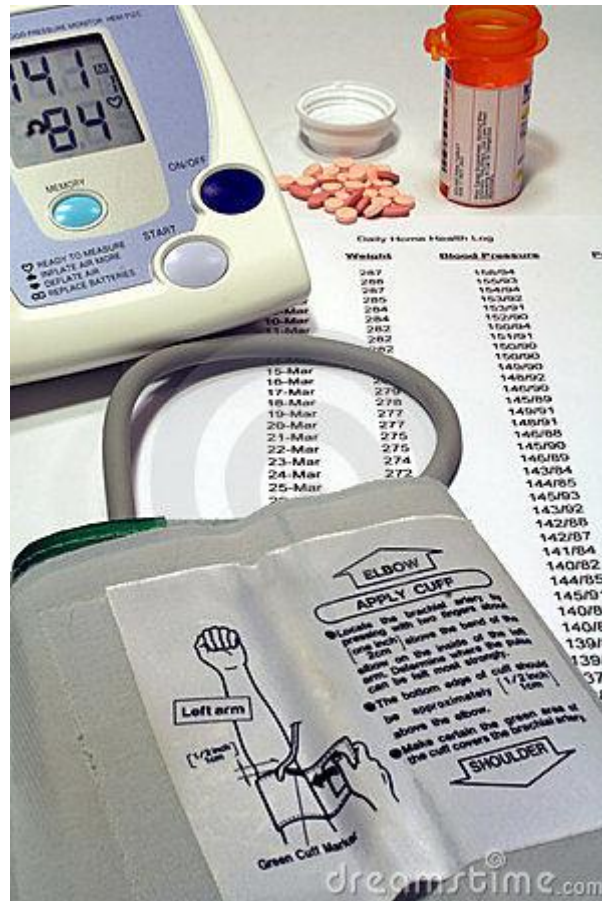# Therapy resistant hypertension

Prevalence and characteristics

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Abstract

Background

Hypertension is a common problem in Dutch general practice. Although many hypertensive patients are adequately treated, a substantial number of patients do not reach treatment goals. The most important reasons for treatment failure are white-coat hypertension, non-adherence to treatment or therapy resistant hypertension (TRH).TRH is defined as having an office BP measurement with systolic blood pressure ≥ 140 mmHg while using three different classes of antihypertensive agents, ideally including a diuretic, in an adequate dose. Patients with TRH bear an increased risk for target organ damage, cardiovascular morbidity and mortality compared to patients with adequately controlled hypertension. At the moment, reliable information about TRH is scarce, and better understanding of the prevalence and characteristics of TRH can make an earlier diagnosis of TRH possible. In this way, patients can benefit from the diagnostic and therapeutic considerations available.

Research questions
1. What is the prevalence of TRH in the Dutch general practice population?
2. What are the baseline characteristics of patients with TRH?

Methods

We performed a descriptive study with the database of the Nijmegen Monitoring Project (NMP), the academic general practice-based research network of the Radboud University Nijmegen Medical Centre. First, we established the prevalence of hypertension in the general practice population. Second, we determined the prevalence of TRH in the hypertensive population. The prevalence of TRH was corrected for non-adherence to therapy. Third, we compared baseline characteristics of TRH patients with controlled hypertension patients. Descriptive analyses were used to determine the baseline characteristics for TRH. We analysed these characteristics with the unpaired t-test and the chi-quadrate test. Finally, we have made preparations to create a predictive model which helps to identify patients with a higher risk of TRH at the moment of diagnosis of hypertension.

Results

In the NMP population the prevalence of hypertension was 11.9%. The prevalence of TRH in the hypertensive population amounted to 5.4%. The characteristics at baseline of 66 TRH patients and 777 controlled hypertension patients were analysed. TRH patients were significantly more male, smokers, and of older age. Angina pectoris, peripheral arterial disease and fasting blood glucose were more prevalent in TRH.

Conclusion

The prevalence of TRH in a Dutch general practice database was 5.4%, this is less than observed in other studies. Baseline characteristics we found differed partly from other studies, but age is a strong characteristic that is found in all studies. Further study will be needed for determining the predicting characteristics of TRH in newly diagnosed hypertensive patients.

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Introduction

With a prevalence of 6.4% in 2001, essential hypertension is a common problem in the Dutch general practice population.[1] However, recent studies about prevalence in the general practice are scarce. The majority of patients with hypertension receive therapy.[2, 3] Although many hypertensive patients are adequately treated, a substantial number of patients do not reach treatment goals.[2] The most important reasons for treatment failure are white-coat hypertension, non-adherence to treatment or therapy resistant hypertension (TRH).[4, 5] TRH is defined as having an office BP measurement with SBP≥ 140 mmHg while using three different classes of antihypertensive agents, ideally including a diuretic, in an adequate dose.[6] True TRH is difficult to measure as it is not clearly distinguishable from non-adherence to treatment. Patients with TRH bear an increased risk for target organ damage, cardiovascular morbidity and mortality compared to patients with adequately controlled hypertension. The increased risk in TRH patients is related to high blood pressure levels and the presence of concomitant co-morbidities.[7] Previous research suggests that TRH could be an independent risk factor for cardiovascular disease.[8]

Reliable data of prevalences and patients characteristics of patients with TRH are scarce, and available studies present conflicting results. The prevalence of true TRH is estimated between 7.6% and 11.8% in the total hypertensive population.[2, 4, 9, 10] There are several difficulties in estimating the true prevalence of TRH. First, ruling out the white-coat effect is challenging. In one study one tried to rule out white-coat hypertension by ambulatory blood pressure measurement. The investigators demonstrated that TRH, based on office blood pressure measurements, was for one third based on white-coat hypertension.[4] However, this study did not reflect the general practice hypertensive population, as a number of patients were derived from specialized clinics. Moreover, many patients were excluded, like patients that took ≤ 2 or ≥ 4 antihypertensive drugs.[5] Second, it is difficult to measure non adherence, because reliable data about compliance are not available in most retrospective studies.[10] Third, BP measurements were inadequate in some studies, sometimes only one measurement was taken to diagnose TRH.[2, 9, 10] In conclusion, studies describing the true prevalence of TRH in unselected hypertensive patients in the general practice are scarce and reliable evidence is lacking.[11, 12]

Previous research showed several discriminating characteristics for TRH, such as higher systolic and diastolic blood pressure[10, 13], high body mass index (BMI)[2, 9, 10], diabetes mellitus[2, 10] and kidney disease[9, 10]. While, one study used medical records from outpatient clinics[10], other studies were performed in the general population or in referral centres. In addition, most of the studies, used characteristics, collected at the start of the study, which was not equal to time of diagnosis of hypertension. We found no studies with TRH patient characteristics at the date of diagnosis of hypertension.

A predictive model to calculate the risk of TRH in newly diagnosed hypertensive patients, suitable for general practice, is currently not available. To our knowledge only three studies are done in the Western population to determine predictors of TRH. The first was a prospective study among healthy male employees of two factories in Italy. This study investigated baseline characteristics and distinguished pulse pressure, albumin/creatinine ratio, serum cholesterol and fraction excretion of sodium (FENa) as baseline predictors for

TRH. However, it concerned a young group of healthy workers and part of the participants had already treated hypertension at baseline. So, this study did not include baseline predictors at the time of diagnosing hypertension.[14] The second study was a large prospective patient-control study designed to compare the effect of two treatments. For this reason participants were included if they were between 40 and 79 years old and had at least three cardiovascular risk factors. So, this was a selected group of patients with the main purpose to investigate the effect of two treatment options. Predictors for TRH in this study were diabetes mellitus, left ventricular hypertrophy, male sex, fasting glucose and BMI.[8] The third study investigated home blood pressure measurement for BP control. The conclusion of this study was that the height of home mean pulse pressure/diastolic pressure at baseline was predictive for TRH. However, this study included only 9 TRH patients, too small to draw any conclusion on predictive variables at baseline.[15] In conclusion, little is known about characteristics that can predict the risk of TRH in newly diagnosed hypertension patients.

Our study had the following objectives. First, we planned to determine the prevalence of hypertension in general practice. Secondly, we identified the TRH patients and calculated the prevalence of TRH in the hypertensive population. Thirdly, we studied the characteristics of TRH, controlled and uncontrolled hypertension at the diagnosis date of hypertension. Finally, we planned to develop a predictive model that identifies patients with a high risk of TRH in newly diagnosed hypertensive patients. This model may allow earlier diagnosis of TRH, so these patients may benefit from special diagnostic and therapeutic interventions.[16] Data is not shown in this report due to lack of time.

Methods

Database

We used data from nine general practices participating in a network of general practices in the eastern part of the Netherlands (the Nijmegen Monitoring Project). All patient data are recorded using Electronic Medical Records. The network started in the beginning of the eighties to monitor the management of hypertension, diabetes mellitus, and chronic obstructive pulmonary disease. In the beginning a paper form was filled in for each condition-related consultation. For hypertension several aspects were registered: the diagnostic process; cardiovascular risk factors; type of treatment (with or without medication); initiation of drug treatment; type of medication; changes in medication or dosage; and control/evaluation moments.[17, 18] Later, all practices were computerized and the paper form was digitalized and integrated within the General Practice Information System (GPIS). Nowadays, a standard dataset is extracted from the GPIS including demographic information, consultations, prescriptions, and episodes of disease. The episodes are coded according to the International Classification of Primary Care (ICPC). In this study, historical data from the paper and digitized forms were linked to contemporary data from the GPIS. The study was performed according to the Code of Conduct for Health Research which has been approved by the Data Protection Authorities for conformity with the applicable Dutch privacy legislation.

Study population

All patients registered on the 1st of July 2010 were included in the analysis of prevalence of hypertension. To calculate the prevalence of TRH, we included all patients with an episode of hypertension at the 1st of July 2010. We used an observation period (from the 1st of July 2010 till the 1st of July 2011) to establish the diagnosis of TRH. TRH was diagnosed if all systolic blood pressure (SBP) readings were ≥ 140 mmHg, the patient used ≥ 3 types of antihypertensive drugs during the observation period, and was therapy complaint. Hypertensive patients without any blood pressure measurements, patients that died during the observation period or left the practice were excluded.

To determine the characteristics of two subgroups of patients: TRH, and controlled hypertension patients, we excluded all patients with an unknown diagnosis date, a diagnosis date before 2003, and uncontrolled hypertension patients. We excluded patients before 2003 because data collection on patient characteristics was still on the paper forms and was rather minimal leaving many characteristics important for our study missing. Uncontrolled hypertension patients were excluded, because this was a mixed group of TRH patients, controlled patients, and non-adherence patients. Finally, we had to exclude patients with the information of the diagnosis in the GPIS system, because extraction of this information was too time consuming to be included during the internship.

Definitions

Hypertension was defined as a SBP ≥ 140 mmHg (or SBP ≥ 160 mmHg if the patient ≥ 80 years old) measured on multiple visits.[6] In our database we included the diagnosis hypertension documented as an episode of essential hypertension (ICPC code K86) or hypertension with organ damage and/or secondary hypertension (ICPC code K87). The

prevalence of hypertension was evaluated on the 1st of July 2010 in the total patient population.

Patients with controlled hypertension had an episode of hypertension and a SBP < 140 mmHg or in case the patient was ≥ 80 years old, a SBP < 160 mmHg in the observation period.

Uncontrolled hypertension was defined as an episode of hypertension in combination with all SBP reading ≥ 140 mmHg or in case the patient is ≥ 80 years old, all SBP ≥ 160 mmHg in the observation period, and they used < 3 classes of antihypertensive medication or ≥ 3 classes of antihypertensive medication in combination with prescriptions for < 270 days in the observation period.

In the Netherlands TRH is defined as having an office BP measurement with SBP ≥ 140 mmHg (or SBP ≥ 160 mmHg in case the patient is ≥ 80 years old) while using three different classes of antihypertensive agents, ideally including a diuretic, in an adequate dose.[6]
In our study, requirements for the diagnoses of TRH were:
1. All SBP readings ≥ 140 mmHg (or SBP ≥ 160 mmHg in case the patient is ≥ 80 years old);
2. Use of three different classes of antihypertensive agents;
3. Use of each of these agents for ≥ 270 days in the observation period.

We defined the use of three different classes of medications as prescribed or distributed in the observation period. We divided the antihypertensive medication in six classes: diuretics (exclusive of loop diuretics), beta-blockers (exclusive of sotalol), calcium channel blockers (CCB), angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) and other antihypertensive medication. We used ATC (Anatomical Therapeutic Chemical classification system) codes to classify the groups of antihypertensive medications as described in table 1. There are combination tablets that contain 2 or 3 classes of antihypertensive medication. If patients used 3 classes of antihypertensive medication, we checked for how many days the classes of antihypertensive medication were prescribed in the observation period. We combined the amount of tablets prescribed of a certain class of antihypertensive medication with the amount of tablets used on one day to get the total amount of days prescribed. If ≥ 3 classes of antihypertensive medication were prescribed each for ≥ 270 days then the patient was regarded to be therapy adherent. This group was used to calculate the prevalence of TRH divided by the number of hypertensive patients with a blood pressure measurement in the observation period.

Table 1. ATC codes and classes of antihypertensive medication			
	ATC code	Combination with diuretics	Combination with CCB
Diuretics	C03* exclusion of C03CA*		
Beta-blockers	C07* exclusion of C07AA07	C07BB* or C07CB*	
CCB	C08*		
ACE-inhibitors	C09A* or C09B*	C09BA*	C09BB*
ARB	C09C* or C09D*	C09DA* or C09DX*	C09DB* or C09DX*
Others	C02* or C09XA*	C09XA52	

Determination of prevalence

For the prevalence of hypertension we collected all patients with an episode of hypertension. We included the first documented episode of hypertension (ICPC code K86 or K87) of a patient including the start date.

To determine the prevalence of TRH we used SBP readings from the office in the observation period exclusively, and excluded measurements at home or ambulatory blood pressure monitoring. We collected all the prescriptions of medication with an ATC code starting with C02, C03, C07, C08 or C09 and recorded the following variables of these prescriptions: complete ATC code, dosage scheme and amount of tablets prescribed.

Description of characteristics of patient with TRH

Patient characteristics were included on the date of intake of hypertension, with exception of the DBP and SBP, which had to be recorded in the year before the diagnosis. Medical history included characteristics of the demography of the patients as age and sex, but also characteristics as smoking (ICPC code P17) and family history for cardiovascular diseases (ICPC code P29.01). Physical examination included DBP, SBP, body mass index (BMI kg/m^2) and waist circumference. Laboratorial results included total cholesterol, HDL-cholesterol, triglyceride, fasting blood glucose, estimated glomerular filtration rate (eGFR) and potassium. Finally, we collected data on the next diagnoses: diabetes mellitus (ICPC code T90), angina pectoris (K74), congestive heart failure (K77), myocardial infarction (K75), CVA (K90), TIA (K89) and peripheral arterial disease (K92).

Analyses

All the characteristics included in the total hypertensive population and the TRH population were investigated with descriptive analyses (mean, SD and frequency). The variables in the TRH group were compared to the variables in the controlled hypertension group with the unpaired t-test or the chi-squared test. Analyses were performed by SPSS statistical software version 19 (SPSS, Inc., Chicago, Illinois).

Results

Population

The NMP database holds the data of 53150 subjects on the 1th of July 2010. The table below illustrates that the total group of adults in the NMP database on 1 July 2010 was comparable with the Dutch adult population on 1 July 2010.

	NMP population	Dutch population
Table 2. *Comparison of the NMP population with the Dutch population for gender and age.*		
Age, year	(n=53150)	(n=16606135)
0-17	11711 (22)	3504666 (21)
18-49	23292 (44)	7174283 (43)
50-64	11159 (21)	3353383 (20)
65-79	5711 (11)	1916525 (12)
>=80	1277 (2)	657278 (4)
Male	26587 (50)	8219951 (49)
Female	26563 (50)	8386184 (51)
Values are expressed as numbers (percentage).		

Prevalence of hypertension

The prevalence of hypertension in the NMP population was 11.9% on 1 July 2010. The prevalence of hypertension in the adult (≥ 18 years) NMP population was 15.3%. Figure 1 depicts the distribution of the prevalence of hypertension for sex and age. We also used the data from CBS (central bureau of statistics) to calculate with weighting factors for age groups and sex how the prevalence would be in the Dutch population on 1 July 2010. The prevalence in the total Dutch population would also be 11.9%.

Figure 1. *Distribution of hypertension for different age groups and gender.*
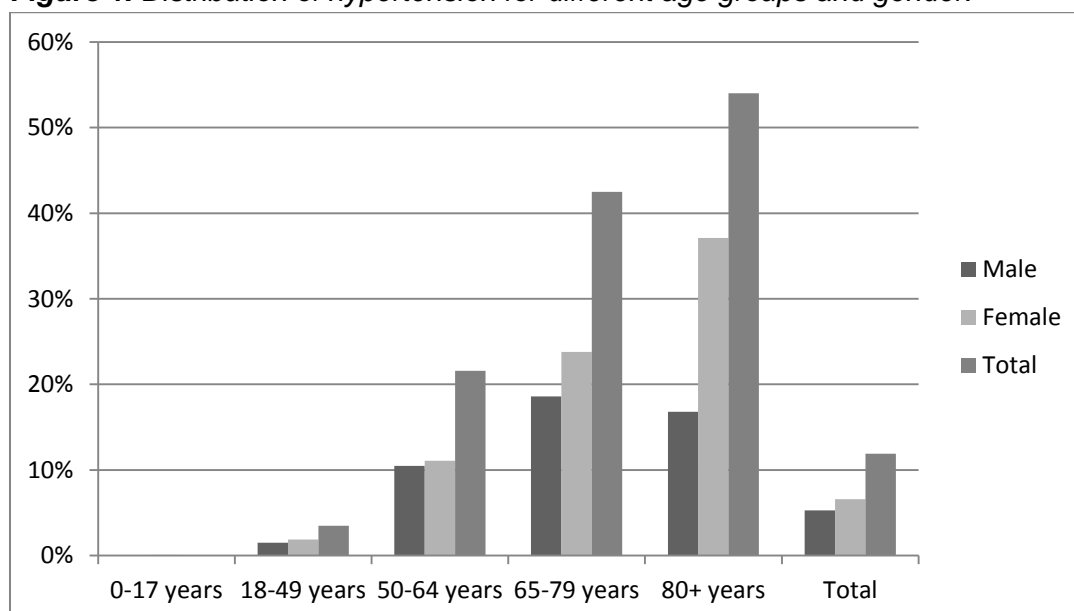
Prevalence of therapy resistant hypertension (TRH)

Figure 2 depicts the selection of patients with TRH. The prevalence of TRH in the hypertensive NMP population was 5.4%. Figure 3 and 4 show how the prevalence of TRH is distributed for sex and age. TRH is most prevalent in age group 65 till 80 years and among males. Table 3 depicts the classes of antihypertensive medication used by TRH patients. Diuretics and beta-blockers are the most prescribed.

Figure 2. Inclusion and exclusion of patients for the calculation of therapy resistant hypertension
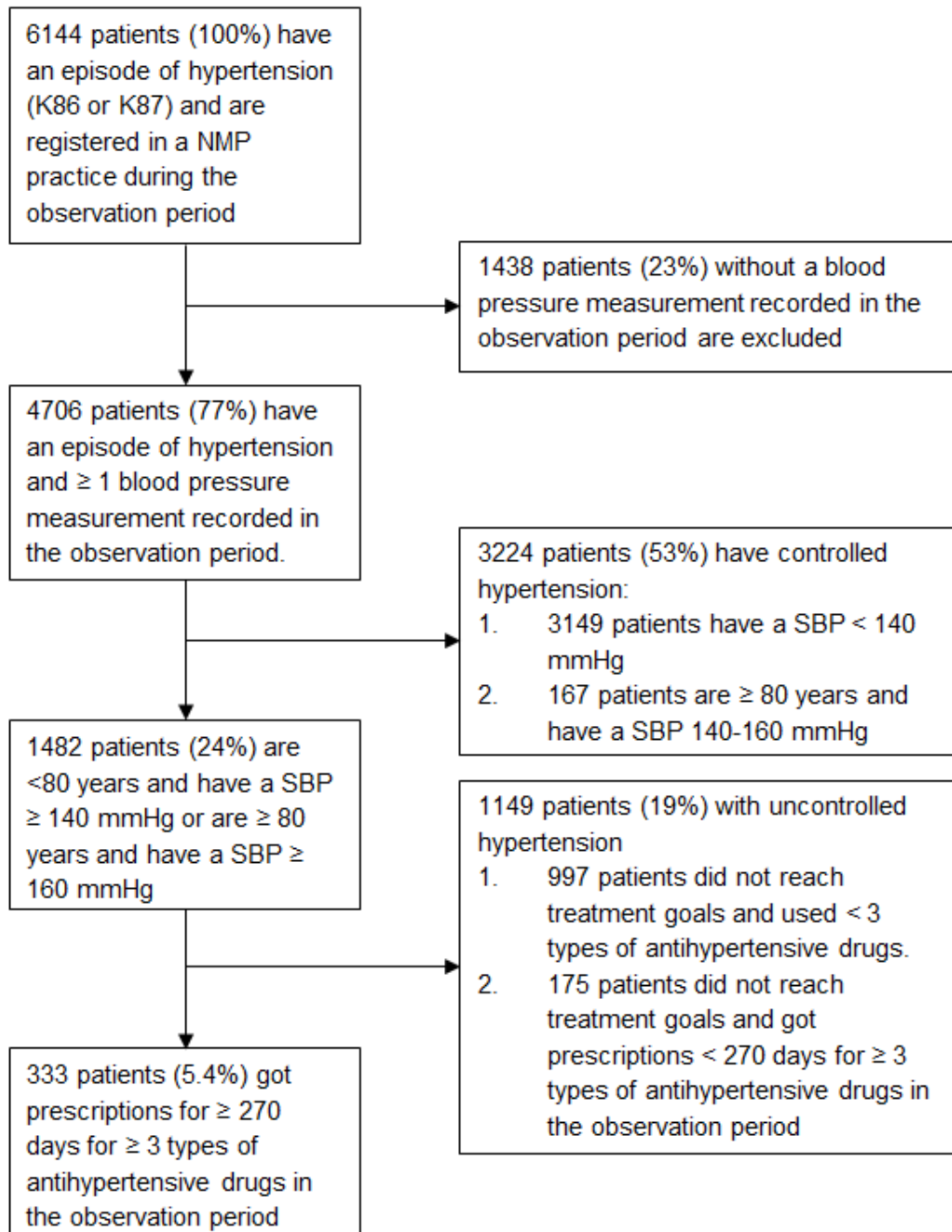
Figure 3. *Distribution of controlled, uncontrolled and TRH for different age groups.*
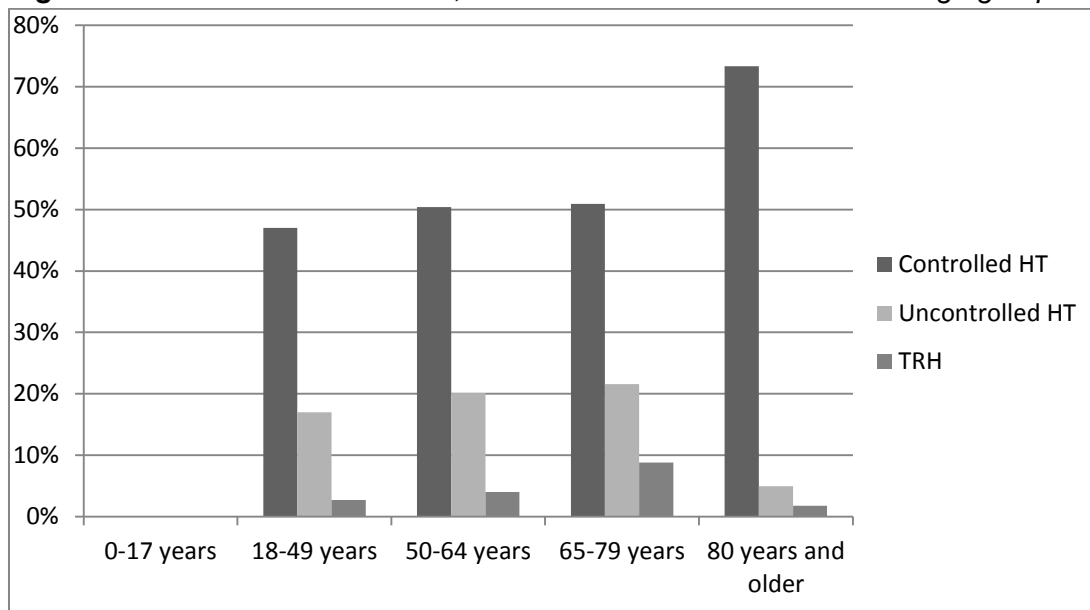

Figure 4. *Distribution of controlled, uncontrolled and TRH, for gender.*
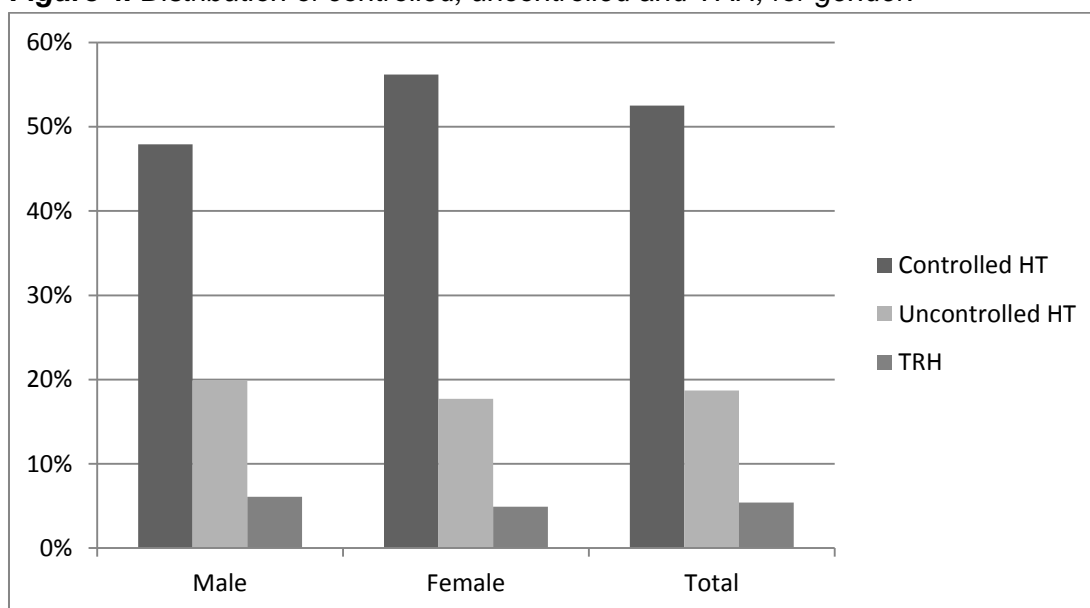
Table 3. *Different antihypertensive drugs classes used by TRH patients*	
Pharmaceuticals class	TRH (n=333)
Diuretics	292 (88)
Beta blockers	284 (87)
Calcium channel blockers	189 (58)
ACE-inhibitors	175 (53)
ARB	154 (46)
Others	21 (6)
Values are expressed as numbers (percentage).	

Baseline characteristics

The baseline characteristics from the GPIS system could not yet been extracted at the moment, so data from 2465 patients were available. The data before 2003 on many variables were missing, so we excluded all patients before 2003 and 1120 patients were left. Finally, we excluded the uncontrolled patients from our comparison, because this was a biased group of patients, and if the treatment was upgraded patients would have controlled hypertension, white-coat hypertension or TRH. So, 66 TRH patients and 777 patients with controlled hypertension were included for the analyses of the baseline characteristics. Table 4, 5 and 6 list the baseline demographics, physical and biochemical characteristics and the baseline comorbidities. The tables also show the differences of the baseline characteristics between the TRH group and the controlled group. The main baseline differences were gender, age, smoking, angina pectoris, peripheral arterial disease and fasting blood glucose.

TABLE 4. *Baseline patient and physical characteristics at time of hypertension (HT) diagnosis in patients with therapy resistant (TRH) and controlled hypertension.*

	TRH (n=66)	TRH % missing	Controlled HT (n=777)	Controlled HT % missing	P value
Men, n (%)	41 (62.1)	0	329 (42.3)	0	.00
Age, mean ± SD	60.7 ± 9.3	0	58.3 ± 11.8	0	.00
Smokers, n (%)	22 (33.3)	0	141 (18.7)	3	.00
Family history for cardio-vascular disease, n (%)	24 (46.2)	21	298 (47.3)	19	.87
SBP (mmHg), mean ± SD	185 ± 19	31	171 ± 15	27	.23
PP (mmHg), mean ± SD	88 ± 18	31	73 ± 17	27	.47
BMI (kg/m^2), mean ± SD	28 ± 5	21	28 ± 5	15	.57
Waist circumference (cm), mean ± SD	99 ± 11	77	94 ± 12	80	.70

P values denote TRH group compared with the controlled HT group.

TABLE 5. *Baseline biochemical characteristics at time of hypertension (HT) diagnosis in patients with therapy resistant (TRH) and controlled hypertension.*

	TRH (n=66)	TRH % missing	Controlled HT (n=777)	Controlled HT % missing	P value
eGFR	74.6 ± 15.0	27	75.2 ± 14.9	18	.97
Total cholesterol	5.7 ± 1.1	26	5.8 ± 1.1	12	.50
HDL-cholesterol	1.4 ± .4	35	1.4 ± .4	17	.82
Triglyceride	1.6 ± .8	44	1.9 ± 6.7	26	.73
Serum potassium	4.2 ± .5	53	4.2 ± .5	44	.24
Fasting blood glucose	6.0 ± 1.3	23	5.6 ± .9	18	.01

Values are expressed as mean ± SD. P values denote TRH group compared with the controlled HT group.

TABLE 6. *Baseline comorbidities at time of hypertension (HT) diagnosis in patients with therapy resistant (TRH), controlled and uncontrolled hypertension groups.*

	TRH (n=66)	TRH % missing	Controlled HT (n=777)	Controlled HT % missing	P value
Diabetes mellitus	8 (12.5)	3	103 (13.5)	2	.82
Angina pectoris	5 (7.7)	2	19 (2.5)	1	.02
Congestive heart failure	0 (.0)	2	2 (.3)	1	.68
Myocardial infarction	2 (3.1)	2	18 (2.3)	1	.71
CVA	4 (6.2)	2	27 (3.5)	1	.28
TIA	1 (1.5)	2	10 (1.3)	1	.87
peripheral arterial disease	7 (10.8)	2	13 (1.7)	1	.00

Values are expressed as numbers (percentage). P values denote TRH group compared with the controlled HT group.

Discussion

The prevalence of hypertension in the NMP database was 11.9%. TRH occurred in 5.4% of the hypertensive population and in 7.0% of the hypertensive population with a blood pressure measurement in the observation period. In comparison to patients with controlled hypertension those with TRH were more often male, of older age and smokers. They also suffered more often from angina pectoris, peripheral arterial disease and higher fasting blood glucose.

Our result in perspective of previous research
The finding that 11.9% of patients have hypertension is higher than the 6.4% reported by the NIVEL in 2001, another study among a sample of general practices in the Netherlands.[1] Increased awareness of general practitioners for cardiovascular risk management and an actual increasing prevalence may explain this difference. Another factor may be difference in registration as the general practices in our study are used to registration, as they have been participating in the practice based research network since 1986. Data from a recent study in a random sample of the Dutch population showed prevalences that varied between 16% in the youngest group (30-39 years) and 62% in the oldest group (60-70 years), and between 8% and 55% for males and females respectively.[19] This is considerably higher than prevalences that we describe in our study, see figure 1. This could be the result of differences in treatment state, as the general practice population consists on patients that were treated with medication. Moreover, diagnosis in general practice is based on more blood pressure measurements at different moments. In addition, there could be a response bias of people with known medical conditions.

The prevalence of TRH in our study was lower than other recent studies suggested. A retrospective study in general practices in the United States showed a prevalence of TRH of 9.1%.[10] The NHANES study in the United States showed a prevalence of 8.9%.[2] These two studies probably overestimated the prevalence of TRH, because they did not correct for therapy compliance. Furthermore, these studies only had one blood pressure measurement moment during the study period, which could overestimate the occurrence of resistant hypertension if an elevated reading was an isolated occurrence. In a recent Spanish study, one tried to approach the true prevalence of TRH and reported a prevalence of 7.6%.[4] However, this study also included patients from specialised clinics instead exclusively from the general practice. It is likely that these patients had increased risk of TRH, leading to biased prevalences. So, the study population was considered to be selected and not reflecting the general hypertensive population, causing the reported prevalence to be overestimated.[5]

The present study specifically evaluated the relationship between treatment resistant hypertension and patients characteristics. Our results differed from previous work on patients characteristics of TRH patients. Earlier studies showed opposite results in terms of gender [2, 10], but we found that male sex was related to TRH. These studies suggested that age can be determining for TRH as baseline characteristic and our study corroborates this finding.[2, 10] These studies found characteristics, like higher BMI and the presence of diabetes, which we did not find.[2, 10] The differences are probably related to the fact that we included characteristics at the time of diagnosis of hypertension and not at the time of the

study. Another reasonable cause for these differences can be that we had a too small population of TRH patients for the determination of the baseline characteristics. In our study we found that glucose value is related to TRH and not diabetes, possibly only uncontrolled diabetes is determining for TRH and not diabetes. Earlier studies used patients from referral centres, what causes a selected population.[13, 20] In our study the selection bias was small, because we used all data from patients diagnosed for hypertension after 2002 available in the NMP database.

Strengths and limitations
This study was performed in general practice, the setting where most of the hypertension and TRH patients will be diagnosed. The database contains unselected data since many years, including data about hypertension diagnosis and treatment, this made it possible to depict a precise prevalence of hypertension and TRH. Besides, we were able to correct the prevalence of TRH for therapy compliance. A further strength is that we analysed the characteristics of TRH at the time of diagnosis of hypertension, the time that all patients are still untreated.

The NMP database is a retrospective database and not designed for this specific research question. The database exists mainly of Caucasian people, so statements about immigrants cannot be made. The prevalence of TRH was specified for patients with an ongoing record for the whole observation period with at least one blood pressure measurement. This means that patients who left, died or had no blood pressure measurement in the observation period were excluded.

The prevalence of TRH in our study could be potentially an underestimation of the true prevalence:
- If blood pressure measurements and prescriptions were lacking, because the patient was under control of a specialist, mostly for TRH.
- If the treatment of patients without blood pressure measurements or with uncontrolled hypertension was upgraded and adequate, a small number would have TRH.

The prevalence of TRH could also be overestimated:
- Since we were unable to correct for white-coat hypertension, because data of home or ambulatory blood pressure measurement were not or only limited available in our database.
- Since we have corrected for vascular stiffness with a cut off point of 80 years (SBP ≥ 160 mmHg). However, a part of the patients < 80 years of age can also suffer from vascular stiffness, which leads to higher SBP measurements and to overestimation of TRH.

Overall, the prevalence of TRH would probably be an overestimation of the true prevalence.

A number of hypertensive patients had no BP measurement in the study period. This could be for several reasons: uncontrolled hypertension, only mild hypertension without medication or under control of a specialist.

The adequacy of the dosage of the antihypertensive drugs were not checked, because the Dutch guideline for hypertension advises to add another drug, when treatment goals are not reached, instead of up titrating drugs already prescribed.[6] We left the group of uncontrolled

patients out of the analyses to describe the characteristics of TRH patients, because this was a mixed group. Part of the group will be non-adherence to therapy, and part will finally, when therapy is upgraded, have controlled hypertension or TRH.

Further perspectives
Only the data of 66 TRH patients were available for the analyses of the baseline characteristics of TRH. A larger number will be required to make a predictive model to calculate the risk of TRH in newly diagnosed hypertensive patients. A predictive model can still be made with this database, but more time is required to extract all data needed. In addition, larger numbers of TRH patients will enable more reliable analyses of the baseline characteristics distinctive for TRH. The real prevalence of TRH in the general practice can be assessed more precisely in a prospective multicentre trial of general practices with ambulatory blood pressure monitoring at home and many years of follow up.

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