Uncontrolled arterial hypertension in primary care – patient characteristics and associated factors

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Summary

PRINCIPLES: Most patients with arterial hypertension are treated in primary care. The objective is to assess characteristics of patients with uncontrolled arterial hypertension and its associated determinants in Swiss primary care.

METHOD: Data on 122 adult patients with uncontrolled hypertension (mm Hg >140 systolic and/or >90 diastolic) was collected from the baseline data of the on-going randomised controlled "CoCo" trial: Colour-coded Blood Pressure Control. Patient and general practitioner characteristics were analysed to investigate the relationship between BP and patient characteristics.

RESULTS: From October 2009 to March 2011 30 general practitioners recruited 122 patients; median age 64 years (IQR 54.8–72), 50% male, median BMI 28.3 kg/m^2 (IQR 25.3–31.7), 21.5% smokers. 65.6% performed home blood pressure measurement, 88.5% received pharmacological treatment, 41.8% mono-therapy. Most frequent dual drug combinations: diuretics/angiotensin-receptor-blockers (33.3%), angiotensin-converting-enzyme-inhibitors/beta blockers (both 28.1%). BMI, smoking and age were independent predictors for elevated systolic blood pressure when controlled for gender, home blood pressure measurement, education, pulse rate and number of antihypertensive substances. We found a significant non-linear association between systolic blood pressure and number of antihypertensive substances. Age and any amount of antihypertensive substances were independently and inversely correlated with diastolic blood pressure. The findings did not change when additionally controlled for general practitioner clustering effect.

CONCLUSION: Smoking and high BMI are strong and independent factors associated with higher blood pressure levels in patients with uncontrolled arterial hypertension. A high rate of monotherapy and a decrease in the incremental gain on blood pressure control when more antihypertensive agents are used highlight the importance of adequate pharmacological treatment as well as risk factor control.

Key words: arterial hypertension; blood pressure; primary care; home blood pressure measurement; general practitioner

Abbreviations

ACEI Angiotensin converting enzyme inhibitors
AH Arterial hypertension
ARB Angiotensin receptor blockers
BB Beta blocker
BP Blood pressure
CCB Calcium channel blockers
EPR Electronic patient record
GP General practitioner
HBPM Home blood pressure measurement
PC Primary care

Introduction

Data on patients with arterial hypertension (AH) from the US and Europe show insufficient blood pressure (BP) control, even though effective antihypertensive treatments as well as guideline recommendations are available [1]. Considering that AH is the most prevalent cardiovascular risk factor worldwide [2] and that even mild AH is associated with increased risk of cardiovascular morbidity and mortality [3, 4], it is important to emphasise the need for strict BP control [5] and to get deeper insight into factors that hinder its achievement.

Most of the international data on BP control originate from national surveys, population based studies or secondary care, despite the fact that the majority of patients are treated in a primary care (PC) setting. Data on patients with uncontrolled AH in PC in Switzerland are limited and vary, reporting AH control rates among patients with pharmacotherapy between 12.5% to 50% [6, 7]. Even the studies performed in the PC setting of countries in which the general practitioner (GP) holds a strong gate-keeping function [8, 9] are often restricted to certain ages or to already existing antihypertensive medications. Since the gate-keeping system in Switzerland is not generally established and is limited to certain insurance models which are currently chosen by the minority of the population, direct knowledge transfer is limited.

Therefore, the objective of this study is to investigate the characteristics of patients with insufficiently controlled BP in Swiss PC and to assess factors associated with uncontrolled BP.

Materials and methods

Recruiting, inclusion and exclusion criteria

Data originated from baseline data of the on-going pragmatic "CoCo"-Trial: **Co**lour-coded Blood Pressure **Co**ntrol (*Trial Registration Number:* NCT01013467) [10] that investigates the effect of a colour coded BP monitoring on adherence and BP control. GPs were recruited via direct emailing, announcing the study in a Swiss PC journal and by information events. Patients were recruited by their participating GP.

Inclusion criteria
– BP >140 mm Hg systolic and/or >90 mm Hg diastolic in the practice measurement (two consecutive measurements carried out in the practice, measured by the GP or practice assistant at the start of the study. Both measurements must meet the inclusion criteria with the second measurement qualifying for inclusion). 140 mm Hg systolic and/or 90 mmHg diastolic was chosen as cut-off according to current Swiss guidelines for the treatment of AH [11]
– No change in AH medication within the last month
– Patient able to perform self-monitoring
– Written informed consent

Exclusion criteria
– Insufficient knowledge of the German language for instruction and BP recording with a booklet
– BP above 180 mm Hg systolic and/or 110 mm Hg diastolic (due to safety/risk considerations)
– Serious general or psychological illness (malignant tumours, serious depressive episodes or evidence of dementia)

GPs asked all consecutively appearing patients with known AH and fitting inclusion criteria for consent to participate in the study. Also patients without known diagnoses of AH who underwent routine BP measurement at the practice where asked for consent to participate in the study if the practice measurement was >140 mm Hg systolic or >90 mm Hg diastolic and no exclusion criteria existed. The inclusion and exclusion criteria were low threshold in order to reflect real life situation. Inclusion began in October 2009 and ended in March 2011.

Blood pressure measurement

In accordance with guidelines [12, 13] two consecutive oscillometric BP readings were performed in seated position after a resting period of at least 5 minutes. The physicians all used the same validated BP measuring devices (MioStar Cardioplus 500) which were provided by the Institute of General Practice and Health Services Research. GPs were instructed to choose appropriate cuffs according to the upper-arm circumference of the patients.

Socio-demographic and clinical information

Additional socio-demographic and clinical information (age, weight, height, smoking habits, years of education [starting in primary school], previous home-BP-measurement [HBPM]) were collected. Antihypertensive medication was classified as follows: Angiotensin receptor block-ers (ARB), Calcium channel blockers (CCB), Beta-block-ers (BB), Angiotensin converting enzyme inhibitors (ACEI), diuretics and other antihypertensive drugs.

Data processing

The anonymous data forms were faxed to the project leaders and data was entered by an independent employee. All patients gave written informed consent.

The study protocol was approved by the ethics committee of Zurich (Kantonale Ethikkommission (KEK) Zürich (EK-1738).

Statistical analysis

Continuous variables were tested for normal distribution by the Shapiro-Wilk test and presented accordingly as median and interquartile range (IQR) or as mean and standard deviation (SD), categorical data are presented as frequencies. We compared patient and GP characteristics using non parametric (wilcoxon rank sum) and parametric (unpaired t-test) tests, depending on normal distribution tests. Univariate linear regression analyses were performed to investigate the relationship between systolic and diastolic BP and all available patient characteristics. To investigate the independent association between BP measures and patient characteristics, multiple linear regression was applied. For the multiple linear regression models the same patient characteristics were considered as for the univariate analyses, irrespective of the significance levels based on the univariate analysis. The possibility of a non-linear relationship between BP measurements and the number of antihypertensive agents was taken into account by introducing a quadratic term of the predictor variable into the model. The purpose of introducing the quadratic term was to investigate the possibility of diminishing efficacy of multiple combination therapy on BP control. Goodness of fit (R^2) was compared between models (i.e. linear- and non-linear modelling) by F-tests. We further used multilevel regression analysis with the GP as cluster level thus taking into account that patient observations are not independent, i.e. observations in one cluster tend to be more similar to each other than to individuals in the rest of the sample. The amount of clustering (i.e., the variation that is explained by the GP level) was assessed by calculating the intraclass correlation coefficient (ICC) ranging from 0% (i.e., no evidence for clustering) to 100% (i.e., all the variation in BP difference is explained on GP level). A two-sided alpha of 0.05 was set as level of significance for all comparisons.

All analyses were calculated using the STATA statistical package, version 11.2 (Stata Incorporation, College Station, TX, USA).

Results

Between end of October 2009 and March 2011, 122 patients were included in the study.

Patient characteristics

Data on 122 adult patients with uncontrolled AH (above 140 mm Hg systolic and/or 90 mm Hg diastolic) [11] was collected. In table 1 the detailed study population characteristics can be appreciated. 43.8% of the patients were

overweight (BMI between 25 and 30 kg/m^2), 34.7% were obese (BMI 30 kg/m^2 and more), median BMI was 28.3 kg/m^2 (IQR 25.3–31.7). Slightly greater than half (52.1%) of patients were persistent (21.5%) or ex-smokers (30.6%). The mean systolic and diastolic BP was 157 and 92 mm Hg (SD 15.3 and 9.7). The majority performed HBPM at the time of inclusion into the study (65.6%). 60.0% of patients met inclusion criteria for both systolic and diastolic BP, 36.7% only for systolic and 3.3% only for diastolic BP. Data on patients receiving and not receiving pharmacological AH treatment were pooled for all further analyses since at the time of inclusion into the study besides diastolic BP no difference in patient characteristics (e.g., HBPM, gender, age, BMI, education pulse rate, smoking status and systolic BP) existed.
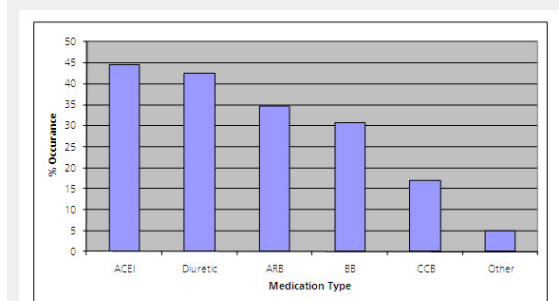
Medication

88.5% of the patients received antihypertensive treatment, in 41.8% a mono-therapy, followed by a dual therapy (30.3%). 16.4% received three or more antihypertensive agents. In total, 46.7% of patients with uncontrolled AH received 2 or more antihypertensive agents (fig. 1).
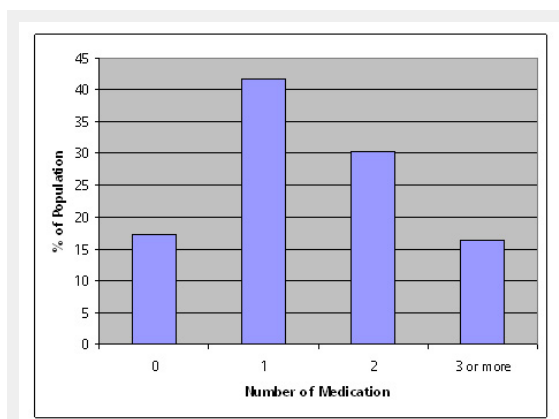
Figure 1

Distribution of number of antihypertensive agents per patient. Total population n = 122. The majority of patients received a monotherapy.

Figure 2

Overall distribution of antihypertensive agents. Other refers to imidazolin receptor antagonist (= moxonidin; causes blood pressure lowering by central adrenergic stimuli with resulting reduction in peripheral vascular resistance). ACEI and diuretics were the overall most commonly prescribed antihypertensive substances.
BB = beta blockers; CCB = calcium channel blockers; ARB = angiotensin receptor blockers; ACEI = angiotensin converting enzyme inhibitors.

The overall most commonly prescribed antihypertensive agents were ACEI (44.6%), followed by diuretics (42.6%) and ARB (34.7%), BB (30.7%) and CCB (16.8 %) (fig. 2). ACEI were the most commonly prescribed monotherapy (39.2%), followed by ARB (29.4%), BB (17.7%), diuretics (9.8%) and CCB (6.9%).

The most established dual drug combinations were diuretic + ARB (33.3%), followed by diuretic + ACEI, as well as diuretic + BB (both 28.1%) (fig. 3).

Influence of patient characteristics on blood pressure

The univariate regression analyses of patient characteristics influencing systolic and diastolic BP are presented in table 2. Smoking status (former and current compared to never smokers) was significantly and positively associated with systolic BP, whereas BMI only showed a trend for positive association (p = 0.071). The number of antihypertensive agents showed no linear relationship with systolic BP. However, taking into account a non-linear association (i.e., including a quadratic term) revealed a significant association between systolic BP and number of antihypertensive agents. Amount of antihypertensive agents (linear as well as non-linear term) and age were significantly associated with lower diastolic BP, whereas BMI and pulse rate were positively associated with diastolic BP.

The multivariate analyses for patient characteristics influencing systolic and diastolic BP are presented in table 3. Smoking status (current compared to never smokers), BMI and age were independently and positively associated with higher systolic BP. There was a significant and independent negative association between systolic BP and number of antihypertensive agents. The non-linear (quadratic) term of the number of AH agents was significantly and positively associated with systolic BP, suggesting a decrease of the incremental efficacy of additional antihypertensive substances in lowering systolic BP. Age and the number of
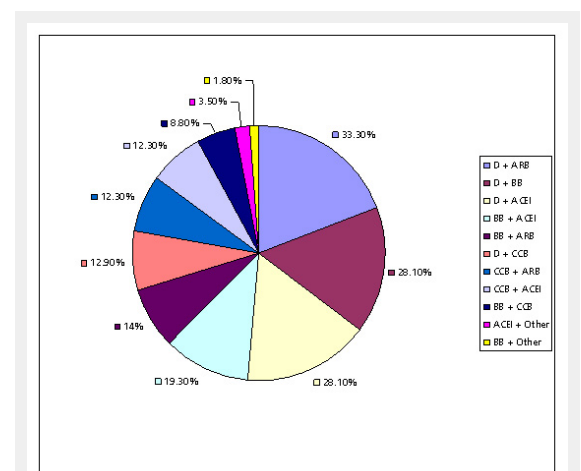
Figure 3

Distribution of antihypertensive dual drug combinations. Composition of dual combination therapies used in the study population (n = 57 with 2 or more antihypertensive drugs). Other refers to imidazolin receptor antagonist. The most commonly prescribed dual drug combination was diuretics with angiotensin receptor blockers.
D = diuretics; BB = beta blockers; CCB = calcium channel blockers; ARB = angiotensin receptor blockers; ACEI = angiotensin converting enzyme inhibitors.

antihypertensive substances were independently and negatively associated with diastolic BP. Goodness of fit for the multivariate model (R^2) was significantly increased when a non-linear association between systolic BP and number of BP medications was taken into account, resulting in R^2 values of 21.6% (linear model) and 30.0% (non-linear model), respectively (p = 0.01 for comparison). For diastolic BP the non-linear model did not result in an increased goodness of fit in the multivariate model. Corresponding R^2 values for linear and non-linear model were 31.7% and 33.7% (p = 0.10 for comparison). The main findings of the multivariate analyses concerning independent associations between patient characteristics and BP were not changed when additionally controlled for the GP as potential cluster effect: In a multilevel regression analysis no clustering effect of GPs on systolic (ICC = 0.04%, p = 0.998) and diastolic (ICC = 10.50%, p = 0.237) BP could be found. The mean number of patients included by GPs in to the study was 4.06 (range 1–8).

GP characteristics

30 GPs from three German speaking cantons, mainly urban (n = 10) and suburban (n = 13) areas of Switzerland (rural n = 7) participated in the study. Significantly more GPs were male (73.3% vs 26.7 %, p <0.05). Thirteen GPs worked in single handed and 17 in group practices. They were all either specialised in internal (n = 15) or general medicine (n = 15). The female participants were significantly younger (median 50 vs 58.5 years, IQR 40–51 vs 48–62, p <0.05) and worked a significantly shorter period of time in the practice (median 2 vs 26, IQR 1–17 vs 3–27, p <0.05), even though the time since completion of the board examination was comparable between the genders (overall mean 28 years). Male and female GPs worked mainly full time, female GPs were more likely to use electronic patient records (EPR) (71.4% vs 23.8%, p <0.05). EPRs have been implemented in practice routine, on average, for 3.5 years (IQR 1–6 years).

Discussion

Our study in patients with uncontrolled AH in Swiss PC showed that in this real life setting about 40% of patients were under single pharmacological treatment. We further found a non-linear (quadratic) relationship between the number of antihypertensive agents and systolic BP. Age, overweight and smoking resulted as predominant factors associated with the level of systolic BP in patients having insufficient BP control.

Table 1: Patient characteristics.	
Age (years)	64 (54.8–72.0)
Male (%)	50
BMI (kg/m^2)	28.3 (25.3–31.7)
Normal (BMI 18.5–25 kg/m^2), (%)	21.5
Overweight (BMI 25–30 kg/m^2), (%)	43.8
Obese (BMI >30 kg/m^2), (%)	34.7
Smoking status (%)	
Never smoked	47.9
Stopped smoking	30.6
Still smoking	21.5
Education (years)	10.0 (8.25–14.0)
Previous home BP-measurement (%)	65.6
Antihypertensive treatment (%)	82.8
Systolic BP (mm Hg)	157.3 (15.3)
Diastolic BP (mm Hg)	91.9 (9.7)
Pulse rate (per minute)	75.0 (11.1)
Continuous variables are presented as median (IQR) or mean (SD).	

Table 2: Patient characteristics and univariate influence on systolic and diastolic blood pressure.				
Characteristics	**Univariate analysis systolic BP**		**Univariate analysis diastolic BP**	
	Regression coefficient	**95% CI**	**Regression coefficient**	**95% CI**
Home-BP-measurement (ref = no)	0.54	–5.83 to 6.92	–2.13	–6.12 to 1.86
Gender (ref = male)	–2.98	–8.89 to 2.92	–1.14	–4.88 to 2.58
Linear *Number of antihypertensive agents*	0.53	–2.53 to 3.59	–3.51	–5.36 to –1.67*
Nonlinear *Number of antihypertensive agents linear term* *Quadratic Term Number of antihypertensive agents*	–12.48 4.10	–22.56 to –2.39* 1.06 to 7.14*	–9.43 1.86	–15.57 to –3.28* 0.01 to 3.71*
Age (years)	0.13	–0.10 to 0.36	–0.33	–0.46 to –0.20*
BMI (kg/m^2)	0.55	–0.05 to 1.15	0.45	0.08 to 0.82*
Education (years)	–0.57	–1.26 to 0.13	–0.21	–0.65 to 0.22
Ex-smoker (ref = non-smoker)	8.62	1.93 to 15.30*	–0.81	–5.20 to 3.57
Current smoker (ref = non-smoker)	9.46	2.24 to 16.67*	1.79	–2.95 to 6.53
Pulse rate (counts/min)	–0.12	–0.38 to 0.13	0.16	0.00 to 0.31*
*p <0.05				

Factors influencing systolic and diastolic BP

Although with these data and study design we cannot postulate a causal relation, a relation between BMI and smoking and insufficient BP control is to be presumed. In the literature elevated BMI and older age are known factors associated with high systolic BP [4, 14–16] and weight reduction has shown to significantly reduce systolic BP [17]. Our data are in line with these findings, where BMI and age were independent positive predictors for systolic BP when controlled for gender, HBPM, treatment and education. The observed inverse correlation between diastolic BP and age is a known phenomenon explained by the diminished elastic capacity of the large arteries with increasing age, leading to reduced distension during the systole and consequently lower diastolic BP [15, 18–20].

In our study smoking seemed to have the most significant effect on systolic BP with one third of the patients being former smokers and a fifth still active smokers. We did not find an association between diastolic BP and smoking, a finding which is in congruence with other epidemiological data in the literature [21]. However, interventional and epidemiological data on the effect of smoking cessation on BP have shown conflicting results [22].

Our conclusions on factors influencing BP control drawn from a study population only consisting of patients with uncontrolled AH seem justified when considering the results of a recent Swiss study also including patients with controlled AH (<140/90 mm Hg) [23]; there the BP control rate was higher in non-smokers and in patients with a BMI <25 kg/m^2.

Home blood pressure measurement and medication

In our study population most patients performed HBPM before inclusion into the study and diastolic BP was linearly negatively associated with the amount of antihypertensive substances, suggesting good adherence with therapy.

It is known, that the efficacy of antihypertensive treatment proven in clinical trials is not always reflected in the real life of clinical practice [24]. Reasons for insufficient BP control are diverse, lack of adherence and insufficient self-monitoring have been shown to play an important role on the patients' side [25–29], reluctance to intensify therapy can be a reason in patients and physicians [24]. In addition, among GPs uncertainness and scepticism whether guideline recommendations are always adequate for the individual patient exist [30].

Guidelines promote an early dual combination treatment [11, 12]. We observed a gap between this guideline recommendation and practice, since about half of the patients under pharmacological treatment and uncontrolled AH received only a monotherapy.

Overall, the most commonly prescribed antihypertensive agents were ACEI followed by diuretics and ARB, BB and CCB. As stated in Guidelines for the Management of AH [11, 12], randomised trials comparing antihypertensive substances show that for similar BP reductions, differences in the incidence of cardiovascular morbidity and mortality between different drug classes are small, thus strengthening the conclusion that their benefit largely depends on BP lowering per se. Depending on co-morbidities, there is evidence in favour of certain drug classes versus others either as initial treatment or as part of a combination. Also side effects may influence the choice of therapy. Since co-morbidities and side effects were not recorded in our data, no statement can be made concerning the guideline conformity with respect to the chosen substances, particularly the high use of beta-blockers as monotherapy.

Our adjusted results estimated an average decrease in systolic BP due to an antihypertensive monotherapy compared to no treatment of 10.66 mm Hg (i.e. –15.58 mm Hg of the linear term plus 4.92 mm Hg of the quadratic term) and an average diastolic decrease of 6.46 mm Hg (i.e. –7.97 mm Hg plus 1.51 mm Hg) (table 3). These effects are comparable to randomised trials comparing antihypertensive agents with placebo [31].

We observed a non-linear (quadratic) association between BP measures and number of antihypertensive substances which was stronger for systolic BP. These findings reflect the diminishing efficacy of multiple combination therapy on BP control; the incremental effect of an antihypertensive monotherapy declines with every additional substance, a conclusion also recently drawn by Justin et al. [32].

Multimorbidity and polypharmacy is a common problem in PC associated with increased risk of interactions and side effects. In this setting "more is not always better" [33]. Therefore the important goal of good BP control has to consider not only the most adequate and evidence based

Table 3: Patient characteristics and multivariate influence on systolic and diastolic blood pressure.

Characteristics	Multivariate analysis systolic BP		Multivariate analysis diastolic BP	
	Regression coefficient	95% CI	Regression coefficient	95% CI
Home-BP-measurement (ref = no)	–0.37	–6.67 to 5.92	2.58	–1.2 to 6.44
Gender (ref = male)	–2.56	–8.19 to 3.06	–1.62	–5.07 to 1.83
Number of antihypertensive agents	–15.58	–25.48 to –5.68*	–7.97	–14.04 to –1.90*
Quadratic term *Number of antihypertensive agents*	4.92	1.98 to 7.86*	1.51	–0.29 to 3.32
Age (years)	0.37	0.13 to 0.61*	–0.25	–0.40 to –0.10*
BMI (kg/m^2)	0.78	0.18 to 1.38*	0.11	–0.25 to 0.47
Education (years)	–0.41	–1.06 to 0.24	–0.30	–0.70 to 0.10
Ex-smoker (ref = non-smoker)	6.03	–0.52 to 12.58	–2.27	–6.28 to 1.75
Current smoker (ref = non-smoker)	13.17	6.10 to 20.19*	–0.82	–5.12 to 3.47
Pulse rate (counts/min)	–0.09	–0.33 to 0.15	0.08	–0.07 to 0.22
*p <0.05				

treatment but also has to reflect the benefits and risks. In addition, as shown in our study and mentioned above, other factors for insufficient BP control as overweight and smoking are frequent concomitant problems. Multifaceted interventions, including modification of lifestyle, with smoking cessation and weight reduction, should be raised implicitly and offered to patients, especially to the ones already receiving a dual antihypertensive combination therapy. From the management of other chronic diseases in PC, such as diabetes, it is known that interventions with the greatest positive effect on outcomes include support in behaviour change [30, 34–37].

Strengths and limitations

Certain limitations concerning the generalisability of our data have to be taken into account: Previous studies from the PC setting have shown that variations between GPs occur [38–40], meaning that patient observations are not independent, i.e. observations in one cluster tend to be more similar to each other than to individuals in the rest of the sample. In our study population no such expected cluster effect was observed, meaning that the variations in patient observations are not explained by the attending GP. This finding might indicate that our GP population represents a special selection. Even though we could not find a GP clustering effect on BP, such effects cannot always be ruled out with certainty. Participating GPs differed from Swiss GP population statistics, performed by the Swiss Medical Association [41], in the following points: More than half of the participating GPs worked in group practices, whereas usually this is the case in one third of Swiss GPs. The number of GPs with electronic patient records was also higher than average, with 36% compared to the reported data of 13% in Switzerland [42, 43]. Only GPs from three cantons of the German speaking part of Switzerland were recruited for participation and most participants were located in urban or suburban areas. For Swiss standards, the participating GPs treated a proportionally large amount of patients in managed care or HMO systems [44]. On the other hand the gender and age distribution compared well with the annual statistics on GPs [41]. The participating physicians also reflected the traditional characteristics of a Swiss GP, specialising in internal or general medicine without additional specialisation.

Each participating GP received along with the study folder a list and instructions to register all patients they asked to participate and all patients who declined to participate. However, this list was not completed by the majority of GPs and therefore could not be considered for analysis. No patients were excluded by the study investigators. The GPs were responsible for making sure that the inclusion and exclusion criteria were met, hence, correct inclusion and exclusion has to be trusted. Nevertheless, the low-threshold inclusion criteria were strengths because they offered a view on real life PC patients with AH and on the spectrum of treatment. On the other hand, certain clinical details which could influence the reason for uncontrolled AH, e.g., renal function, hyperaldosteronism, effect of BP-influencing medications such as NSAR are lacking. Since the current manuscript concentrates on the baseline-measurements only performed at the practices white coat hyper-

tension in some cases cannot be excluded. Nevertheless, it seems justified to rely on the presumption that GPs know about white coat hypertension and took this consideration into account before including the patient into the study.

From our study data no statements on the prevalence of uncontrolled AH in Swiss PC can be derived. But considering the existing data on high prevalence of (uncontrolled) AH in Switzerland [6, 7] and worldwide [1], our findings are of importance.

Conclusions

Smoking and high BMI are strong and independent factors associated with higher BP levels in patients with uncontrolled AH. A high rate of monotherapy and a decrease in the incremental gain on BP control when more antihypertensive agents are used highlight the importance of adequate pharmacological treatment as well as risk factor control.

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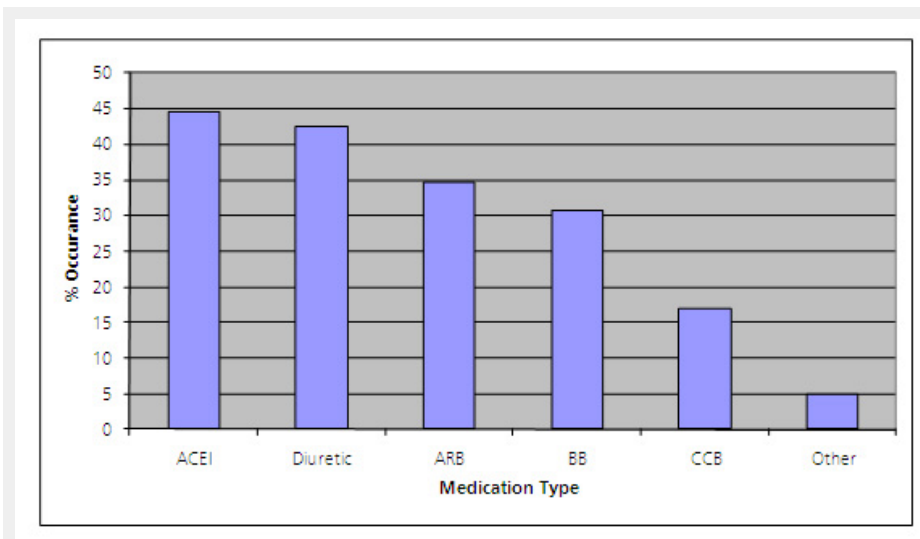
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Figures (large format)
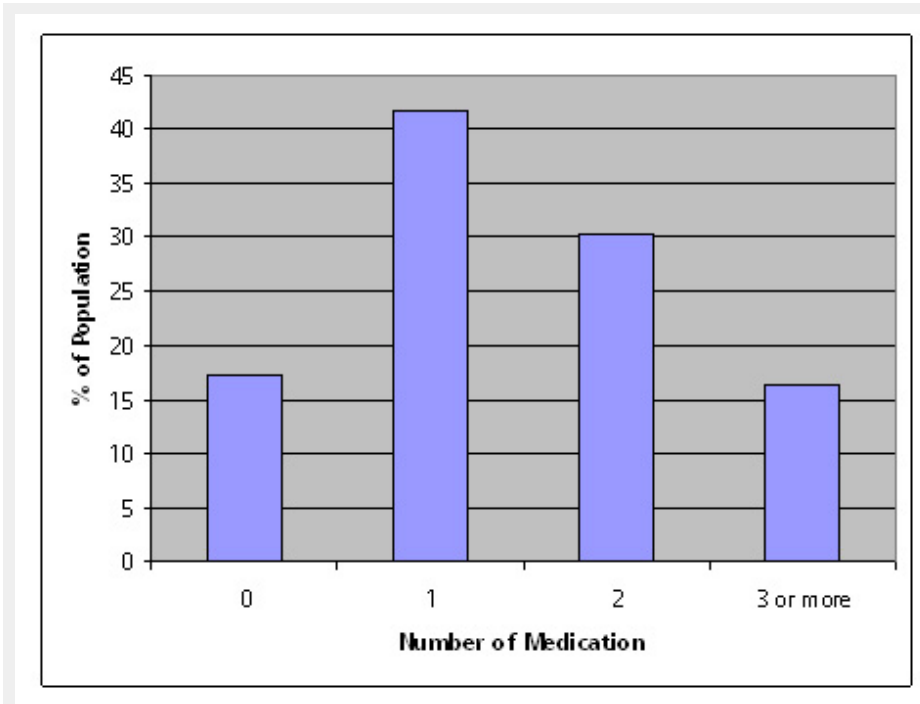
Figure 1

Distribution of number of antihypertensive agents per patient. Total population n = 122. The majority of patients received a monotherapy.
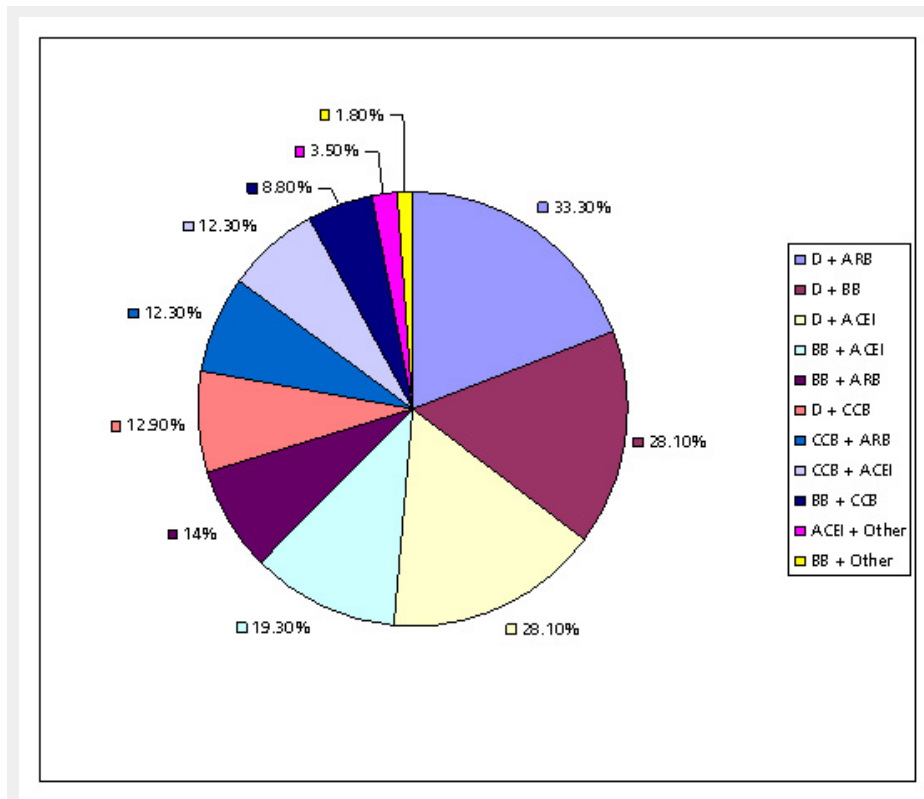

Figure 2

Overall distribution of antihypertensive agents. Other refers to imidazolin receptor antagonist (= moxonidin; causes blood pressure lowering by central adrenergic stimuli with resulting reduction in peripheral vascular resistance). ACEI and diuretics were the overall most commonly prescribed antihypertensive substances.
BB = beta blockers; CCB = calcium channel blockers; ARB = angiotensin receptor blockers; ACEI = angiotensin converting enzyme inhibitors.

Figure 3

Distribution of antihypertensive dual drug combinations. Composition of dual combination therapies used in the study population (n = 57 with 2 or more antihypertensi drugs). Other refers to imidazolin receptor antagonist. The most commonly prescribed dual drug combination was diuretics with angiotensin receptor blockers.

D = diuretics; BB = beta blockers; CCB = calcium channel blockers; ARB = angiotensin receptor blockers; ACEI = angiotensin converting enzyme inhibitors.