Resistant Hypertension and Risk of Adverse Events in Individuals With Type 1 Diabetes: A Nationwide Prospective Study

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Diabetes Care 2020;43:1885–1892 | https://doi.org/10.2337/dc20-0170

OBJECTIVE

To estimate the risk of diabetic nephropathy (DN) progression, incident coronary heart disease (CHD) and stroke, and all-cause mortality associated with resistant hypertension (RH) in individuals with type 1 diabetes stratified by stages of DN, renal function, and sex.

RESEARCH DESIGN AND METHODS

This prospective study included a nationally representative cohort of individuals with type 1 diabetes from the Finnish Diabetic Nephropathy Study who had purchases of antihypertensive drugs at (±6 months) baseline visit (1995–2008). Individuals (*N* = 1,103) were divided into three groups: *1*) RH, *2*) uncontrolled blood pressure (BP) but no RH, and *3*) controlled BP. DN progression, cardiovascular events, and deaths were identified from the individuals' health care records and national registries until 31 December 2015.

RESULTS

At baseline, 18.7% of the participants had RH, while 23.4% had controlled BP. After full adjustments for clinical confounders, RH was associated with increased risk of DN progression (hazard ratio 1.95 [95% CI 1.37, 2.79], *P* = 0.0002), while no differences were observed in those with no RH (1.05 [0.76, 1.44], *P* = 0.8) compared with those who had controlled BP. The risk of incident CHD, incident stroke, and all-cause mortality was higher in individuals with RH compared with those who had controlled BP but not beyond albuminuria and reduced kidney function. Notably, in those with normo- and microalbuminuria, the risk of stroke remained higher in the RH compared with the controlled BP group (3.49 [81.20, 10.15], *P* = 0.02).

CONCLUSIONS

Our findings highlight the importance of identifying and providing diagnostic and therapeutic counseling to these very-high-risk individuals with RH.

Hypertension is a major risk factor for micro- and macrovascular complications in individuals with type 1 diabetes (1,2). We have previously reported that a large number of the antihypertensive drug–treated individuals with type 1 diabetes failed to reach the recommended blood pressure (BP) targets that may partly be explained by poor adherence to treatment and a suboptimal antihypertensive drug regimen (3). Some of these individuals have treatment-resistant hypertension (RH) (4). RH is defined as a BP above the treatment target if using a minimum of three or more

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Received 24 January 2020 and accepted 30 March 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.12137604.

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antihypertensive drugs at optimal doses, of which one is a diuretic. Also, individuals with controlled BP using four or more antihypertensive drugs are considered resistant to treatment (5). Even though the definition is arbitrary with respect to the number of medications required, it may assist health care professionals to identify individuals at risk who may benefit from special diagnostic and therapeutic interventions (5).

Notably, the prevalence of RH is slightly higher in individuals with type 1 diabetes than in the general hypertensive population. In the nationwide Finnish Diabetic Nephropathy (FinnDiane) Study cohort, the prevalence of RH was 17.0% (BP target <140/90 mmHg), while pooled data from Europe and North America estimated that 14.8% of treated individuals with hypertension have RH (3,6). Similarly, a study from Italy indicated that ~14.9% of treated individuals with type 2 diabetes have RH (7). However, the true prevalence of RH is unknown because these population-based studies were unable to exclude cases of pseudoresistance (i.e., white coat hypertension, nonadherence to medication, suboptimal drug regimen) (5). Therefore, the term apparent treatment-RH is more precise and widely used in population-based studies (5,8,9).

A few observational studies have demonstrated that RH is independently associated with an increased risk of all-cause mortality and adverse cardiovascular and renal outcomes compared with those with controlled BP or non-RH in the general hypertensive population (10–14). These studies, however, varied by definitions of RH and non-RH and follow-up times. Although the association between RH and diabetes has frequently been reported (15,16), longitudinal studies on the risk of adverse outcomes related to RH in the diabetes population are rare. Only one study has reported an association between RH and all-cause mortality in individuals with type 2 diabetes (7). In contrast to the general hypertensive population, that study found that once indices of target organ damage were considered, RH did not predict death among individuals with type 2 diabetes. However, to date, no studies have estimated the long-term risk of adverse outcomes associated with RH in a type 1 diabetes population.

It is well known that chronic kidney disease (CKD) is among the most frequent secondary causes of RH and associated with worse outcomes (5). We previously showed that RH increases with albuminuria and reduced renal function in individuals with type 1 diabetes (3). Colleagues from Italy have reported that among individuals with type 2 diabetes and severe diabetic kidney disease, the presence of RH was associated with worse renal outcomes (17). While the associations among hypertension, cardiovascular events (1,18,19), and diabetic nephropathy (DN) (20) are well established in type 1 diabetes, data are scarce on the long-term prognosis and potential associations with severe outcomes in individuals with RH. Therefore, we estimated the risk of DN progression, incident coronary heart disease (CHD) and stroke, as well as all-cause mortality associated with RH in a nationally representative cohort of individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The current study is part of the ongoing, nationwide, multicenter FinnDiane Study with the main aim of identifying genetic, clinical, and environmental risk factors for diabetic complications in individuals with type 1 diabetes. A more detailed description of the study has been reported elsewhere (21,22). Briefly, all individuals with type 1 diabetes from >80 hospitals and health centers across Finland were asked to participate (see Supplementary Table 8 for a list of the FinnDiane Study centers). Type 1 diabetes was defined by age at onset of diabetes <40 years, C-peptide ≤0.3 nmol/L, and insulin treatment initiated within 1 year of diagnosis. Written informed consent was obtained from each patient. The study protocol was approved by the ethics committee of the Helsinki and Uusimaa Health District. The study was carried out in accordance with the Declaration of Helsinki.

At baseline, all participants underwent a clinical examination, including blood and urine sampling. Details of the clinical characteristics of the individuals were obtained from medical records by the attending physician using a standardized questionnaire. Each participant also completed a detailed questionnaire on life style, smoking habits, and family history. The measurement of height, weight, and waist and hip circumferences was performed in light clothing. At the baseline visit, BP was measured twice with 2-min intervals in the sitting position after a 10-min rest using a mercury sphygmomanometer or an automated standardized BP device. The mean of these two measurements was calculated. Early-morning blood samples were drawn and analyzed for HbA_{1c}, serum creatinine, and lipids. The DN status was defined on the basis of the albumin excretion rate (AER) in at least two of three overnight or 24-h urine collections. Normal AER was defined as <20 μg/min or <30 mg/24 h, microalbuminuria as AER ≥20 but <200 μg/min or ≥30 but <300 mg/24 h, and macroalbuminuria as AER ≥200 μg/min or ≥300 mg/24 h. Individuals, who had end-stage renal disease (ESRD) at baseline were excluded. At baseline, individuals were further classified into two DN status groups: those with normal AER or microalbuminuria and those with macroalbuminuria. The estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation (23). Similarly for further analyses, the individuals were divided into two renal function groups: eGFR ≥60 mL/min/1.73 m^2 and eGFR <60 mL/min/1.73 m^2. As a measure of insulin sensitivity, we used an equation for the estimated R_d (24).

DN status and progression to a higher level of albuminuria or ESRD were derived from the individuals' health care records and multiple national registries until the end of year 2015. Follow-up data on cardiovascular events (i.e., CHD, stroke) were identified by 31 December 2015 from the Finnish Care Register of Health Care, which is the national hospital discharge register in Finland. CHD events included the first acute myocardial infarction (ICD-8/9 410–412, ICD-10 I21–I23) and coronary procedure (coronary bypass graft surgery or angioplasty on the basis of the Nordic Classifications of Surgical Procedures). Stroke included the first cerebrovascular accident (ICD-8/9 430–434, ICD-10 I60–I64). All deaths, including fatal cardiovascular events, were identified from the Cause of Death Register until 31 December 2015.

Information on purchases of antihypertensive drugs 6 months before and after the baseline visit were obtained from the Finnish Drug Prescription Register (maintained by the National Social Insurance Institution since 1994, which contains information on all prescribed, purchased, and reimbursed medications

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in outpatient care). Medications were coded according to the Anatomic Therapeutic Chemical (ATC) classification on the basis of the 2019 ATC Index Version. Antihypertensive drugs were divided into eight classes: ACE inhibitors (ATC C09A, C09B), angiotensin II antagonists (C09C, C09D), diuretics (C03, C07BB, C09BA, C09DA), β-blocking agents (C07), calcium channel blockers (C08, C07FB, C09BB, C09DB), imidazoline receptor blockers (C02AC), prazosin (C02CA01), and minoxidil (C02DC01). Individuals taking single-pill combinations of antihypertensive drugs were counted as taking separate classes of each drug.

RH was defined as above-goal elevated BP despite the concurrent use of three or more antihypertensive drug classes, one of which was a diuretic, or controlled BP by using four or more antihypertensive drugs (5). The BP treatment goals were based on American Diabetes Association guidelines (25,26). About two-thirds of the individuals had their baseline visit in 2000 or before. Therefore, in the main analysis, the BP threshold was set <130/85 mmHg, which was the recommended BP target for individuals with diabetes at the time when most of the BP measures were obtained (25). Thus, controlled BP was defined as BP <130/85 mmHg and uncontrolled as BP ≥130/85 mmHg (25). In addition, supplementary analysis was applied by a more stringent BP target of <130/80 mmHg, which was the target between 2001 and 2012 (26) and is currently the recommended target for individuals with diabetes according to the American College of Cardiology and the American Heart Association (AHA) (27). We identified 1,103 individuals from the FinnDiane cohort who were taking antihypertensive medication 6 months before and after the baseline visit. We divided them into three groups: *1*) RH (uncontrolled BP despite concurrent use of three or more antihypertensive drugs of different classes, one of which is a diuretic, or controlled BP but required four or more antihypertensive drugs), *2*) no RH (uncontrolled BP with two or fewer antihypertensive drugs or with three drugs, one of which is not a diuretic) and *3*) controlled BP with three or fewer antihypertensive drugs.

Statistical Analysis

Data are expressed as mean ± SD for normally distributed variables, as median with interquartile range (IQR) for non-normally distributed values, and as percentages for binary variables. The statistical significance differences between two groups for normally distributed variables were tested by using ANOVA; otherwise, Kruskal-Wallis tests were used. Categorical variables were tested with Pearson χ^2 test or two-tailed Fisher exact test. The cumulative incidence of DN progression, incident CHD and stroke, and all-cause mortality was estimated using the Kaplan-Meier method, and the log-rank test was used to test the differences among the study groups.

Cox proportional hazard regression models were used to calculate the hazard ratio (HR) for each outcome separately. The results are presented as HR with 95% CI. The multivariable models were adjusted for sex, age, current and history of smoking, waist-to-hip ratio (WHR), triacylglycerol, HbA_{1c}, previous CHD, previous stroke, DN status, and renal function, when applicable. The time-dependent effects of the variables were tested by using Schoenfeld residuals against the follow-up time. When the Cox proportional hazard assumption was violated, the models were fitted in two different ways. If an effect of an independent variable was time varying, the variable was stratified. Continuous measurements were categorized, if applicable (see Table 2 and Supplementary Tables 1–7). If an effect of the dependent variable was time varying, follow-up time was stratified into distinct intervals, following the method of Zhang et al. (28) (Supplementary Appendix 1). Separate models were applied for the two DN status and renal function groups, for men and women separately, and finally, for a BP threshold <130/80 mmHg. All statistical analyses were performed with *R* version 3.5.3 statistical software (29).

RESULTS

Characteristics of the Study Population

This study comprised 1,103 individuals with type 1 diabetes who were on antihypertensive treatment at baseline, 56% of whom were men. The mean age was 43.7 ± 10.4 years, and diabetes duration was 26.3 ± 9.7 years. Almost one-third of the individuals had decreased renal function (eGFR <60 mL/min/1.73 m^2), and >40% had DN (AER ≥200 μg/min or ≥300 mg/24 h). The prevalence of RH was 18.7%; 57.9% had uncontrolled BP but no RH, and 23.4% had controlled BP. In this cohort, only seven individuals with RH had controlled BP but required four or more antihypertensive drugs. About one-quarter of the individuals with RH were taking three antihypertensive drugs, including an ACE inhibitor, a diuretic, and a calcium channel blocker. Similarly, one-quarter of them were taking four drugs combined also with β-blocking agents. One-half of the individuals with no RH and ~60% of those with controlled BP were taking only one drug. The prevalence of RH was higher in men than in women (22.5% vs. 13.7%). With the more stringent BP target (<130/80 mmHg), the prevalence of individuals with RH (19.2%) increased, while that of controlled BP (15.3%) decreased.

The characteristics of the individuals with respect to the three groups (RH, no RH, controlled BP) are presented in Table 1. Those with RH showed the highest prevalence of DN and more often reduced renal function than those with controlled BP. They also had a worse lipid profile and higher WHR as well as worse glycemic control and lower insulin sensitivity than those with controlled BP. No differences were observed regarding smoking and prevalence of previous CHD. Individuals with no RH also had a worse clinical profile than those with controlled BP. However, no differences were observed in glycemic control, HDL cholesterol, DN status, renal function, smoking, and previous cardiovascular events.

During a median of 14.8 (IQR 11.9–17.0) follow-up years (15,082 person-years), 321 (29.1%) individuals progressed to a higher level of albuminuria or ESRD, 239 (21.7%) experienced an incident CHD, and 138 (12.5%) experienced an incident stroke. Moreover, 302 (27.4%) individuals died during the follow-up. Crude event rates and Kaplan-Meier estimates were the highest in those with RH compared with those who had no RH or controlled BP.

Risk of DN Progression

The 15-year cumulative risk of DN progression was the highest in those with RH (56.6% [95% CI 48.6, 63.3], $P < 0.0001$), while no differences in risk were observed between those with no RH (24.9% [21.2, 28.5], $P = 0.9$) and

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Table 1—Baseline characteristics of the study participants (N = 1,103)

Characteristic	RH (n = 206, 18.7%)	P value	No RH (n = 639, 57.9%)	P value	Controlled BP (n = 258, 23.4%)
Men	68.0	<0.0001	57.3	0.0007	44.6
Age (years)	45.6 ± 10.3	<0.0001	44.2 ± 11.3	<0.0001	39.4 ± 10.3
Age at onset of diabetes (years)	13.0 (9.0–21.0)	0.01	14.0 (9.0–22.0)	0.002	12.0 (7.0–17.0)
Diabetes duration (years)	30.0 ± 8.4	<0.0001	28.7 ± 10.8	0.0005	26.1 ± 9.9
Systolic BP (mmHg)	154 ± 20	<0.0001	147 ± 15	<0.0001	120 ± 8
Diastolic BP (mmHg)	85 ± 10	<0.0001	84 ± 10	<0.0001	74 ± 7
BMI (kg/m^2)	26.5 ± 3.6	0.0005	25.9 ± 3.6	0.02	25.3 ± 3.9
Waist circumference (cm)	92.8 ± 13.0	<0.0001	89.3 ± 11.1	<0.0001	85.4 ± 12.1
WHR	0.92 ± 0.09	<0.0001	0.89 ± 0.08	<0.0001	0.86 ± 0.08
HbA_{1c} (%)	8.9 ± 1.5	0.04	8.6 ± 1.4	0.9	8.6 ± 1.5
HbA_{1c} (mmol/mol)	74 ± 16	0.04	70 ± 16	0.9	70 ± 16
Total cholesterol (mmol/L)	5.37 ± 1.22	0.001	5.16 ± 0.87	0.03	5.01 ± 0.95
HDL cholesterol (mmol/L)	1.18 ± 0.39	0.0003	1.31 ± 0.38	0.7	1.32 ± 0.38
LDL cholesterol (mmol/L)	3.33 ± 0.92	0.008	3.26 ± 0.82	0.01	3.10 ± 0.86
Triglycerides (mmol/L)	1.45 (1.09–2.30)	<0.0001	1.13 (0.81–1.66)	0.02	1.02 (0.79–1.44)
Estimated R_d (mg · kg^{-1} · min^{-1})	4.0 ± 1.4	<0.0001	4.6 ± 1.4	0.0007	4.9 ± 1.4
Lipid-lowering treatment	31.1	<0.0001	20.5	0.01	12.8
Nephropathy status		<0.0001		0.5	
Normal AER	14.6	NA	34.6	NA	32.6
Microalbuminuria	11.1	NA	29.3	NA	32.9
Macroalbuminuria	74.3	NA	36.1	NA	34.5
eGFR (mL/min/1.73 m^2)	43.3 (23.8–67.2)	<0.0001	80.5 (61.5–96.4)	0.2	82.6 (61.6–101.7)
Renal status (mL/min/1.73 m^2)		<0.0001		0.3	
eGFR >90	12.1	NA	34.2	NA	38.8
eGFR 60–90	20.4	NA	42.4	NA	37.3
eGFR <60	67.5	NA	23.4	NA	23.9
Laser treatment	76.7	0.0004	56.9	0.3	60.7
Current smoker	20.6	0.3	22.6	0.5	25.1
History of CHD	11.6	0.3	6.6	0.4	8.5
History of stroke	7.3	0.0005	3.1	0.07	0.8
Number of antihypertensive drugs	3.4 ± 0.5	<0.0001	1.4 ± 0.5	0.6	1.4 ± 0.7
1	NA	NA	60.1	NA	66.7
2	NA	NA	37.4	NA	22.1
3	63.1	NA	2.5	NA	11.2
≥4	36.9	NA	NA	NA	NA

Data are mean ± SD, median (IQR), or %. P values represent comparisons with controlled BP group. NA, not applicable.

controlled BP (25.0% [19.4, 30.3]) (Fig. 1*A*). Table 2 shows the unadjusted and multivariable Cox proportional hazards models for these three groups and severe outcomes. After adjusting for all covariates, the risk of DN progression remained nearly two times higher in those with RH (HR 1.95 [95% CI 1.37, 2.79]) compared with those who had controlled BP. The risk was even higher in those with macroalbuminuria and RH (2.17 [1.41, 3.34]) (Supplementary Table 4) and in those with eGFR <60 mL/min/1.73 m^2 (2.00 [1.24, 3.22]) (Supplementary Table 6). Men with RH had an almost two times higher risk of progression compared with those who had controlled BP (Supplementary Table 1). However, in women, the effect of no RH was time varying, and therefore, time-adjusted analysis was performed, showing a twofold higher risk only after 4.2 years of follow-up in those with RH compared with those who had controlled BP (Supplementary Fig. 2*E*). Finally, with the more stringent BP target, the association between DN progression and RH remained higher after full adjustments (Supplementary Table 7).

Risk of Cardiovascular Events

In those with RH, the 15-year cumulative risk of CHD was 35.1% (95% CI 27.1, 42.3, $P < 0.0001$), while the risk was 24.8% (21.0, 28.5, $P = 0.0003$) in those with no RH and 12.8% (8.1, 17.3) in those with controlled BP (Fig. 1*B*). Similarly, the risk of stroke was 24.2% (17.0, 31.1, $P < 0.0001$), 14.2% (11.1, 17.1, $P = 0.008$), and 7.3% (3.9, 10.6), respectively (Fig. 1*C*). After adding kidney disease markers (i.e., stages of DN and renal function) into the multivariable Cox models, no differences were observed between the groups and the CHD risk (Table 2). Because the kidney disease markers were strong predictors in the models, we also stratified the individuals into two DN status and two renal function groups. These stratifications as well as the stratification by sex (Supplementary Tables 1–6) showed no differences between the individuals with RH and those who had controlled BP.

After adjusting for clinical confounders, including DN status (Table 2), RH was associated with stroke (HR 2.00 [95% CI 1.07, 3.71]. However, this association

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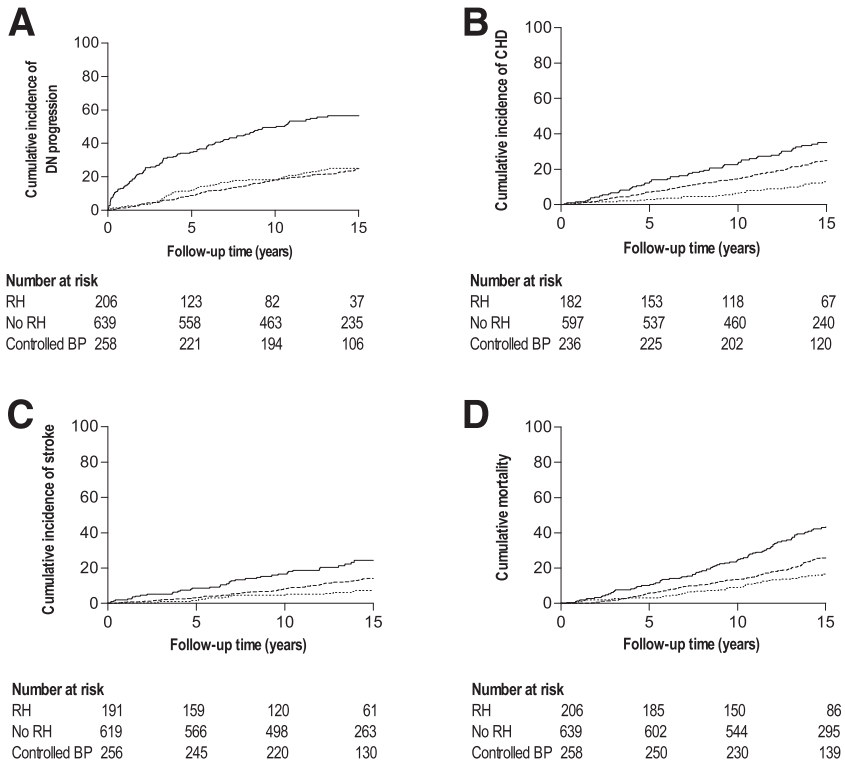

Figure 1—Fifteen-year cumulative risk of DN progression (*A*), incident CHD (*B*), incident stroke (*C*), and all-cause mortality (*D*) in individuals with controlled BP (dotted line), with no RH (dashed line), and with RH (solid line) and type 1 diabetes.

disappeared after further adjustment for renal function. A similar pattern was seen when women were separately analyzed; the higher stroke risk in those with RH remained in the presence of clinical confounders, but no differences were observed among the groups after additional adjustment for renal function (Supplementary Table 2). Importantly, before the development of macroalbuminuria, the risk of stroke was 3.5-fold higher in those with RH compared with those who had controlled BP, while those with no RH did not differ from those with controlled BP (Supplementary Table 3). With the BP target <130/80 mmHg, the risk estimates of incident CHD and stroke were slightly lower, and when accounting for clinical confounders, the differences disappeared even earlier (Supplementary Table 7).

Risk of All-Cause Mortality

The 15-year cumulative risk of all-cause mortality was 42.9% (95% CI 35.4, 47.1, $P < 0.0001$) in those with RH, 25.7% (22.0, 29.1, $P = 0.002$) in those with no RH, and 16.7% (12.7, 20.5) in those with controlled BP (Fig. 1*D*). After adjusting for clinical confounders, RH was associated with all-cause mortality compared with those with controlled BP, while no differences were observed in those with no RH compared with those who had controlled BP (Table 2). However, when kidney disease markers were added into the multivariable models, there were no differences among the groups. The risk of death did not differ when comparing the RH or no RH and controlled BP groups within the DN strata (Supplementary Tables 3 and 4). However, when we divided the individuals into two renal function groups, the risk remained slightly higher in those with RH, who had an eGFR ≥60 mL/min/1.73 m^2, compared with those who had controlled BP (Supplementary Table 5). Also, in women, the risk of all-cause mortality was 90% higher in those with RH compared with those with controlled BP when adjusting for potential confounders (Supplementary Table 2). With the more stringent BP target (i.e., 130/80 mmHg), the risk estimates of all-cause mortality did not change, and again, when kidney disease markers were added into the model, the difference disappeared (Supplementary Table 7).

CONCLUSIONS

Our findings from the nationwide Finn-Diane cohort with type 1 diabetes shows that RH is associated with an increased risk of incident CHD, incident stroke, and all-cause mortality, which were, however, attenuated after adjusting for clinical confounders and disappeared when kidney disease markers were added into the models. This is in line with clinical findings showing a strong association between RH and DN that, in turn, is known to be a dominant contributor to excess cardiovascular mortality (30).

Another important finding is that the presence of RH is independently related to a greater risk of DN progression, especially in individuals with advanced DN. Only a few previous studies have reported similar associations between RH and renal outcomes in a CKD population. A multicenter study ($N = 788$) demonstrated that RH was associated with a 2.3-fold higher risk of ESRD (31). Another study ($N = 3,367$) (32) reported that individuals with RH had an ~30% higher risk of renal complications after 5-year follow-up. Moreover, among individuals with type 2 diabetes and CKD from 90 diabetes centers in Italy ($N = 2,778$), RH was related to higher risk of eGFR loss (>30% reduction from baseline) during a 4-year follow-up (17). Despite differences in study populations, definitions of RH, and follow-up times, our findings together with these earlier studies highlight the importance of recognition of RH in individuals with kidney disease.

Previous studies have demonstrated the difficulties to control BP at the late stages of kidney disease both in the general CKD population and in individuals with type 1 diabetes (3,33). Several mechanisms may contribute to the development of treatment resistance in individuals with kidney disease. Reduced kidney function causes impaired salt excretion, overactivation of the renin-angiotensin-aldosterone system, and increased sympathetic nervous system activity. These factors, in turn, lower the response to antihypertensive therapy (5). Because RH and advanced kidney disease is a challenging combination, robust evidence on their close relationship in various clinical conditions, such as in type 1 diabetes, is urgently needed to be able to identify the high-risk

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Table 2—Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality by group

	Model 1	Model 2	Model 3	Model 4	Model 5
DN progression (N = 1,103, 321 events)					
RH	(See Supplementary. Fig. 1*A*)*	(See Supplementary Fig. 1*B*)*	3.07 (2.16, 4.37), <0.0001	2.41 (1.68, 3.44), <0.0001	1.95 (1.37, 2.79), 0.0002
No RH	(See Supplementary Fig. 1*A*)*	(See Supplementary Fig. 1*B*)*	1.07 (0.79, 1.44), 1.0	0.99 (0.72,1.36), 0.9	1.05 (0.76, 1.44), 0.8
Controlled BP	(See Supplementary Fig. 1*A*)*	(See Supplementary Fig. 1*B*)*	Reference	Reference	Reference
Incident CHD (n = 1,015, 321 events)					
RH	2.92 (1.91, 4.47), <0.0001	2.13 (1.38, 3.30), 0.0007	1.76 (1.11, 2.81), 0.02	1.55 (0.97, 2.47), 0.06	1.48 (0.92, 2.37), 0.1
No RH	1.98 (1.36, 2.88), 0.0004	1.47 (1.00, 2.16), 0.05	1.39 (0.93, 2.08), 0.1	1.41 (0.95, 2.11), 0.09	1.42 (0.95, 2.13), 0.08
Controlled BP	Reference	Reference	Reference	Reference	Reference
Incident stroke (n = 1,066, 138 events)					
RH	3.73 (2.13, 6.51), <0.0001	2.84 (1.61, 5.01), 0.0003	2.56 (1.40, 4.68), 0.002	2.00 (1.07, 3.71), 0.03	1.67 (0.90, 3.12), 0.1
No RH	1.96 (1.17, 3.27), 0.01	1.56 (0.93, 2.62), 0.09	1.59 (0.93, 2.71), 0.9	1.61 (0.95, 2.75), 0.08	1.69 (0.99, 2.88), 0.05
Controlled BP	Reference	Reference	Reference	Reference	Reference
All-cause mortality (N = 1,103, 302 deaths)					
RH	3.33 (2.32, 4.80), <0.0001	2.51 (1.73, 3.64), <0.0001	1.72 (1.16, 2.56), 0.007	1.35 (0.91, 2.02), 0.1	1.26 (0.84, 1.88), 0.3
No RH	1.70 (1.21, 2.39), 0.002	1.31 (0.92, 1.84), 0.1	1.18 (0.83, 1.68), 0.3	1.16(0.82, 1.66), 0.4	1.17 (0.82, 1.67), 0.4
Controlled BP	Reference	Reference	Reference	Reference	Reference

Data are HR (95% CI), *P* value (controlled BP reference group). Model 1: unadjusted; model 2: adjusted for age and sex; model 3: model 2 + HbA_{1c}, WHR, triglycerides, smoking, and previous CHD and/or previous stroke; model 4: model 3 + nephropathy status (normal AER, microalbuminuria, macroalbuminuria); and model 5: model 4 + eGFR/renal stage group (eGFR >90, 60–90, and <60 mL/min/1.73 m^2). *Time-varying effect of dependent variable.

individuals who should be provided optimal clinical care and counseling as early as possible (30). Furthermore, clinical controlled trials should be carried out to find the best means to optimize the management of RH throughout the kidney disease spectrum (e.g., the optimum BP targets and drug combinations, the efficacy of procedures and device-based therapies, such as carotid baroreceptor activation) (30). In fact, we are currently investigating a device-based therapy, baroreflex activation therapy, with results to be expected within 2 years (34).

Notably, we found that those with normal AER and microalbuminuria with RH had a 3.5 times higher risk of stroke compared with those who had controlled BP. It is well known that hypertension is one of the strongest risk factors for stroke both in the general population (35) and in type 1 diabetes (19,36). The risk of stroke increases after BP exceeds 130/80 mmHg in individuals with type 2 diabetes (37), while among individuals with type 1 diabetes, a linear increase in systolic BP is observed even earlier (19). Therefore, our findings indicate that it would be important to identify the individuals with RH early to lower their BP aggressively with efficient pharmacotherapy, as well as to improve their adherence to the treatment, and to pay attention to lifestyle factors to achieve the recommended BP treatment targets (38). Numerous studies have suggested that BP control may be less effective in individuals with RH than in those without RH, which might be related to differences in the 24-h BP profiles, differences in the pathophysiology of RH, or greater degrees of target organ damage (5). In the future, pharmacogenomics may provide a more rational and personalized targeted approach to the treatment of individuals with RH (5). The benefit of device-based therapies for improving the prognosis of individuals with RH still needs clarification (5, 39).

Target BP values have been debated for several years and revised several times. As a consequence, there is variation in the diabetes guidelines regarding the definition of normal BP in individuals with type 1 diabetes. The current American Diabetes Association guidelines have set the threshold of BP to 140/90 mmHg, but a more stringent target is recommended for high-risk individuals. Lately, the American College of Cardiology and AHA published new guidelines for hypertension (28). They suppose that the majority of patients with diabetes would fit into the high-risk category (10-year cardiovascular risk >10%), and thus, the new guidelines recommend a more stringent office BP goal (<130/80 mmHg). A current revision of the AHA Scientific Statement on the definition of RH recommends that in addition to a diuretic, the antihypertensive regimen should also include a long-acting calcium channel blocker and a blocker of the renin-angiotensin system (5). In our cohort, 68% had at least these three drugs in their regimen.

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The main strength of our study is that all participants were carefully characterized regarding their medical history as well as the presence and development of diabetic complications as part of the nationwide, multicenter, FinnDiane Study. It is also of note that we were able to link longitudinal data with several high-quality national registers. To our knowledge, this is the first large-scale study that assesses severe outcomes related to RH in individuals with type 1 diabetes. The main limitations relate to the definition of RH. First, the BP values were based on two office-based measurements at a single baseline visit. Consequently, white coat and masked hypertension were not assessed. Second, we cannot exclude that our results are affected by residual confounding; for example, follow-up measurements of BP during the follow-up time were not available, and BP could change over time. However, our study population is well characterized, and the set of covariates were chosen carefully on the basis of the literature. Moreover, although the accuracy and coverage of the Finnish Drug Prescription Register is high, medication doses are not recorded, and therefore, we were not able to confirm whether the antihypertensive drugs were administered at the maximum tolerated doses. However, the drug register is unique, enabling careful characterization of the types of medications purchased from the pharmacies. Finally, adherence to treatment could not be assessed. Therefore, because the definition of RH represents apparent rather than true treatment-RH, our results may overestimate the true prevalence of treatment-RH.

In conclusion, this nationwide FinnDiane Study showed that RH is associated with a higher risk of DN progression in individuals with type 1 diabetes and especially in those with macroalbuminuria. However, RH did not predict incident CHD and stroke or death beyond albuminuria and reduced kidney function. Importantly, in those with normal AER and microalbuminuria, RH was associated with a 3.5 times higher risk of stroke compared with those with controlled BP, while no differences were observed between those with no RH and controlled BP. Therefore, our data suggest that diagnostic and therapeutic counseling should be provided to these very-high-risk individuals with RH to decrease their risk of adverse events.

Acknowledgments. The skilled technical assistance of Anna Sandelin, Mira Rahkonen, Jaana Tuomikangas, and Maikki Parkkonen (Folkhälsan Research Center and University of Helsinki) is gratefully acknowledged. The authors also acknowledge the physicians and nurses at each study center (Supplementary Table 8).

Funding. The study was supported by grants from Folkhälsan Research Foundation; Wilhelm och Else Stockmanns Stiftelse; Academy of Finland (grants 299200, 275614, and 316664); Liv och Hälsa Society; Novo Nordisk Foundation (grant NNFOC0013659); Medical Society of Finland (Finska Läkaresällskapet); Dorothea Olivia, Karl Walter and Jarl Walter Perklén Foundation; Päivikki and Sakari Sohlberg Foundation; Sigrid Juselius Foundation; Finnish Foundation for Cardiovascular Research; University of Helsinki (Clinical Researcher stint); and Helsinki University Hospital Research Funds (EVO).

The funding sources were not involved in the design or conduct of the study.

Duality of Interest. D.G. has received lecture or advisory honoraria from AstraZeneca, Fresenius, GE Healthcare, and Novo Nordisk and support from CVRx and Sanofi to attend medical meetings. P.-H.G. has received lecture honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Eli Lilly, EloWater, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Peer Voice, and Sanofi; is an advisory board member for AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, and Sanofi; and has received investigator-initiated grants from Eli Lilly and Roche. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.L. designed and carried out the data analysis, interpreted the results, wrote the manuscript, and reviewed/edited the manuscript. V.H. contributed to the analysis and interpretation, contributed to the acquisition of data, and revised the manuscript. S.M. contributed to the analysis and revised the manuscript. D.G., C.F., and P.-H.G. contributed to the discussion and reviewed/edited the manuscript. All authors gave their final approval of this version of the manuscript. P.-H.G. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of data and the accuracy of data analyses.

References

1. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, Deckert T. Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. Diabetologia 1987;30:144–148

2. Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. Atherosclerosis 2000;148:159–169

3. Lithovius R, Harjutsalo V, Forsblom C, Saraheimo M, Groop PH; FinnDiane Study Group. Antihypertensive treatment and resistant hypertension in patients with type 1 diabetes by stages of diabetic nephropathy. Diabetes Care 2014;37:709–717

4. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association professional education committee of the council for high blood pressure research. Hypertension 2008;51:1403–1419

5. Carey RM, Calhoun DA, Bakris GL, et al.; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension 2018;72:e53–e90

6. Judd E, Calhoun DA. Management of resistant hypertension: do not give up on medication. Nephrol Self Assess Program 2014;13:57–63

7. Solini A, Penno G, Orsi E, et al.; Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Is resistant hypertension an independent predictor of all-cause mortality in individuals with type 2 diabetes? A prospective cohort study. BMC Med 2019;17:83

8. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation 2011;124:1046–1058

9. Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. Circulation 2012;125:1594–1596

10. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 2012;125:1635–1642

11. Irvin MR, Booth JN III, Shimbo D, et al. Apparent treatment-resistant hypertension and risk for stroke, coronary heart disease, and all-cause mortality. J Am Soc Hypertens 2014;8:405–413

12. Sim JJ, Bhandari SK, Shi J, et al. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. Kidney Int 2015;88:622–632

13. Holmqvist L, Boström KB, Kahan T, et al. Cardiovascular outcome in treatment-resistant hypertension: results from the Swedish Primary Care Cardiovascular Database (SPCCD). J Hypertens 2018;36:402–409

14. Muntner P, Davis BR, Cushman WC, et al.; ALLHAT Collaborative Research Group. Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension 2014;64:1012–1021

15. Sim JJ, Bhandari SK, Shi J, et al. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. Mayo Clin Proc 2013;88:1099–1107

16. Acharya T, Tringali S, Singh M, Huang J. Resistant hypertension and associated comorbidities

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in a veterans affairs population. J Clin Hypertens (Greenwich) 2014;16:741–745
17. Viazzi F, Greco E, Ceriello A, et al.; AMD-Annals Study Group. Apparent treatment resistant hypertension, blood pressure control and the progression of chronic kidney disease in patients with type 2 diabetes. Kidney Blood Press Res 2018;43:422–438
18. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(Suppl. 2):S54–S64
19. Hägg-Holmberg S, Dahlström EH, Forsblom CM, et al.; FinnDiane Study Group. The role of blood pressure in risk of ischemic and hemorrhagic stroke in type 1 diabetes. Cardiovasc Diabetol 2019;18:88
20. Fagerudd JA, Tarnow L, Jacobsen P, et al. Predisposition to essential hypertension and development of diabetic nephropathy in IDDM patients. Diabetes 1998;47:439–444
21. Thorn LM, Forsblom C, Fagerudd J, et al.; FinnDiane Study Group. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care 2005;28:2019–2024
22. Jansson FJ, Forsblom C, Harjutsalo V, et al.; FinnDiane Study Group. Regression of albuminuria and its association with incident cardiovascular outcomes and mortality in type 1 diabetes: the FinnDiane Study. Diabetologia 2018;61:1203–1211
23. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate [published correction appears in Ann Intern Med 2011;155:408]. Ann Intern Med 2009;150:604–612
24. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? Diabetes 2000;49:626–632
25. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2000;23(Suppl. 1):S32–S42
26. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002;25:213–229
27. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines [published corrections appear in Hypertension 2018;71:e136–e139; Hypertension 2018;72:e33]. Hypertension 2018;71:1269–1324
28. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med 2018;6:121
29. R Core Team. R: a language and environment for statistical computing [Internet]. Vienna, Austria, R Foundation for Statistical Computing, 2019. Available from https://www.R-project.org/
30. Rossignol P, Massy ZA, Azizi M, et al.; ERA-EDTA EURECA-m working group; Red de Investigación Renal (REDINREN) network; Cardiovascular and Renal Clinical Trialists (F-CRIN INI-CRCT) network. The double challenge of resistant hypertension and chronic kidney disease. Lancet 2015;386:1588–1598
31. de Beus E, Bots ML, van Zuilen AD, Wetzels JF, Blankestijn PJ; MASTERPLAN Study Group. Prevalence of apparent therapy-resistant hypertension and its effect on outcome in patients with chronic kidney disease. Hypertension 2015;66:998–1005
32. Thomas G, Xie D, Chen HY, et al.; CRIC Study Investigators. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the chronic renal insufficiency cohort study. Hypertension 2016;67:387–396
33. Muntner P, Anderson A, Charleston J, et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis 2010;55:441–451
34. Gordin D, Fadl Elmula FEM, Andersson B, et al.; Nordic BAT Study Group. The effects of baroreflex activation therapy on blood pressure and sympathetic function in patients with refractory hypertension: the rationale and design of the Nordic BAT study. Blood Press 2017;26:294–302
35. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913
36. Rawshani A, Rawshani A, Sattar N, et al. Relative prognostic importance and optimal levels of risk factors for mortality and cardiovascular outcomes in type 1 diabetes mellitus. Circulation 2019;139:1900–1912
37. Hedén Ståhl C, Lind M, Svensson AM, et al. Long-term excess risk of stroke in people with Type 2 diabetes in Sweden according to blood pressure level: a population-based case-control study. Diabet Med 2017;34:522–530
38. Lithovius R, Harjutsalo V, Forsblom C, Saraheimo M, Groop PH. The consequences of failure to achieve targets of guidelines for prevention and treatment of diabetic complications in patients with type 1 diabetes. Acta Diabetol 2015;52:31–38
39. Coppolino G, Pisano A, Rivoli L, Bolignano D. Renal denervation for resistant hypertension. Cochrane Database Syst Rev 2017;2:CD011499

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