high BP according to current guidelines were excluded.[1] The rationale for this approach was based on the assumption that the incidence of hypertensive crisis in these normotensive patients is very low and that risk factors differ considerably between patients with or without hypertension (e.g., pre-eclampsia or drug intoxication as risk factors in normotensive patients). Second, 2 patients who did not give consent to study participation were excluded. Finally, 89 patients constituted the study population (**Figure 1**). The institutional ethical committee approved the study, which was conducted in compliance with the Declaration of Helsinki.

The date of the 24-h ABPM (Boso TM-2430; Boso, Jungingen, Germany or SunTech Oscar 2; SunTech Medical, Morrisville, NC) was utilized to set the start point for each subject. At study start, hypertension was diagnosed in all participants according to current guidelines.[1] Clinical history was assessed in all patients. Urine test, creatinine, potassium, fasting plasma glucose, and thyroid-stimulating hormone were consistently measured in all patients as part of standard of care. Further diagnostic tests for secondary causes (e.g., diagnostic imaging of renal artery and kidneys, cortisol, renin, aldosterone) were performed, if clinical findings suggested such a disorder. An electrocardiogram was performed at the discretion of the treating physician. Antihypertensive treatment was initiated by the treating physician according to current guidelines. Drug therapy was begun, if BP goals were not achieved by lifestyle modification, or intensified, if the patient already had drug therapy and BP was inadequately controlled.

Assessment of risk factors. The following potential risk factors for hypertensive crisis were assessed: age, sex, baseline systolic or diastolic BP, stage of hypertension at the time of diagnosis, duration of known hypertension, presence of hypertensive heart disease or renal disease, body mass index (BMI), grade of obesity, presence of cardiovascular risk factors other than hypertension (diabetes mellitus, smoking, or hyperlipidemia), presence of coronary or peripheral artery disease, presence of cerebrovascular disease, alcohol abuse, depression, somatoform disorder, hyperthyroidism, thyroid-stimulating hormone, creatinine, proteinuria, the number of antihypertensive drugs, nonadherence to medication, and characteristics of the 24-h ABPM (systolic, mean, or diastolic BP values during day- or night-time, presence of nocturnal dipping, and inadequate BP control). Definitions used for these risk factors are provided hereafter.

The stage of hypertension was defined according to current guidelines.[1] Stage 1 hypertension constituted systolic BP of 140–159 mm Hg or diastolic BP of 90–99 mm Hg, stage 2 hypertension systolic BP of ≥160 mm Hg or diastolic BP of ≥100 mm Hg. Hypertensive heart disease was considered present, if electrocardiogram (performed in 60 patients) or echocardiography (performed in 31 patients) were compatible with hypertensive heart disease. Grade of obesity was defined based on the BMI (BMI <30.0 grade 0, BMI 30.0–34.9 grade 1, BMI 35.0–39.9 grade 2, BMI ≥40.0 grade 3).[11,12] Diagnosis of diabetes mellitus was made, if fasting plasma glucose was ≥7 mmol/l on at least two different days or if postprandial plasma glucose was ≥11.1 mmol/l.[13] Coronary artery disease was considered present, if the diagnosis was made earlier based on appropriate diagnostic testing (e.g., coronary angiography) or based on a known previous coronary event. Presence of peripheral artery disease or cardiovascular disease was defined accordingly. Alcohol abuse was considered present, if the daily alcohol consumption exceeded three drinks a day (corresponding to ~30 g/day).[14] Depression or somatoform disorders were considered present, if these diagnoses had been previously made by experienced physicians according to DSM-IV criteria. The number of antihypertensive drugs was assessed baseline. A patient was considered nonadherent to medication, if the treating physician asked the patient whether he took medication irregularly and if irregular mediation use was documented in the medical record. Nocturnal BP dipping was defined as >10% dipping of average mean arterial pressure at night compared to daytime.[15] Inadequate BP control was defined as average systolic BP >140 mm Hg and/or average diastolic BP >90 mm Hg during 24-h ABPM.

Outcome and follow-up. Hypertensive crisis constituted the main outcome. The following criteria had to be fulfilled for the diagnosis of a hypertensive crisis according to current literature: (i) systolic BP ≥200 mm Hg and/or diastolic BP ≥120 mm Hg and (ii) rise in BP was acute.[1,16,17] Thus, the end-point definition included hypertensive urgencies (mildly/asymptomatic acute elevation of BP) as well as hypertensive emergencies (acute elevation of BP with end-organ damage). For the systolic and diastolic BP values, self-reported information on at least two repeated BP measurements at home or record-based information of at least two BP measurements in an office or a hospital setting was required.

End points were assessed ~1–2 years after the 24-h ABPM. Information was obtained from several sources by two specially trained physicians. First, outpatient medical records were reviewed in all patients for a diagnosis or reporting of a hypertensive crisis because most patients had routine follow-up visits at our medical outpatient unit. Second, if no hypertensive crisis was recorded, a structured patient interview by phone was conducted. Third, additional information was obtained from the general practitioner using a structured interview, if the structured patient interview did not provide clear enough information on whether a hypertensive crisis had occurred or not. If a patient experienced more than one hypertensive crisis, only the first event was assessed.

Statistical methods. Data were analyzed using Stata software (Stata 11.0; StataCorp LP, College Station, TX). Student's *t*-test was used for continuous variables after checking for normal distribution. Mann–Whitney rank-sum test was used for non-normally distributed continuous variables. χ^2-analysis was used for categorical variables with cell counts ≥5; if cell counts were <5, Fisher's exact test was used. Cox proportional hazards models were used to compare hypertensive crisis event rates between different risk factor categories. Hazard ratios

and 95% confidence intervals are provided. Cox proportional hazards models were performed for bivariable relationships as well as after adjustment for age and sex. Logistic regression models were used to detect associations between independent variables and dichotomous, time-independent outcomes.

RESULTS

Follow-up was complete in 85 (95.5%) of the 89 participating patients (**Figure 1**). Four patients (4.5%) were lost to follow-up and excluded from the analysis. In none of these patients was hypertensive crisis or death believed to be the cause for the loss (two patients moved away and did not communicate their new address; two patients were either asylum seekers or foreign workers and left the country during follow-up). The mean duration of follow-up was 1.6 ± 0.3 years (range 1.0–2.4 years).

Baseline characteristics are summarized in **Table 1**. The mean age was 53.8 ± 14.9 years (range 19.9–82.6 years). A rather high proportion of patients were obese with a BMI ≥30.0 kg/m^2. Sixty-nine patients (81.2%) had a prescription for one or more antihypertensive drugs. Sixteen patients (18.8%) were primarily treated by lifestyle intervention and received no antihypertensive drugs. The mean number of prescribed antihypertensive drugs was 2.0 ± 1.6 (range 0–6). Sixty-seven patients (78.8%) had an automated BP device for home BP measurement.

Thirteen patients (15.3%) experienced a hypertensive crisis during follow-up. The mean duration between study inclusion and hypertensive crisis was 303 ± 190 days (range 43–613 days). At the time of hypertensive crisis, mean systolic BP was 212 ± 22 mm Hg and mean diastolic BP was 118 ± 14 mm Hg. Eleven patients (84.6%) had symptoms during hypertensive crisis (e.g., headache, dizziness, visual impairment, nausea). During the structured patient interview, six patients reported a specific cause for the hypertensive crisis: three patients were nonadherent to the prescribed antihypertensive drug therapy, two patients reported emotional stress, and one patient suffered from symptomatic hyperthyroidism at the time of hypertensive crisis.

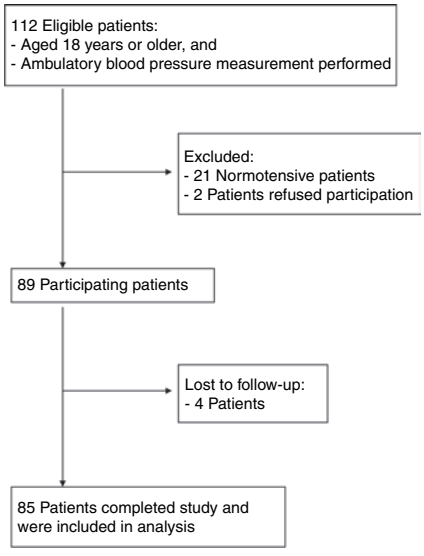

Figure 1 | Flow chart.

Several baseline characteristics significantly differed in patients who experienced a hypertensive crisis and those who did not (**Table 1**). Patients with hypertensive crisis were older, more often were women, had a higher prevalence of hypertensive heart disease or coronary artery disease, and more often had a previous stroke, a thyroid disease, or a somatoform disorder. The number of prescribed antihypertensive drugs was higher among patients with hypertensive crisis. Nonadherence to medication was more prevalent in patients who experienced a hypertensive crisis: 10 of the 13 patients (76.9%) who experienced a hypertensive crisis had a remark in the medical record that the patient was nonadherent. None of the measures derived from 24-h ABPM was significantly different between patients with and without hypertensive crisis.

To detect associations of potential risk factors with hypertensive crisis, Cox proportional hazards models were performed. Several factors were significantly associated with hypertensive crisis in bivariable analysis as well as after adjustment for age and sex (**Table 2**): female sex, higher grades of obesity, the presence of a hypertensive heart disease or a coronary artery disease, the presence of a somatoform disorder, a higher number of antihypertensive drugs, and nonadherence to medication. As measured by the hazard ratio, nonadherence was the most important factor associated with hypertensive crisis. **Figure 2** shows the occurrence of hypertensive crisis subdivided by patients with nonadherence and patients with adherence to medication.

The presence of a somatoform disorder ($P < 0.01$) and a higher number of antihypertensive drugs ($P = 0.04$) were significantly associated with nonadherence to medication. The association remained significant, if the regression model was adjusted by age and sex.

None of the 16 patients who were treated by lifestyle intervention and who did not receive antihypertensive drugs experienced a hypertensive crisis. Therefore, a sensitivity analysis without these 16 patients was performed. In Cox proportional hazards models adjusted for age and sex, the following factors were significantly associated with the occurrence of a hypertensive crisis: female sex ($P < 0.01$), higher grades of obesity ($P = 0.01$), the presence of a somatoform disorder ($P < 0.01$),

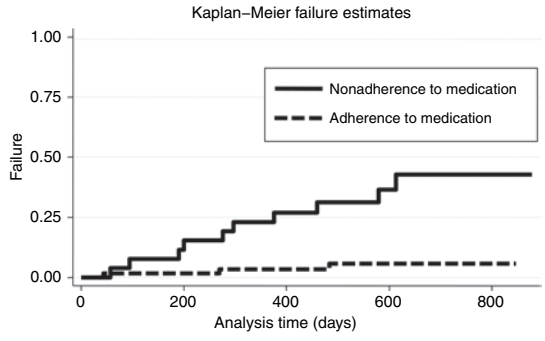

Figure 2 | Kaplan–Meier failure estimates for the occurrence of hypertensive crisis subdivided for patients with nonadherence or adherence to medication.

Table 1 | Baseline characteristics (mean ± s.d. or percentage)

Characteristic	Patients without hypertensive crisis (*N* = 72)	Patients with hypertensive crisis (*N* = 13)	*P* value	All patients (*N* = 85)
Age, years	52.3 ± 15.2	61.8 ± 10.1	0.03	53.8 ± 14.9
Female sex, *n* (%)	23 (31.9)	10 (76.9)	<0.01	33 (38.8)
Systolic BP, mm Hg	137.3 ± 13.0	142.1 ± 16.7	0.24	138.0 ± 13.6
Diastolic BP, mm Hg	80.5 ± 10.9	78.2 ± 11.4	0.49	80.1 ± 10.9
Hypertension, n (%)	72 (100.0)	13 (100.0)	1	85 (100.0)
Stage 1, *n* (%)	53 (73.6)	7 (53.9)	0.15	60 (70.6)
Stage 2, *n* (%)	19 (26.4)	6 (46.1)		25 (29.4)
Body mass index, kg/m^2	29.3 ± 6.3	32.3 ± 6.0	0.11	29.8 ± 6.3
Obesity, n (%)	30 (41.7)	8 (61.5)	0.19	38 (44.7)
Grade 0, *n* (%)	42 (58.3)	5 (38.5)	0.04	47 (55.3)
Grade 1, *n* (%)	20 (27.8)	2 (15.4)		22 (25.9)
Grade 2, *n* (%)	6 (8.3)	5 (38.5)		11 (12.9)
Grade 3, *n* (%)	4 (5.6)	1 (7.7)		5 (5.9)
Hyperlipidemia, *n* (%)	41 (56.9)	10 (76.9)	0.23	51 (60.0)
Diabetes, *n* (%)	14 (19.4)	4 (30.8)	0.46	18 (21.2)
Nicotine, *n* (%)	35 (48.6)	5 (38.5)	0.5	40 (47.1)
Hypertensive heart disease, *n* (%)	15 (20.8)	7 (53.9)	0.01	22 (25.9)
Coronary artery disease, *n* (%)	5 (6.9)	4 (30.8)	0.03	9 (10.6)
Hypertensive renal disease, *n* (%)	8 (11.1)	2 (15.4)	0.65	10 (11.8)
Creatinine, µmol/l	75.6 ± 13.2	79.1 ± 20.7	0.42	76.1 ± 14.5
Renal artery stenosis, *n* (%)	1 (1.4)	0 (0.0)	1	1 (1.2)
Previous stroke, *n* (%)	3 (4.2)	3 (23.1)	0.04	6 (7.1)
Thyroid disease, *n* (%)	10 (13.9)	5 (38.5)	0.03	15 (17.7)
Hyperthyroidism, *n* (%)	0 (0.0)	1 (7.7)	0.15	1 (1.2)
Depression, *n* (%)	13 (18.1)	5 (38.5)	0.1	18 (21.2)
Somatoform disorder, *n* (%)	5 (6.9)	4 (30.8)	0.03	9 (10.6)
Antihypertensive drugs, number of drugs	1.8 ± 1.5	3.0 ± 1.4	<0.01	2.0 ± 1.6
Nonadherence to medication, *n* (%)	16 (22.2)	10 (76.9)	<0.01	26 (30.6)
Achieved BP control during ABPM, *n* (%)	38 (52.8)	7 (53.9)	0.94	45 (52.9)
Alcohol abuse, *n* (%)	12 (16.7)	2 (15.4)	1	14 (16.5)

ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

a higher number of antihypertensive drugs (P = 0.04), and nonadherence to medication (P = 0.02). The presence of a hypertensive heart disease (P = 0.05) or a coronary artery disease (P = 0.06) were close to significance. Thus, these results were similar to the results presented in Table 2.

DISCUSSION

This prospective longitudinal study identified several potential risk factors for hypertensive crisis, namely female sex, the grade of obesity, the presence of a hypertensive heart disease or a coronary artery disease, the presence of a somatoform disorder, a higher number of prescribed antihypertensive drugs, and, most importantly, nonadherence to medication. However, confounding or interaction between these potential risk factors cannot be excluded due to the small sample size. For example, the presence of a somatoform disorder and a higher number of prescribed antihypertensive drugs were significantly associated with nonadherence suggesting a relation between these three factors. This study also suggests that there are specific causes for hypertensive crisis such as hyperthyroidism in some patients.

Previous retrospective studies have presumed that nonadherence to medication is an important risk factor for hypertensive crisis.[3–8] Our results now support this previous finding in a first prospective longitudinal study. This study therefore contributes to the ongoing discussion about whether nonadherence is an explanation for hypertensive crisis or not.[9] Nonadherence was significantly associated with a higher

Table 2 | Variables associated with hypertensive crisis

	Bivariable analysis		Multivariable analysis[a]	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (HR per year increase)	1.04 (1.00–1.08)	0.05	1.03 (0.99–1.07)	0.14
Sex (HR for female vs. male sex)	6.15 (1.69–22.37)	<0.01	5.27 (1.43–19.47)	0.01
Stage of hypertension (HR for stage 2 vs. stage 1)	2.17 (0.73–6.47)	0.16	2.48 (0.81–7.57)	0.11
Grade of obesity (HR per grade increase)	1.68 (1.01–2.79)	0.046	2.28 (1.19–4.37)	0.01
Hypertensive heart disease (HR for presence vs. absence)	3.82 (1.28–11.40)	0.02	4.14 (1.16–14.81)	0.03
Coronary artery disease (HR for presence vs. absence)	4.43 (1.36–14.44)	0.01	3.73 (1.09–12.80)	0.04
Previous stroke (HR for presence vs. absence)	4.39 (1.21–15.97)	0.03	3.02 (0.72–12.72)	0.13
Thyroid disease (HR for presence vs. absence)	3.09 (1.01–9.48)	0.048	1.74 (0.52–5.82)	0.37
Depression (HR for presence vs. absence)	2.36 (0.77–7.21)	0.13	2.13 (0.65–6.98)	0.21
Somatoform disorder (HR for presence vs. absence)	4.55 (1.39–14.87)	0.01	5.05 (1.34–19.03)	0.02
Number of antihypertensive drugs (HR per number of drug increase)	1.45 (1.07–1.97)	0.02	1.68 (1.16–2.44)	<0.01
Nonadherence to medication (HR for nonadherence vs. adherence)	8.51 (2.34–30.95)	<0.01	5.88 (1.59–21.77)	<0.01

CI, confidence interval; HR, hazard ratio.
[a]Adjustment for age and sex.

number of prescribed antihypertensive drugs. This is a well-known phenomenon.[18] Therefore, this study suggests that a higher number of prescribed antihypertensive drugs is not a true risk factor for hypertensive crisis, but related to hypertensive crisis via nonadherence.

In this study, the proportion of women experiencing hypertensive crisis was higher than that of men. Several previous studies found indications of an increased incidence of hypertensive crisis in women, but without satisfying explanations for these findings.[4,19,20] It is well established that women more often suffer from somatoform disorders as compared to men and that this disease is associated with nonadherence.[21–23] Therefore, a plausible explanation for the findings of our study might be that women had a higher prevalence of somatoform disorders predisposing these women to nonadherence. Regression analysis in our study supports this hypothesis.

A further finding was that the risk for hypertensive crisis was associated with the grade of obesity at the time of diagnosis. To the best of the authors' knowledge, this finding has previously not been reported. However, it is known that hypertension control is more difficult in obese than in lean patients. The underlying pathophysiological mechanism is not fully understood, but overactivity of the sympathetic nervous system (e.g., due to hyperleptinemia) or the renin–angiotensin–aldosterone system as well as physical compression of the kidneys seem to play a role in this scenario.[24,25]

Our study has limitations. First, the sample size of 85 patients was small. It was too small for meaningful multivariable regression models involving more than three variables. However, sample size was adequate to identify several significant associations as potential risk factors of hypertensive crises. Second, the patients included in this study had 24-h ABPM at a university hospital which might have led to a selection of patients with rather severe hypertension, thus possibly limiting the generalizability of our data. Third, some hypertensive crises may have been missed because it was impossible to continually monitor BP during follow-up. Furthermore, unequal follow-up periods or patients lost to follow-up may have led to missed hypertensive crises. However, outpatient medical records were reviewed in all and structured interviews were conducted with most study participants. The approach in this study has been proven to be effective in the detection of end points.[26,27] Fourth, to be plausible, the association between medical nonadherence and hypertensive crisis requires a proper definition of nonadherence. Generally, medical adherence is defined as the extent to which a patient takes a medication as prescribed by the treating physician.[28] Patients were considered as being nonadherent, if the treating physician asked the patient whether he took medication irregularly and if irregular mediation use was documented in the medical record. This approach should be appropriate. Methods such as pharmacy refills or electronic monitoring of pill cap openings have been shown to be insensitive methods for measuring medical adherence and are not superior to physician's judgment.[29]

This study has research implications. Several potential risk factors for hypertensive crisis were identified, among them nonadherence to medication. These findings have to be confirmed in a larger independent prospective study extended to a more generalized study population (i.e., a study population also seen by general practitioners). Ideally, such a study should not only incorporate the risk factors assessed in this study, but also extend the baseline assessment by further potential explanatory variables (e.g., measurements of different hormones, including leptin and insulin levels to explore the association between obesity and hypertensive crisis). Such a future study might also assess genetic polymorphisms

associated with hypertensive crisis, increased susceptibility to side effects and medication interactions, and/or vascular properties (such as the measurement of pulse wave velocity or augmentation index).[30–32]

In conclusion, this study identified several risk factors for hypertensive crisis, among them nonadherence to medication. Even though there are open questions, this study suggests that the improvement of medical adherence in antihypertensive drug therapy is important to prevent hypertensive crises. Physicians should be aware of medical nonadherence in some subpopulations such as patients with somatoform disorders.

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