

## **Resistant hypertension and risk of adverse events in individuals with type 1 diabetes: A nationwide prospective study**

Running title: Resistant hypertension and adverse events

Raija Lithovius, PhD<sup>1,2,3</sup>, Valma Harjutsalo, PhD<sup>1,2,3,4</sup>, Stefan Mutter, PhD<sup>1,2,3</sup>, Daniel Gordin, MD, DMSc<sup>1,2,3,5</sup>, Carol Forsblom, DMSc<sup>1,2,3</sup>, Per-Henrik Groop, MD, DMSc<sup>1,2,3,6</sup> on behalf of the FinnDiane Study Group

<sup>1</sup>Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland; <sup>2</sup>Abdominal Center Nephrology, University of Helsinki and Helsinki University Hospital, Finland; <sup>3</sup>Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Finland; <sup>4</sup>National Institute for Health and Welfare, Chronic Disease Prevention Unit, Helsinki, Finland; <sup>5</sup>Joslin Diabetes Center, Harvard Medical School, Boston, MA USA, Department of Diabetes, Central Clinical School, Monash University, Melbourne, VIC, Australia, <sup>6</sup>Department of Diabetes, Central Clinical School, Monash University, Melbourne, VIC, Australia

### **Corresponding author**

Per-Henrik Groop, Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki; Haartmaninkatu 8 (C318b), PO Box 63, 00014 Helsinki University, FINLAND

Phone: +358 500 430436

Email: [per-henrik.groop@helsinki.fi](mailto:per-henrik.groop@helsinki.fi)

### **Word count**

Abstract 250

Main text 3999

**Number of tables and figures 3**

**Abstract**

**Objectives.** 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 ( $\pm 6$  months) baseline visit (1995–2008). Individuals (N=1,103) were divided into three groups: (a) RH, (b) uncontrolled BP, but no RH and (c) controlled BP. DN progression, cardiovascular events and deaths were identified from the individuals' healthcare 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 (HR 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 to controlled BP group (3.49 [1.20, 10.15],  $p=0.02$ ).  
**Conclusion** Our findings highlight importance to identify and provide 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 recently 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 suboptimal antihypertensive drug regimen (3). Some of these individuals have a treatment-resistant hypertension (4). Resistant hypertension is defined as a BP above the treatment target if using a minimum of three or more 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 resistant hypertension is slightly higher in individuals with type 1 diabetes than in the general hypertensive population. In the nationwide Finnish Diabetic Nephropathy Study (FinnDiane) cohort the prevalence of resistant hypertension was 17.0% (BP target <140/90 mmHg), while pooled data from Europe and North America estimated that 14.8% of treated hypertensive individuals have resistant hypertension (3, 6). Similarly, a study from Italy indicated that about 14.9% of the treated individuals with type 2 diabetes have resistant hypertension (7). However, the true prevalence of resistant hypertension is unknown as these population-based studies were unable to exclude the cases with pseudo-resistance (i.e. white-coat hypertension, non-adherence to medication, suboptimal drug regimen) (5). Therefore, the term *apparent treatment-resistant hypertension* (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 to those with controlled BP or non-RH in the general hypertensive population (10-14). These studies, however, varied by definitions of resistant and non-resistant hypertension 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). Recently, colleagues from Italy 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 between 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 the 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 present 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 (Supplemental [Suppl.] Table S8, a list of the FinnDiane Study centers). Type 1 diabetes was defined by age at onset of diabetes <40 years, C-peptide  $\leq 0.3$  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 standardised 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 analysed for HbA<sub>1C</sub>, serum creatinine and lipids. The DN status was defined on the basis of the albumin excretion rate (AER) in at least two out of three overnight or 24h urine collections. Normal AER was defined as AER <20  $\mu\text{g}/\text{min}$  or <30 mg/24h; microalbuminuria as AER  $\geq 20 < 200$   $\mu\text{g}/\text{min}$  or  $\geq 30 < 300$  mg/24h; and macroalbuminuria as

AER  $\geq 200 \mu\text{g}/\text{min}$  or  $\geq 300 \text{ mg}/24\text{h}$ . 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 eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (23). Similarly for further analyses, the individuals were divided into two renal function groups: eGFR  $\geq 60 \text{ ml}/\text{min}/1.73 \text{ m}^2$  and eGFR  $< 60 \text{ ml}/\text{min}/1.73 \text{ m}^2$ . As a measure of insulin sensitivity, we used an equation for the estimated Rd (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 and stroke) were identified by 31 December 2015 from the Finnish Care Register of Health Care, which is the national hospital discharge register in Finland. The CHD events included the first acute myocardial infarction (ICD-8/9: 410–412, ICD-10: I21–I23; and coronary procedure (bypass grafting surgery or angioplasty based on the Nordic Classifications of Surgical Procedures). The 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 containing information on all prescribed, purchased and reimbursed medications in outpatient care). Medications were coded according to the Anatomic Therapeutic Chemical (ATC) classification, based on the 2019 ATC Index Version. Antihypertensive drugs were divided into eight classes: angiotensin-converting-enzyme (ACE)

inhibitors (ATC C09A, C09B), angiotensin II antagonists (C09C, C09D), diuretics (C03, C07BB, C09BA, C09DA),  $\beta$ -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 the ADA guidelines (25, 26). About two-third 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  $\geq 130/85$  mmHg (25). In addition, supplementary analysis was applied by more stringent BP target of  $<130/80$  mmHg, which was the target between 2001 and 2012 (26) and is currently also the recommended target for individuals with diabetes according to the American College of Cardiology and the American Heart Association (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: (a) RH (uncontrolled BP despite concurrent use of  $\geq 3$  antihypertensive drugs of different classes, one of which is a diuretic or controlled BP, but require  $\geq 4$  antihypertensive drugs), (b) no RH (uncontrolled BP with  $\leq 2$  antihypertensive drugs or with 3 drugs, one of which is not a diuretic) and (c) controlled BP, with  $\leq 3$  antihypertensive drugs.

## **Statistical analysis**

Data are expressed as means  $\pm$  SD for normally distributed variables, as medians with interquartile range for non-normally distributed values and binary variables as percentages. The statistical significance differences between two groups for normally distributed variables were tested by using ANOVA, otherwise with Kruskal-Wallis tests. Categorical variables were tested with Pearson's  $\chi^2$  test or two-tailed Fisher's 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 between the study groups.

Cox proportional hazard regression models were used to calculate the 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, WHR, triacylglycerol, HbA<sub>1c</sub>, previous CHD, previous stroke, DN status and renal function, when applicable. The time-dependent effects of the variables were tested by using the 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 Suppl. Tables S1-S7). 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) (Suppl. App.1). Separate models were applied for the two DN status and renal function groups, as well as for men and women separately, and finally as using a BP threshold <130/80 mmHg. All statistical analyses were performed with the R project statistical software, version R 3.5.3 (29).

## **Results**

### **Characteristics of 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  $43.7 \pm 10.4$  years and diabetes duration  $26.3 \pm 9.7$  years. Almost one-third of the individuals had decreased renal function (eGFR  $<60$  ml/min/1.73 m<sup>2</sup>) and more than 40% had DN (AER  $\geq 200$   $\mu$ g/min or  $\geq 300$  mg/24h). 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  $\geq 4$  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 4 drugs, combined also with  $\beta$ -blocking agents. Half of the individuals with no RH and about 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 had also 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 had also 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), in total 321 (29.1%) individuals progressed to a higher level of albuminuria or ESRD, 239 (21.7%)

experienced an incident CHD, and 138 (12.5%) an incident stroke. Moreover, in total 302 individuals died (27.4%) 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 controlled BP (25.0% [19.4, 30.3]) (Figure 1A). 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] (Suppl. Table S4) and in those with eGFR  $<60$  ml/min/1.73 m<sup>2</sup> (2.00 [1.24, 3.22] (Suppl. Table S6). Men with RH had an almost two times higher risk of progression compared with those who had controlled BP (Suppl. Table S1). However, in women the effect of the no RH was time-varying, and therefore, time-adjusted analysis was performed, showing a two-fold higher risk only after 4.2 years of follow-up in those with RH, compared with those who had controlled BP (Suppl. App.1, 2E). Finally, with the more stringent BP target, the association between DN progression and RH remained higher after full adjustments (Suppl. Table S7).

### **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 (Figure 1B). 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 (Figure 1C). 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 (Suppl. Tables S1-S6) 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 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 between the groups after additional adjustment for renal function (Suppl. Table S2). 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 (Suppl. Table S3). 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 (Suppl. Table S7).

### **The 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 (Figure 1D). After adjusting for clinical confounders, RH was associated with all-cause mortality compared to those with controlled BP, while no differences

were observed in those with no RH compared to those who had controlled BP (Table 2). However, when kidney disease markers were added into the multivariable models, there were no differences between the groups. The risk of death did not differ when comparing RH or no RH and controlled BP groups within the DN strata (Suppl. Tables S3, S4). However, when we divided the individuals into two renal function groups, the risk remained slightly higher in those with RH, who had an eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> compared with those who had controlled BP (Suppl. Table S5). Also, in women the risk of all-cause mortality was 90% higher in those with RH compared to those with controlled BP when adjusting for potential confounders (Suppl. Table S2). 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 (Suppl. Table S7).

## **Conclusions**

Our findings from the nationwide FinnDiane 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 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=3367) (32) reported that individuals with RH had almost 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=2778), 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, over-activation of the renin-angiotensin-aldosterone system and increased sympathetic nervous system activity. These factors in turn lower the response to antihypertensive therapy (5). As 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 in order to be able to identify the risk individuals that should be provided optimal clinical care and counseling as early as possible (30). Furthermore, clinical controlled trials should be carried out in order to find out 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 two years (34).

Notably, we found that those with normal AER and microalbuminuria with RH had 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).

The target BP values have been debated for several years and also 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 ADA 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 the American Heart Association 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 recent revision of the AHC Scientific Statement on the definition of RH, recommends that in addition to a diuretic,

the anti-hypertensive 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.

The main strength of our study is that all participants were carefully characterised 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 e.g. 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 based on the literature. Moreover, although the accuracy and coverage of the Finnish Drug 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 medication purchased from the pharmacies. Finally, adherence to treatment could not be assessed. Therefore, because the definition of resistant hypertension represents apparent rather than true treatment-resistant hypertension, our results may overestimate the true prevalence of treatment-resistant hypertension.

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 3.5 times higher risk of stroke compared to 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 in order to decrease their risk of adverse events.

### **Acknowledgements**

The skilled technical assistance of Anna Sandelin, Mira Rahkonen, Jaana Tuomikangas and Maikki Parkkonen (Folkhälsan Research Center and University of Helsinki, Finland) is gratefully acknowledged. The authors also acknowledge the physicians and nurses at each study center (Suppl. Table S8).

### **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 discussion, and reviewed/edited the manuscript. P.-H.G. has full access to all data in the study and takes responsibility for the integrity of data and the accuracy of data analyses. All authors gave their final approval of this version of the manuscript.

### **Funding**



The study was supported by grants from Folkhälsan Research Foundation, Wilhelm and Else Stockmann Foundation, Academy of Finland (299200, 275614 and 316664), Liv och Hälsa Society, Novo Nordisk Foundation (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).

### **Duality of Interest**

P-H.G. has received lecture honoraria from Astellas, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, EloWater, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Peer Voice and Sanofi. P-H.G. is an advisory board member for AbbVie, Astellas, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk and Sanofi. P-H.G. has received investigator-initiated grants from Eli Lilly and Roche. 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. No other potential conflicts of interest relevant to this article were reported. The funding sources were not involved in the design or conduct of the study. All other authors declare that there is no duality of interest associated with this manuscript.

## 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, on behalf of the FinnDiane Study Group. Antihypertensive treatment and resistant hypertension in patients with type 1 diabetes by stages of diabetic nephropathy. *Diabetes Care* 2013;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. 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;17:83-019-1313-x
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, 3rd, 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, Bostrom 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 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 multinational study of vascular disease in diabetes. *Diabetologia* 2001;44 :S54-64
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 9;18:88-019-0891-4
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. 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. *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:S32-S42
26. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002;25(1):213-229
27. Whelton PK, Carey RM, Aronow WS, et al., 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: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension* 2017;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 (2019) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>
- Rossignol P, Massy ZA, Azizi M, et al., ERA-EDTA EURECA-m working group, Red de Investigacion 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
30. 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
31. 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
32. 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
33. 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
  34. 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
  35. 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
  36. Heden Stahl C, Lind M, 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
  37. 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
  38. Coppolino G, Pisano A, Rivoli L, Bolignano D. Renal denervation for resistant hypertension. *Cochrane Database Syst Rev*;2:CD011499

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

Characteristics	Resistant hypertension (n=206 / 18.7%)	<i>P</i> value	No RH (n=639 / 57.9%)	<i>P</i> 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 <sup>2</sup> )	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
Waist-to-hip ratio	0.92 ± 0.09	<0.0001	0.89 ± 0.08	<0.0001	0.86 ± 0.08
Hemoglobin A <sub>1C</sub> (%)	8.9 ± 1.5	0.04	8.6 ± 1.4	0.9	8.6 ± 1.5
Hemoglobin A <sub>1C</sub> (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)
eGDR* (mg kg <sup>-1</sup> min <sup>-1</sup> )	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 <sup>2</sup> )	43.3 (23.8–67.2)	<0.0001	80.5 (61.5–96.4)	0.2	82.6 (61.6–101.7)
Renal status (%)		<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 the antihypertensive drugs (mean)	3.4 ± 0.5	<0.0001	1.4 ± 0.5	0.6	1.4 ± 0.7
1 drug (%)	NA	NA	60.1	NA	66.7
2 drugs (%)	NA	NA	37.4	NA	22.1
3 drugs (%)	63.1	NA	2.5	NA	11.2
≥4 drugs (%)	36.9	NA	NA	NA	NA

Data are mean ±SD, median (interquartile range) or %. *P* values represent comparisons with controlled BP group. \*eGDR, estimated glucose disposal rate, †AER, albumin excretion rate

Table 2. Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality according to the three groups: RH, no RH and controlled BP in individuals with type 1 diabetes

	Model 1	Model 2	Model 3	Model 4	Model 5
<b>DN progression</b> (N=1103, 321 events)					
RH	(see Suppl. Fig. 1A)*	(see Suppl. Fig. 1B)*	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 Suppl. Fig. 1A)*	(see Suppl. Fig. 1B)*	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 Suppl. Fig. 1A)*	(see Suppl. Fig. 1B)*	ref.	ref.	ref.
<b>Incident CHD</b> (N=1015, 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	ref.	ref.	ref.	ref.	ref.
<b>Incident stroke</b> (N=1066, 138 events)					
RH	3.73 (2.13, 6.51), <0.0001	2.84 (1.61, 5.01), .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	ref.	ref.	ref.	ref.	ref.
<b>All-cause mortality</b> (N=1103, 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), 0.3	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	ref.	ref.	ref.	ref.	ref.

Data are HR (95% CI) and *P* values (*Controlled BP* reference group); \*Time-varying effect of dependent variable

Model 1: Unadjusted;

Model 2: Adjusted for age and sex

Model 3: Model 2 + HbA<sub>1c</sub>, WHR, Triglycerides, smoking and previous CHD and/or previous stroke

Model 4: Model 3 + nephropathy status (Normal AER, microalbuminuria, macroalbuminuria)

Model 5: Model 4 + eGFR / Renal stage group (eGFR >90, 60-90 and <60 ml/min/1.73 m<sup>2</sup>)

**Figure legends**

Figure 1. 15-year cumulative risk of DN progression (A), incident CHD (B), incident stroke (C) and all-cause mortality (D) in those with controlled BP (dotted line), with no RH (dashed line) and with RH (solid line) in individuals with type 1 diabetes

**Supplementary (Suppl.) Table 1.** Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality according to the three groups: RH, no RH and controlled BP in men with type 1 diabetes; RH 140 (22.5%); no RH 366 (58.9%); Controlled BP 115 (18.5%)

	Model 1	Model 2	Model 3	Model 4	Model 5
<b>DN progression</b> (N=621, 189 events)					
RH	3.34 (2.14, 5.23), <0.0001	3.70 (2.35, 5.83), <0.0001	2.70 (1.67, 4.35), <0.0001	2.21 (1.36, 3.59), 0.001	1.98 (1.21, 3.24), 0.006
No RH	1.06 (0.69, 1.65), 0.8	1.13 (0.73, 1.75), 0.6	1.05 (0.67, 1.66), 0.8	1.05 (0.67, 1.64), 0.8	1.14 (0.72, 1.80), 0.6
Controlled BP	Reference	Reference	Reference	Reference	Reference
<b>Incident CHD</b> (N=564, 132 events)					
RH	2.52 (1.36, 4.67), 0.003	2.03 (1.09, 3.77), 0.02	1.73 (0.89, 3.36), 0.1	1.45 (0.74, 2.83), 0.3	1.41 (0.72, 2.78), 0.2
No RH	1.82 (1.03, 3.22), 0.04	1.49 (0.84, 2.64), 0.2	1.44 (0.79, 2.62), 0.2	1.45 (0.80, 2.65), 0.2	1.46 (0.80, 2.65), 0.3
Controlled BP	Reference	Reference	Reference	Reference	Reference
<b>Incident stroke</b> (N=599, 92 events)					
RH	2.26 (1.17, 4.37), 0.01	2.04 (1.05, 3.95), 0.03	2.00 (0.98, 4.12), 0.06	1.48 (0.70, 3.14), 0.3	1.21 (0.56, 2.62), 0.6
No RH	1.28 (0.70, 2.36), 0.4	1.17 (0.63, 2.15), 0.6	1.30 (0.69, 2.48), 0.4	1.30 (0.69, 2.48), 0.4	1.27 (0.67, 2.41), 0.5
Controlled BP	Reference	Reference	Reference	Reference	Reference
<b>All-cause mortality</b> (N=621, 181 deaths)					
RH	2.16 (1.35, 3.46), 0.001	1.87 (1.17, 2.99), 0.009	1.33 (0.81, 2.21), 0.2	0.95 (0.57, 1.58), 0.8	0.86 (0.51, 1.47), 0.6
No RH	1.24 (0.80, 1.93), 0.3	1.10 (0.71, 1.71), 0.7	1.04 (0.66, 1.63), 0.9	1.00 (0.64, 1.57), 1.0	0.99 (0.63, 1.56), 1.0
Controlled BP	Reference	Reference	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

Model 1: Unadjusted

Model 2: Adjusted for age/age group (age ≤35, 36-45, 46-55 and >55 years)

Model 3: Model 2 + HbA<sub>1c</sub>, WHR, triglycerides, smoking and previous CHD and/or previous stroke

Model 4: Model 3 + nephropathy status

Model 5: Model 4 + eGFR/renal stage group (eGFR >90, 60-90 and <60 ml/min/1.73 m<sup>2</sup>)



**Suppl. Table 2.** Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality according to the three groups: RH, no RH and controlled BP in women with type 1 diabetes; RH 66 (13.7%), no RH (56.6%), controlled BP 143 (29.7%)

	Unadjusted	Model 1	Model 2	Model 3	Model 4
<b>DN progression</b> ( N=482, 132 events)					
RH					
No RH	(see Suppl. Fig. 2A)*	(see Suppl. Fig. 2B)*	(see Suppl. Fig. 2C)*	(see Suppl. Fig. 2D)*	(see Suppl. Fig. 2E)*
Controlled BP					
<b>Incident CHD</b> (N=451, 107 events)					
RH					
No RH	(see Suppl. Fig. 3A)*	(see Suppl. Fig. 3B)*	(see Suppl. Fig. 3C)*	(see Suppl. Fig. 3D)*	(see Suppl. Fig. 3E)*
Controlled BP					
<b>Incident stroke</b> ( N=465, 46 events)					
RH	7.15 (2.51, 20.31), 0.0002	5.54 (1.91, 16.09),0.002	4.16 (1.37, 12.60), 0.01	3.09 (1.01, 9.46), 0.05	2.44 (0.78, 7.66), 0.1
No RH	3.39 (1.31, 8.75), 0.01	2.63 (0.99, 6.98 ), 0.05	2.38 (0.89, 6.38), 0.08	2.38 (0.89, 6.36), 0.08	2.34 (0.88, 6.28), 0.09
Controlled BP	Reference	Reference	Reference	Reference	Reference
<b>All-cause mortality</b> ( N=482, 121 deaths)					
RH	5.66 (3.17, 10.10), <0.0001	3.97 (2.18, 7.22), <0.0001	2.59 (1.34, 4.99), 0.004	2.26 (1.18, 4.35), 0.01	1.95 (1.02, 3.75), 0.04
No RH	2.35 (1.38, 4.00), 0.002	1.78 (1.02, 3.08), 0.04	1.43 (0.80, 2.55), 0.2	1.46 (0.82, 2.61), 0.2	1.78 (0.99, 3.18), 0.05
Controlled BP	Reference	Reference	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group). \*Time-varying effect of dependent variable.

Model 1: Unadjusted

Model 2: Adjusted for age/age group (age ≤35, 36-45, 46-55 and >55 years)

Model 3: Model 2 + HbA<sub>1c</sub>, WHR, triglycerides, smoking and previous CHD and/or previous stroke

Model 4: Model 3 + nephropathy status

Model 5: Model 4 + eGFR/renal stage (eGFR >90, 60-90 and <60 ml/min/1.73 m<sup>2</sup>)

**Suppl. Table 3.** Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality according to the three groups: RH, no RH and controlled BP in individuals with normal AER or microalbuminuria and type 1 diabetes

	Model 1	Model 2	Model 3	Model 4
<b>DN progression</b> (N=630, 95 events)				
RH			0.51 (0.16, 1.61), 0.2	0.50 (0.16, 1.58), 0.2
No RH	(see Suppl. Fig. 4A)*	(see Suppl. Fig. 4B)*	0.87 (0.51, 1.50), 0.6	0.87 (0.50, 1.49), 0.6
Controlled BP			Reference	Reference
<b>Incident CHD</b> (N=573, 100 events)				
RH	3.74 (1.68, 8.33), 0.001	1.85 (0.81, 4.25), 0.1	1.52 (0.64, 3.63), 0.3	1.51 (0.63, 3.60), 0.3
No RH	2.78 (1.51, 5.11), 0.001	1.84 (0.99, 3.45), 0.05	1.67 (0.88, 3.15), 0.1	1.69 (0.89, 3.19), 0.1
Controlled BP	Reference	Reference	Reference	Reference
<b>Incident stroke</b> (N=616, 56 events)				
RH	4.99 (1.81, 13.78), 0.002	3.19 (1.13, 8.97), 0.03	3.55 (1.22, 10.35), 0.02	3.49 (1.20, 10.15), 0.02
No RH	2.60 (1.17, 5.81), 0.02	1.95 (0.86, 4.39), 0.1	2.01 (0.88, 4.58), 0.1	2.01 (0.89, 4.58), 0.09
Controlled BP	Reference	Reference	Reference	Reference
<b>All-cause mortality</b> (N=630, 109 deaths)				
RH	2.93 (1.49, 5.76), 0.002	1.48 (0.74, 2.99), 0.3	1.44 (0.66, 3.10), 0.3	1.32 (0.61, 2.88), 0.5
No RH	1.70 (1.02, 2.81), 0.04	1.15 (0.69, 1.93), 0.6	1.30 (0.77, 2.19), 0.3	1.32 (0.78, 2.22), 0.3
Controlled BP	Reference	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group). \*Time-varying effect of dependent variable.

Model 1: Unadjusted

Model 2: Adjusted for age/age group (age  $\leq 35$ , 36-45, 46-55 and  $>55$  years) and sex

Model 3: Model 2 + HbA<sub>1c</sub>, WHR/WHR group (men WHR  $<0.95$ , 0.96-0.99,  $\geq 1.0$ ; women WHR  $<0.80$ , 0.81-0.85,  $\geq 0.86$ ), triglycerides, smoking and previous CHD and/or previous stroke

Model 4: Model 3 + eGFR/renal stage (eGFR  $>90$ , 60-90 and  $<60$  ml/min/1.73 m<sup>2</sup>)

**Suppl. Table 4.** Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality according to the three groups: RH, no RH and controlled BP in individuals with macroalbuminuria and type 1 diabetes

	Model 1	Model 2	Model 3	Model 4
<b>DN progression</b> (N=473, 226 events)				
RH	2.91 (1.98, 4.28), <0.0001	3.35 (2.24, 5.01), <0.0001	3.18 (2.05, 4.93), <0.0001	2.17 (1.41, 3.34), 0.0004
No RH	0.95 (0.64, 1.41), 0.8	1.02 (0.69, 1.53), 0.9	1.01 (0.66, 1.55), 1.0	0.99 (0.64, 1.51), 0.9
Controlled BP	Reference	Reference	Reference	Reference
<b>Incident CHD</b> (N=442, 139 events)				
RH	1.84 (1.10, 3.07), 0.02	(see Suppl. Fig. 5A)*	1.40 (0.80, 2.45), 0.2	1.32 (0.75, 2.33), 0.3
No RH	1.51 (0.93, 2.46), 0.1		1.18 (0.70, 2.00), 0.5	1.18 (0.69, 1.99), 0.5
Controlled BP	Reference		Reference	Reference
<b>Incident stroke</b> (N=450, 82 events)				
RH	2.18 (1.10, 4.33), 0.03	1.62 (0.80, 3.29), 0.2	1.50 (0.69, 3.23), 0.3	1.12 (0.51, 2.45), 0.8
No RH	1.54 (0.79, 3.01), 0.2	1.25 (0.63, 2.47), 0.5	1.25 (0.61, 2.55), 0.5	1.31 (0.64, 2.69), 0.5
Controlled BP	Reference	Reference	Reference	Reference
<b>All-cause mortality</b> (N=473, 193 deaths)				
RH	2.41 (1.51, 3.83), 0.0002	1.83 (1.13, 2.95), 0.01	1.32 (0.79, 2.20), 0.3	1.14 (0.68, 1.93), 0.6
No RH	1.71 (1.08, 2.70), 0.02	1.32 (0.82, 2.11), 0.2	1.17 (0.72, 1.90), 0.5	1.19 (0.73, 1.93), 0.5
Controlled BP	Reference	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group). \*Time-varying effect of dependent variable.

Model 1: Unadjusted

Model 2: Adjusted for age and sex

Model 3: Model 2 + HbA<sub>1c</sub>, WHR/WHR group (men WHR <0.95, 0.96-0.99, ≥1.0; women WHR <0.80, 0.81-0.85, ≥0.86), triglycerides /triglycerides control (triglycerides <2.3, 2.3-4.5, and >4.5 mmol/l), smoking and previous CHD and/or previous stroke

Model 4: Model 3 + eGFR/renal stage (eGFR >90, 60-90 and <60 ml/min/1.73 m<sup>2</sup>)

**Suppl. Table 5.** Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality according to the three groups: RH, no RH and controlled BP in individuals with eGFR  $\geq$  60 ml/min/1.73 m<sup>2</sup> and type 1 diabetes

	Model 1	Model 2	Model 3	Model 4
<b>DN progression</b> (N=749, 111 events)				
RH				
No RH	(see Suppl. Fig. 6A)*	(see Suppl. Fig. 6B)*	(see Suppl. Fig. 6C)*	(see Suppl. Fig. 6D)*
Controlled BP				
<b>Incident CHD</b> (N=703, 132 events)				
RH	2.45 (1.20, 5.01), 0.01	1.57 (0.75, 3.27), 0.2	1.40 (0.64, 3.06), 0.4	1.26 (0.57, 2.80), 0.6
No RH	2.48 (1.50, 4.10), 0.0004	1.82 (1.09, 3.06), 0.02	1.77 (1.03, 3.03), 0.04	1.81 (1.05, 3.11), 0.03
Controlled BP	Reference	Reference	Reference	Reference
<b>Incident stroke</b> (N=735, 59 events)				
RH	2.64 (0.91, 7.61), 0.07	1.91 (0.65, 5.62), 0.2	2.30 (0.77, 6.92), 0.1	2.48 (0.82, 7.50), 0.1
No RH	2.46 (1.16, 5.22), 0.02	1.98 (0.92, 4.26), 0.08	2.05 (0.95, 4.44), 0.07	2.16 (1.00, 4.68), 0.05
Controlled BP	Reference	Reference	Reference	Reference
<b>All-cause mortality</b> (N=749, 136 deaths)				
RH	3.25 (1.76, 6.01), 0.0002	2.15 (1.15, 4.02), 0.02	2.20 (1.13, 4.31), 0.02	2.04 (1.04, 4.02), 0.04
No RH	1.91 (1.19, 3.07), 0.007	1.43 (0.88, 2.32), 0.1	1.48 (0.90, 2.45), 0.1	1.50 (0.91, 2.48), 0.1
Controlled BP	Reference	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group). \*Time-varying effect of dependent variable.

Model 1: Unadjusted

Model 2: Adjusted for age/age group (age  $\leq$ 35, 36-45, 46-55 and  $>$ 55 years) and sex

Model 3: Model 2 + HbA<sub>1C</sub>/glycemic control (HbA<sub>1C</sub>  $<$ 7.5, 7.5-8.99;  $>$ 9.0 %), WHR, triglycerides, smoking and previous CHD and/or previous stroke

Model 4: Model 3 + eGFR/renal stage (eGFR  $>$ 90, 60-90 and  $<$ 60 ml/min/1.73 m<sup>2</sup>)

**Suppl. Table 6.** Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality according to the three groups: RH, no RH and controlled BP in individuals with eGFR < 60 ml/min/1.73 m<sup>2</sup> and type 1 diabetes

	Model 1	Model 2	Model 3	Model 4
<b>DN progression</b> (N=349, 210 events)				
RH	1.96 (1.33, 2.89), 0.0007	2.13 (1.43, 3.18), 0.0002	2.25 (1.45, 3.47), 0.0003	2.00 (1.24, 3.22), 0.004
No RH	0.81 (0.54, 1.22), 0.3	0.88 (0.58, 1.33), 0.5	0.95 (0.61, 1.47), 0.8	1.00 (0.62, 1.62), 1.0
Controlled BP	Reference	Reference	Reference	Reference
<b>Incident CHD</b> (N=308, 107 events)				
RH	1.71 (0.95, 3.05), 0.07	1.46 (0.81, 2.63), 0.2	1.31 (0.70, 2.44), 0.4	1.21 (0.64, 2.26), 0.5
No RH	1.38 (0.77, 2.47), 0.3	1.10 (0.61, 1.99), 0.7	0.91 (0.49, 1.71), 0.8	0.87 (0.47, 1.64), 0.7
Controlled BP	Reference	Reference	Reference	Reference
<b>Incident stroke</b> (N=326, 78 events)				
RH	1.87 (0.92, 3.79), 0.08	1.57 (0.77, 3.21), 0.2	1.53 (0.72, 3.27), 0.3	1.36 (0.63, 2.96), 0.4
No RH	1.53 (0.75, 3.09), 0.2	1.30 (0.64, 2.63), 0.5	1.43 (0.68, 3.03), 0.3	1.36 (0.64, 2.90), 0.4
Controlled BP	Reference	Reference	Reference	Reference
<b>All-cause mortality</b> (N=349, 165 deaths)				
RH	1.74 (1.07, 2.82), 0.02	1.54 (0.94, 2.52), 0.08	1.16 (0.70, 1.94), 0.5	1.01 (0.60, 1.69), 0.9
No RH	1.48 (0.91, 2.41), 0.1	1.20 (0.73, 1.97), 0.5	0.97 (0.58, 1.60), 0.9	0.90 (0.54, 1.50), 0.7
Controlled BP	Reference	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

Model 1: Unadjusted

Model 2: Adjusted for age/age group (age ≤35, 36-45, 46-55 and >55 years) and sex

Model 3: Model 2 + HbA<sub>1c</sub>, WHR, triglycerides/ triglycerides control (triglycerides <2.3, 2.3-4.5, and >4.5 mmol/l), smoking and previous CHD and/or previous stroke

Model 4: Model 3 + eGFR/renal stage (eGFR >90, 60-90 and <60 ml/min/1.73 m<sup>2</sup>)

**Suppl. Table 7.** Cox regression models for DN progression, incident CHD and stroke, and all-cause mortality according to the three groups: RH, no RH and controlled BP in individuals with type 1 diabetes when the BP threshold was set <130/80 mmHg

	Model 1	Model 2	Model 3	Model 4	Model 5
<b>DN progression</b> (N=1103, 321 events)					
RH		3.47 (2.41, 5.00), <0.0001	2.76 (1.85, 4.12), <0.0001	2.17 (1.44, 3.26), 0.0002	1.67 (1.11, 2.52), 0.01
No RH	(see Suppl. Fig. 7A)*	0.96 (0.68, 1.36), 0.8	0.93 (0.65, 1.34), 0.7	0.91 (0.63, 1.31), 0.6	0.93 (0.65, 1.34), 0.7
Controlled BP		Reference	Reference	Reference	Reference
<b>Incident CHD</b> (N=1015, 239 events)					
RH	2.39 (1.50, 3.80), 0.0002	1.92 (1.20, 3.07), 0.007	1.57 (0.96, 2.59), 0.07	1.43 (0.87, 2.36), 0.1	1.36 (0.82, 2.27), 0.2
No RH	1.45 (0.95, 2.22), 0.08	1.25 (0.81, 1.91), 0.3	1.17 (0.75, 1.82), 0.5	1.22 (0.78, 1.89), 0.4	1.23 (0.79, 1.92), 0.3
Controlled BP	Reference	Reference	Reference	Reference	Reference
<b>Incident stroke</b> (N=1066, 138 events)					
RH	3.16 (1.69, 5.91), 0.003	2.59 (1.38, 4.87), 0.003	2.38 (1.21, 4.68), 0.01	1.90 (0.95, 3.80), 0.07	1.52 (0.75, 3.09), 0.2
No RH	1.59 (0.89, 2.86), 0.1	1.41 (0.78, 2.53), 0.2	1.47 (0.80, 2.72), 0.2	1.53 (0.83, 2.83), 0.2	1.57 (0.85, 2.90), 0.1
Controlled BP	Reference	Reference	Reference	Reference	Reference
<b>All-cause mortality</b> (N=1103, 302 deaths)					
RH	2.96 (1.96, 4.46), <0.0001	2.46 (1.62, 3.72), <0.0001	1.72 (1.11, 2.66), 0.01	1.32 (0.85, 2.06), 0.2	1.23 (0.79, 1.93), 0.3
No RH	1.41 (0.96, 2.08), 0.08	1.25 (0.85, 1.84), 0.3	1.16 (0.79, 1.73), 0.4	1.12 (0.76, 1.66), 0.6	1.13 (0.77, 1.68), 0.5
Controlled BP	Reference	Reference	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group). \*Time-varying effect of dependent variable.

Model 1: Unadjusted

Model 2: Adjusted for age/age group (age ≤35, 36-45, 46-55 and >55 years)

Model 3: Model 2 + HbA<sub>1c</sub>, WHR, triglycerides, smoking and previous CHD and/or previous stroke

Model 4: Model 3 + nephropathy status

Model 5: Model 4 + eGFR/ renal stage (eGFR >90, 60-90 and <60 ml/min/1.73 m<sup>2</sup>)

**Suppl. Table 8.** List of physicians and nurses at each of the FinnDiane centers participating in patient recruitment and characterization

**The Finnish Diabetic Nephropathy Study Centers**

Anjalankoski Health Center	S.Koivula, T.Uggeldahl
Central Finland Central Hospital, Jyväskylä	T.Forslund, A.Halonen, A.Koistinen, P.Koskiahio, M.Laukkanen, J.Saltevo, M.Tiihonen
Central Hospital of Åland Islands, Mariehamn	M.Forsen, H.Granlund, A.-C.Jonsson, B.Nyroos
Central Hospital of Kanta-Häme, Hämeenlinna	P.Kinnunen, A.Orvola, T.Salonen, A.Vähänen
Central Hospital of Kymenlaakso, Kotka	R.Paldanius, M.Riihelä, L.Ryysy
Central Hospital of Länsi-Pohja, Kemi	H.Laukkanen, P.Nyländen, A.Sademies
Central Ostrobothnian Hospital District, Kokkola	S.Anderson, B.Asplund, U.Byskata, P.Liedes, M.Kuusela, T.Virkkala
City of Espoo Health Center:	
Espoonlahti	A.Nikkola, E.Ritola
Tapiola	M.Niska, H.Saarinen
Samaria	E.Oukko-Ruponen, T.Virtanen
Viharlaakso	A.Lyytinen
City of Helsinki Health Center:	
Puistola	H.Kari, T.Simonen
Suutarila	A.Kaprio, J.Kärkkäinen, B.Rantaeskola
Töölö	P.Kääriäinen, J.Haaga, A-L.Pietiläinen
City of Hyvinkää Health Center	S.Klemetti, T.Nyandoto, E.Rontu, S.Satuli-Autere
City of Vantaa Health Center:	
Korso	R.Toivonen, H.Virtanen
Länsimäki	R.Ahonen, M.Ivaska-Suomela, A.Jauhiainen
Marttilaakso	M.Laine, T.Pellonpää, R.Puranen
Myyrämäki	A.Airas, J.Laakso, K.Rautavaara
Rekola	M.Erola, E.Jatkola
Tikkurila	R.Lönnblad, A.Malm, J.Mäkelä, E.Rautamo
Heinola Health Center	P.Hentunen, J.Lagerstam
Helsinki University Central Hospital, Department of Medicine, Division of Nephrology	M.Fedoroff, D.Gordin, O.Heikkilä, K.Hietala, J.Fagerudd, M.Korolainen, L.Kyllönen, J.Kytö, S.Lindh, K.Pettersson-Fernholm, M.Rosengård-Bärlund, A.Sandelin, L.Thorn, J.Tuomikangas, T.Vesisenaho, J.Wadén
Herttoniemi Hospital, Helsinki	V.Sipilä
Hospital of Lounais-Häme, Forssa	T.Kalliomäki, J.Koskelainen, R.Nikkanen, N.Savolainen, H.Sulonen, E.Valtonen
Hyvinkää Hospital	L. Norvio, A.Hämäläinen
Iisalmi Hospital	E.Toivanen
Jokilaakso Hospital, Jämsä	A.Parta, I.Pirttiniemi
Jorvi Hospital, Helsinki University Central Hospital	S.Aranko, S.Ervasti, R.Kauppinen-Mäkelin, A.Kuusisto, T.Leppälä, K.Nikkilä, L.Pekkonen
Jyväskylä Health Center, Kyllö	K.Nuorva, M.Tiihonen
Kainuu Central Hospital, Kajaani	S.Jokelainen, K.Kananen, M.Karjalainen, P.Kemppainen, A-M.Mankinen, A.Reponen
Kerava Health Center	M.Sankari
Kirkkonummi Health Center	H.Stuckey, P.Suominen
Kivelä Hospital, Helsinki	A.Lappalainen, M.Limatainen, J.Santaholma
Koskela Hospital, Helsinki	A.Aimolahti, E.Huovinen
Kotka Health Center	V.Iikka, M.Lehtimäki
Kouvola Health Center	E.Pälikkö-Kontinen, A.Vanhanen
Kuopio University Hospital	E.Koskinen, T.Siitonen
Kuusamo Health Center	E.Huttunen, R.Ikäheimo, P.Karhapää, P.Kekäläinen, M.Laakso, T.Lakka, E.Lampainen,
Kuusankoski Hospital	L.Moilanen, S. Tanskanen, L.Niskanen, U.Tuovinen, I.Vauhkonen, E.Voutilainen
Laakso Hospital, Helsinki	T.Kääriäinen, E.Isopoussu
Lahti City Hospital	E.Kilkkä, I.Koskinen, L.Riihelä
Lapland Central Hospital, Rovaniemi	T.Meriläinen, P.Poukka, R.Savolainen, N.Uhlenius
Lappeenranta Health Center	A.Mäkelä, M.Tanner
Lohja Hospital	L.Hyvärinen, K.Lampela, S.Pöykkö, T.Rompasaari, S.Severinkangas, T.Tulokas
Länsi-Uusimaa Hospital, Tammisaari	P. Erola, L.Härkönen, P.Linkola, T.Pekkanen, I.Pulli, E.Repo
Loimaa Health Center	T.Granlund, K.Hietanen, M.Porrassalmi, M.Saari, T.Salonen, M.Tiikkainen,
Malmi Hospital, Helsinki	I.-M.Jousmaa, J.Rinne
Mikkeli Central Hospital	A.Mäkelä, P.Eloranta
Mänttä Regional Hospital	H.Lanki, S.Moilanen, M.Tilly-Kiesi
North Karelian Hospital, Joensuu	A.Gynther, R.Manninen, P.Nironen, M.Salminen, T.Vänttinen
Nurmijärvi Health Center	I.Pirttiniemi, A-M.Hänninen
Oulaskangas Hospital, Oulainen	U-M.Henttula, P.Kekäläinen, M.Pietarinen, A.Rissanen, M.Voutilainen
Oulu Health Center	A.Burgos, K.Urtamo
Oulu University Hospital	E.Jokelainen, P-L.Jylkkä, E.Kaarlela, J.Vuolaspuro
Päijät-Häme Central Hospital	L.Hiltunen, R.Häkkinen, S.Keinänen-Kiukaanniemi
Palokka Health Center	R.Ikäheimo
Pieksämäki Hospital	H.Haapamäki, A.Helanterä, S.Hämäläinen, V.Ilvesmäki, H.Miettinen
Pietarsaari Hospital	P.Sopanen, L.Welling
Pori City Hospital	V.Sevtsenko, M.Tamminen
Porvoo Hospital	M-L.Holmbäck, B.Isomaa, L.Sarelin
Raahe Hospital	P.Ahonen, P.Merisalo, E.Muurinen, K.Sävelä
Rauma Hospital	M.Kallio, B.Rask, S.Rämö
Riihimäki Hospital	A.Holma, M.Honkala, A.Tuomivaara, R.Vainionpää
	K.Laine, K.Saarinen, T.Salminen
	P.Aalto, E.Immonen, L.Juurinen

Salo Hospital	A.Alanko, J.Lapinleimu, P.Rautio, M.Virtanen
Satakunta Central Hospital, Pori	M.Asola, M.Juhola, P.Kunelius, M.-L.Lahdenmäki, P.Pääkkönen, M.Rautavirta
Savonlinna Central Hospital	T.Pulli, P.Sallinen, M.Taskinen, E.Tolvanen, T.Tuominen, H.Valtonen, A.Vartia, S-L.Viitanen
Seinäjoki Central Hospital	O.Antila, E.Korpi-Hyövälti, T.Latvala, E.Leijala, T.Leikkari, M.Punkari, N.Rantamäki, H.Vähävuori
South Karelia Central Hospital, Lappeenranta	T.Ensala, E.Hussi, R.Härkönen, U.Nyholm, J.Toivanen
Tampere Health Center	A.Vaden, P.Alarotu, E.Kujansuu, H.Kirkkopelto-Jokinen, M.Helin, S.Gummerus, L.Calonius, T.Niskanen, T.Kaitala, T.Vatanen
Tampere University Hospital	P. Hannula, I.Ala-Houhala, R.Kannisto, T.Kuningas, P.Lampinen, M.Määttä, H.Oksala, T.Oksanen, A.Putila, H.Saha, K.Salonen, H.Tauriainen, S.Tulokas
Tiirismaa Health Center, Hollola	T.Kivelä, L.Petlin, L.Savolainen
Turku Health Center	A.Artukka, I.Hämäläinen, L.Lehtinen, E.Pyysalo, H.Virtamo, M.Viinikkala, M.Vähätalo
Turku University Central Hospital	K.Breitholz, R.Eskola, K.Metsärinne, U.Pietilä, P.Saarinen, R.Tuominen, S.Äyräpää
Vaajakoski Health Center	K.Mäkinen, P.Sopanen
Valkeakoski Regional Hospital	S.Ojanen, E.Valtonen, H.Ylönen, M.Rautiainen, T.Immonen
Vammala Regional Hospital	I.Isomäki, R.Kroneld, L.Mustaniemi, M.Tapiolinna-Mäkelä
Vaasa Central Hospital	S.Bergkulla, U.Hautamäki, V-A.Myllyniemi, I.Rusk



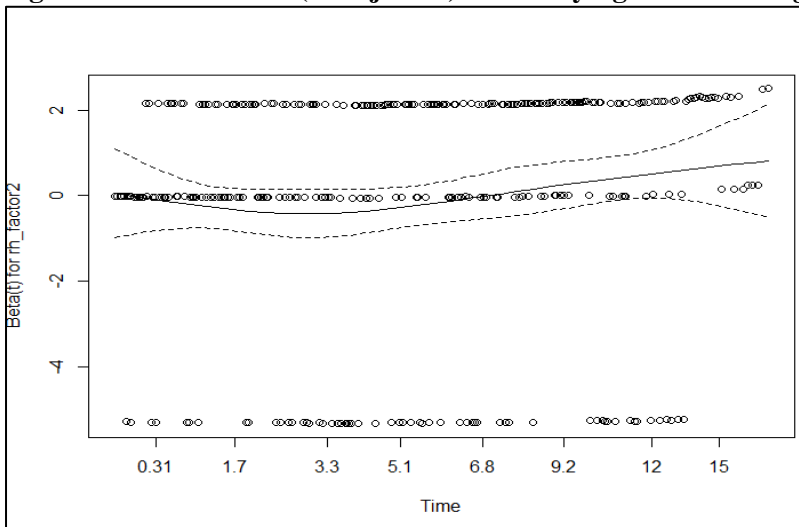
## Supplementary figures

### To test time-varying effects

The time-dependent effects of the variables were tested by using the Schoenfeld residuals against the follow-up time (*cox.zph*, *Survival package in R*) (30). The assumption is that the hazard rate of an individual is constant over time. When the proportional hazards assumption of the Cox model is not fulfilled, the effect of the covariate is time-varying. When a time-varying effect emerged in an independent variable, we stratified the variable. When the effect occurred in the dependent variable, we visually inspected how the covariate on DN progression (or other outcomes) varied over time (29). Following the method of Zhang et al. (29), we stratified the follow-up time into distinct intervals, so that the proportional hazard assumption was fulfilled for each time interval.

### 1. Risk of DN progression in all individuals (see Table 1 in the main text)

**Fig. 1A. In the Model 1 (unadjusted) time-varying effect of RH group 2 (no RH)**



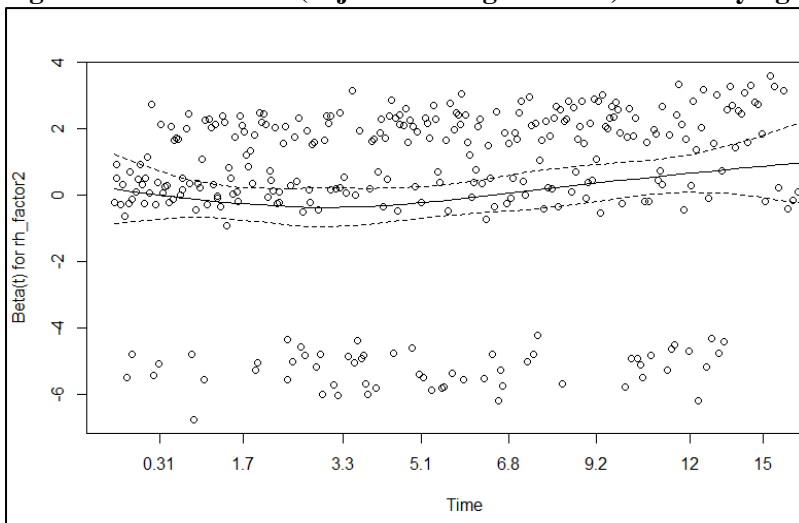
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 5.0	≥ 5.0
RH	3.49 (2.28, 5.32), <0.0001	3.23 (2.02, 5.15), <0.0001
No RH	0.71 (0.46, 1.11), 0.1	1.26 (0.83, 1.90), 0.3
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of DN progression was higher in individuals with RH during the both time periods, while the risk did not differ in those with no RH compared with those who had controlled BP.

**Fig. 1B. In the Model 2 (adjusted for age and sex) time-varying effect of RH group 2 (no RH)**



By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

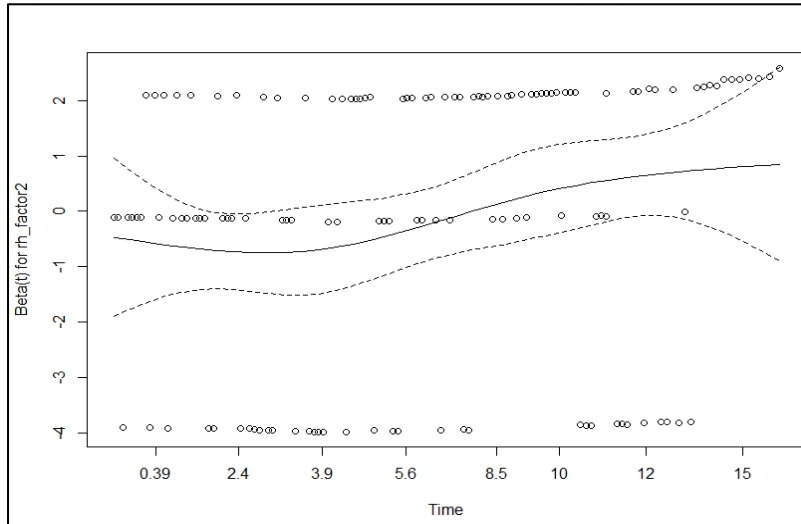
Follow-up (years)	< 5.5	≥ 5.5
RH	3.63 (2.39, 5.50), <0.0001	4.22 (2.52, 7.04), <0.0001
No RH	0.75 (0.49, 1.14), 0.1	1.53 (0.98, 2.38), 0.3
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of DN progression was higher in individuals with RH during the both time periods, while the risk did not differ in those with no RH compared with those who had controlled BP.

## 2. The risk of DN progression in women (see Suppl. Table 2)

**Fig. 2A. In the Model 1 (unadjusted) time-varying effect of RH group 2 (no RH)**



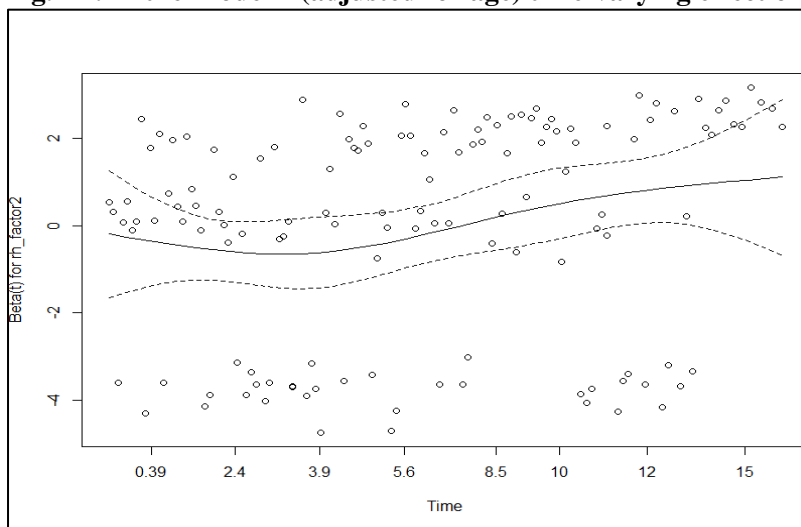
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 4.4	≥ 4.4
RH	3.19 (1.71, 5.94), 0.0003	4.22 (2.13, 8.38), <0.0001
No RH	0.39 (0.19, 0.79), 0.009	1.43 (0.82, 2.50), 0.2
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of DN progression in those with no RH was even lower during the first time period (< 4.4 years), compared with those who had controlled BP, but no differences were observed afterwards (≥ 4.4 years).

**Fig. 2B. In the Model 2 (adjusted for age) time-varying effect of RH group 2 (no RH)**



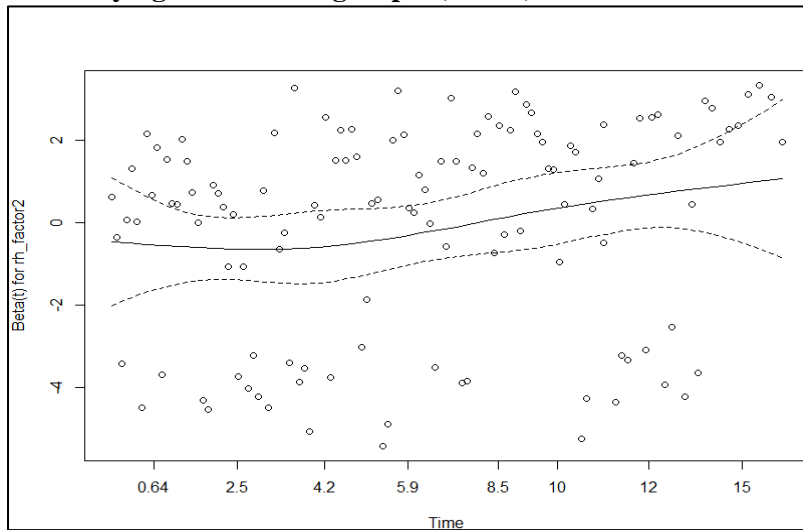
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 4.0	≥ 4.0
RH	3.67 (1.90, 7.11), 0.0001	5.29 (2.71, 10.34), <0.0001
No RH	0.34 (0.15, 0.75), 0.007	1.63 (0.94, 2.81), 0.08
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of DN progression in those with no RH was even lower during the first time period (< 4.0 years), compared with those who had controlled BP, but no differences were observed afterwards ( $\geq 4.0$  years).

**Fig. 2C. In the Model 3 (adjusted for age, HBA<sub>1c</sub>, WHR, triglycerides, smoking, previous CHD, previous stroke) time-varying effect of RH group 2 (no RH)**



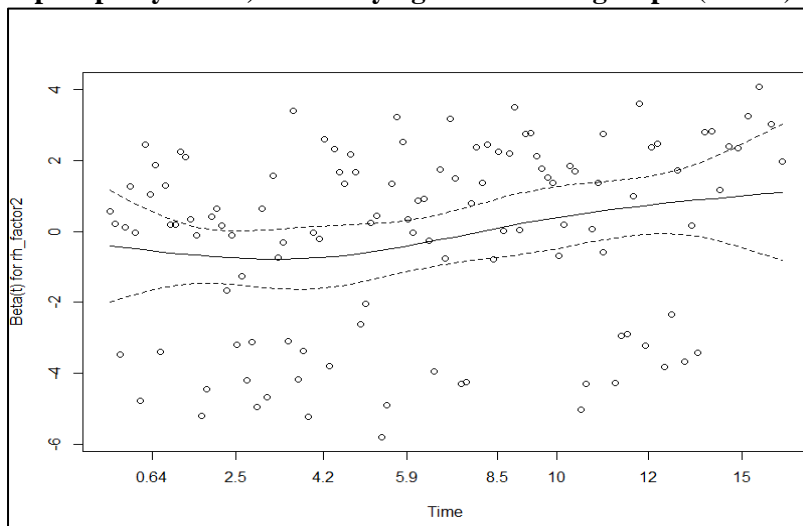
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 4.0	$\geq 4.0$
RH	3.14 (1.48, 6.69), 0.003	4.42 (2.15, 9.11), <0.0001
No RH	0.34 (0.14, 0.78), 0.01	1.41 (0.80, 2.49), 0.2
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of DN progression in those with no RH was even lower during the first time period (< 4.0 years), compared with those who had controlled BP, but no differences were observed afterwards ( $\geq 4.0$  years).

**Fig. 2D. In the Model 3 (adjusted for age, HBA<sub>1c</sub>, WHR, triglycerides, smoking, previous CHD, previous stroke, nephropathy status) time-varying effect of RH group 2 (no RH)**



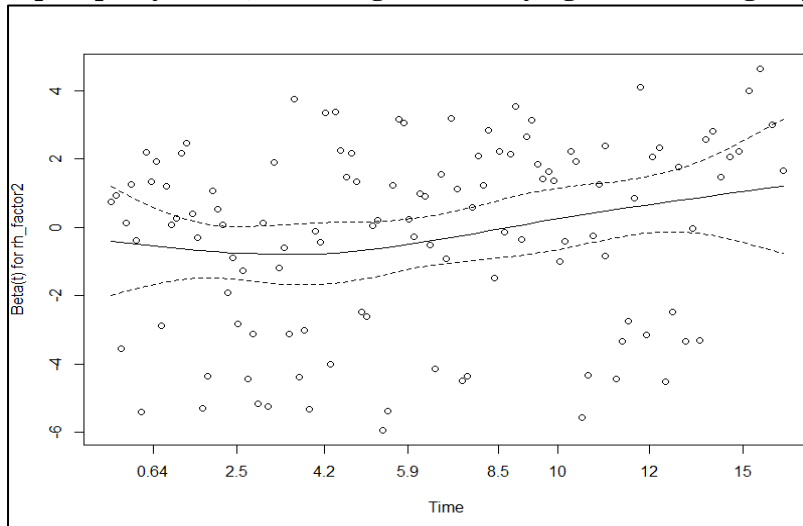
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 4.2	$\geq 4.2$
RH	2.47 (1.18, 5.17), 0.01	3.12 (1.49, 6.54), 0.003
No RH	0.32 (0.14, 0.75), 0.009	1.37 (0.77, 2.44), 0.3
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of DN progression in those with no RH was even lower during the first time period (< 4.2 years), compared with those who had controlled BP, but no differences were observed afterwards ( $\geq 4.2$  years).

**Fig. 2E. In the Model 3 (adjusted for age, HBA<sub>1c</sub>, WHR, triglycerides, smoking, previous CHD, previous stroke, nephropathy status, renal stage) time-varying effect of RH group 2 (no RH)**



By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

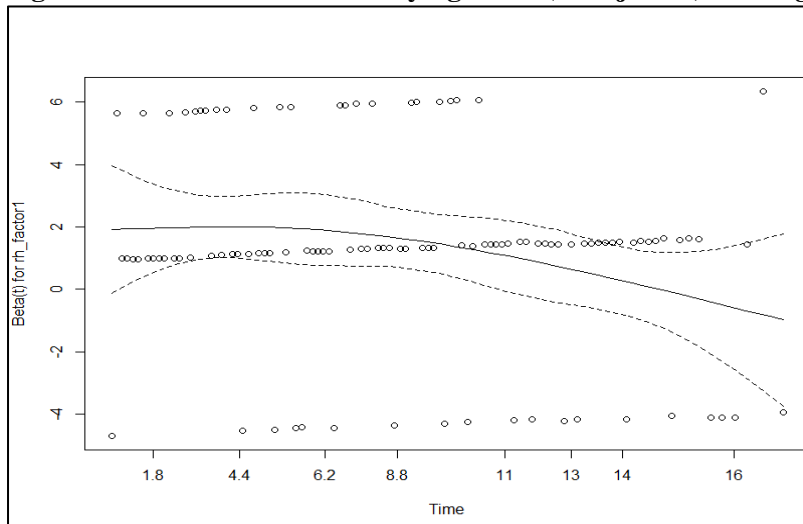
Follow-up (years)	< 4.2	≥ 4.2
RH	1.78 (0.85, 3.72), 0.1	2.14 (1.01, 4.52), 0.05
No RH	0.33 (0.14, 0.79), 0.01	1.31 (0.73, 2.36), 0.3
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of DN progression in those with no RH was even lower during the first time period (< 4.2 years), compared with those who had controlled BP, but no differences were observed afterwards (≥ 4.2 years).

### 3. The risk of CHD in women (see Suppl. Table 2)

**Fig. 3A. In the Model 1 time-varying effect (unadjusted) of RH group 1 (RH)**



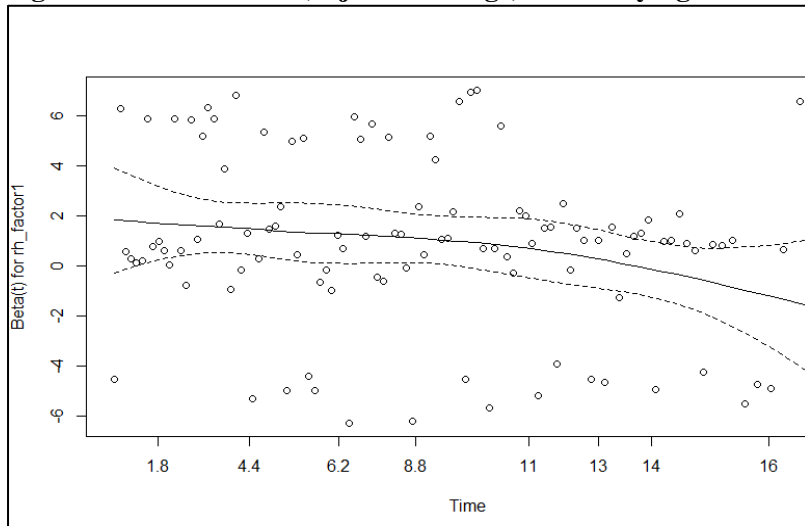
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 6.2	≥ 6.2
RH	5.85 (2.06, 16.60), 0.0009	2.71 (1.23, 5.97), 0.01
No RH	2.65 (1.01, 6.95), 0.05	1.96 (1.07, 3.61), 0.03
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of CHD was higher in individuals with RH during the both time periods (especially during <6.2 years follow-up), and the risk was also higher in those with no RH, compared with those who had controlled BP.

**Fig. 3B. In the Model 2 (adjusted for age) time-varying effect of RH group 1 (RH)**



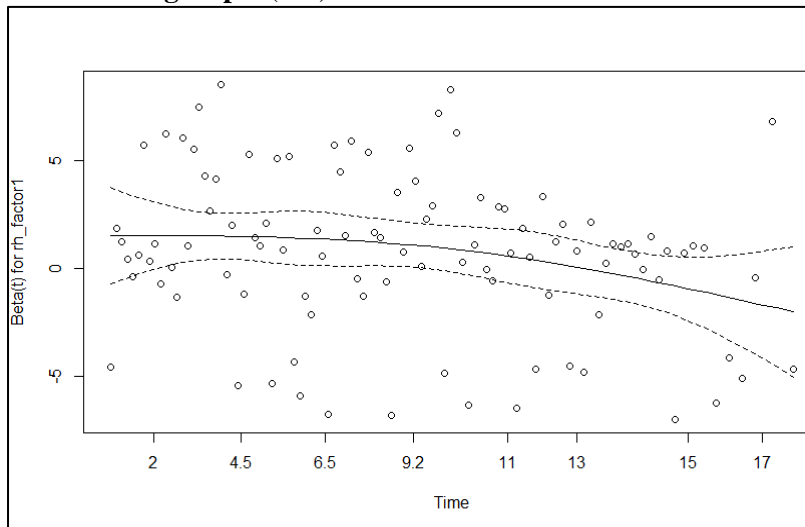
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 6.2	≥ 6.2
RH	3.56 (1.24, 10.26), 0.02	1.76 (0.78, 3.93), 0.2
No RH	1.66 (0.62, 4.42), 0.3	1.38 (0.74, 2.58), 0.3
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of CHD was higher in individuals with RH only during the first time period (<6.2 years), but not afterwards, while the risk did not differ in those with no RH, compared with those who had controlled BP.

**Fig. 3C. In the Model 3 (adjusted for age, HBA<sub>1c</sub>, WHR, triglycerides, smoking, previous stroke) time-varying effect of RH group 1 (RH)**



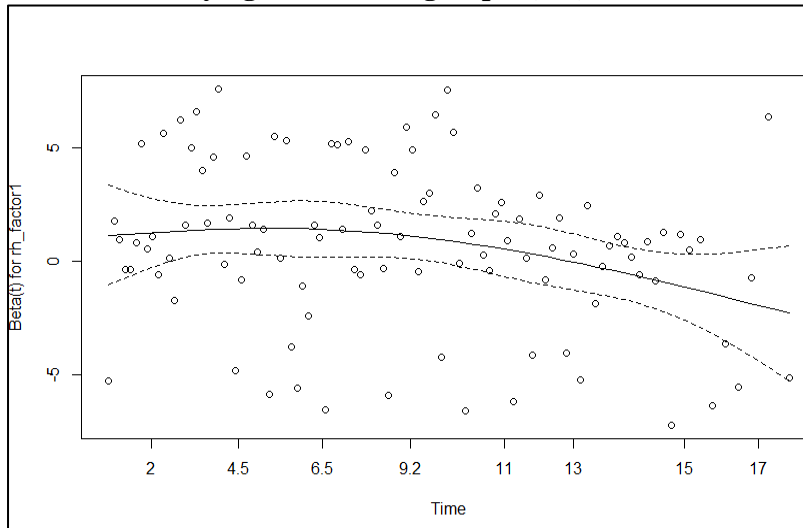
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 6.5	≥ 6.5
RH	2.90 (0.99, 8.51), 0.05	1.65 (0.71, 3.80), 0.2
No RH	1.46 (0.54, 3.93), 0.4	1.38 (0.72, 2.64), 0.3
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The CHD risk did not differ in those with RH or no RH, compared with those who had controlled BP.

**Fig. 3D. In the Model 3 (adjusted for age, HBA<sub>1c</sub>, WHR, triglycerides, smoking, previous stroke, nephropathy status) time-varying effect of RH group 1 (RH)**



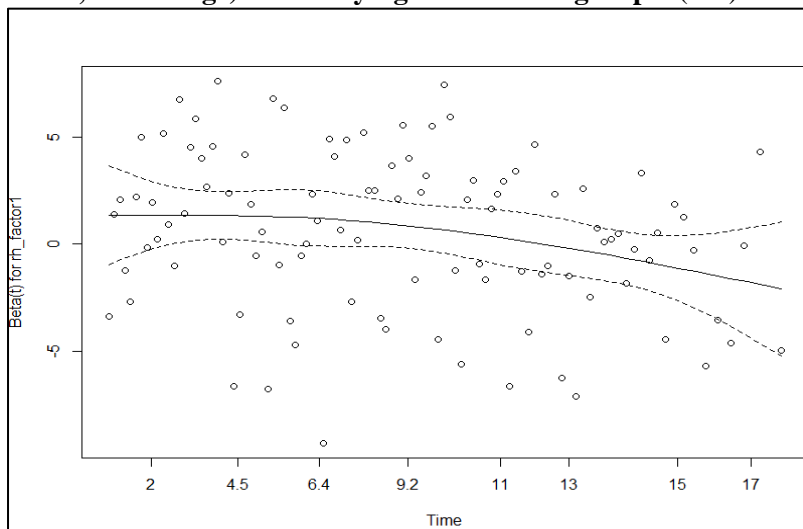
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 9.0	≥ 9.0
RH	2.65 (1.05, 6.65), 0.04	1.15 (0.43, 3.06), 0.8
No RH	1.45 (0.62, 3.38), 0.4	1.39 (0.69, 2.82), 0.3
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

After full adjustment the CHD risk was higher in women with RH during the first time period (< 9 years), but not afterwards, while the risk did not differ in those with no RH, compared with those who had controlled BP.

**Fig. 3E. In the Model 3 (adjusted for age, HBA<sub>1c</sub>, WHR, triglycerides, smoking, previous stroke, nephropathy status, renal stage) time-varying effect of RH group 1 (RH)**



By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

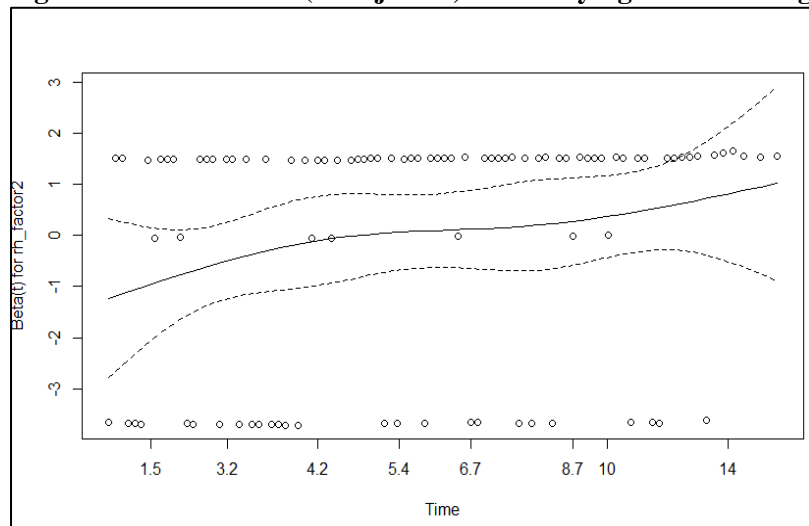
Follow-up (years)	< 9.0	≥ 9.0
RH	2.47 (0.98, 6.23), 0.05	1.09 (0.41, 2.91), 0.8
No RH	1.45 (0.62, 3.37), 0.4	1.40 (0.69, 2.84), 0.3
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The CHD risk did not differ in those with RH or no RH, compared with those who had controlled BP.

#### 4. Risk of DN progression in those with normal AER and microalbuminuria (see Suppl. Table 3)

**Fig. 4A. In the Model 1 (unadjusted) time-varying effect of RH group 2 (no RH)**



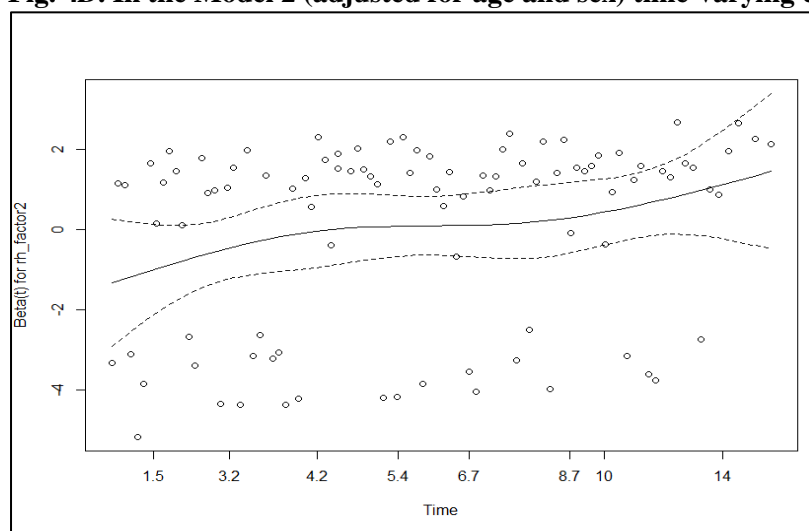
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 5.4	≥ 5.4
RH	0.81(0.27, 2.41), 0.7	1.08 (0.30, 3.93), 0.9
No RH	0.63 (0.33, 1.18), 0.1	1.55 (0.77, 3.11), 0.2
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The DN progression risk did not differ in those with RH or no RH, compared with those who had controlled BP.

**Fig. 4B. In the Model 2 (adjusted for age and sex) time-varying effect of RH group 2 (no RH)**



By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

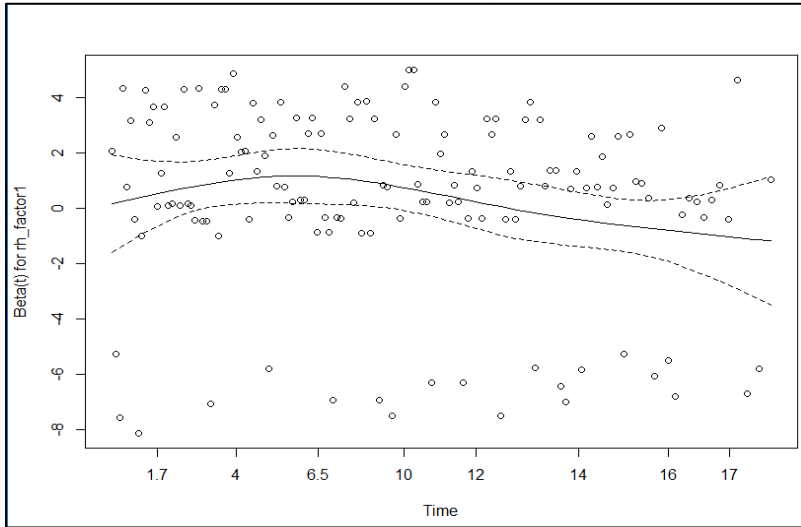
Follow-up (years)	< 4.2	4.2 – 7.5	> 7.5
RH	0.69 (0.20, 2.39), 0.5	0.94 (0.20, 4.55), 0.9	1.53 (0.30, 7.87), 0.6
No RH	0.43 (0.21, 0.89), 0.02	1.40 (0.60, 3.25), 0.4	1.94 (0.74, 5.09), 0.2
Controlled BP	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

During the first 4.2 years the risk of DN progression was slightly lower in those with no RH, while no differences were observed in those with RH, compared with those who had controlled BP.

## 5. Risk of CHD in individuals with macroalbuminuria (see Suppl. Table 4.)

**Fig. 5A. In the Model 2 (adjusted for age and sex) time-varying effect of RH group 1 (RH)**



By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

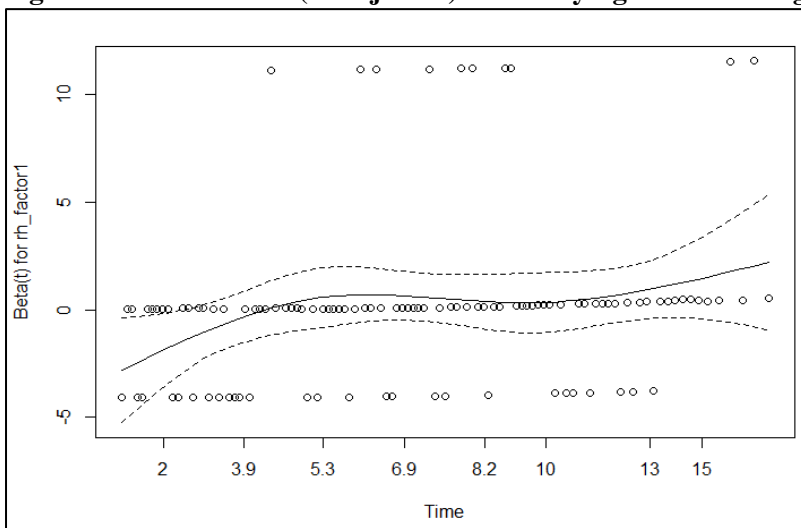
Follow-up (years)	< 4.0	4.0 – 10.0	> 10.0
RH	1.81 (0.59, 5.53), 0.3	2.60 (0.87, 7.77), 0.09	0.89 (0.42, 1.87), 0.8
No RH	1.03 (0.34, 3.12), 1.0	1.60 (0.54, 4.70), 0.4	1.12 (0.59, 2.14), 0.7
Controlled BP	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The CHD risk did not differ in those with RH or no RH, compared with those who had controlled BP.

## 6. Risk of DN progression in those with eGFR $\geq 60$ ml/min/1.73 m<sup>2</sup> (see Suppl. Table 5.)

**Fig. 6A. In the Model 1 (unadjusted) time-varying effect of RH group 1 (RH)**



By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

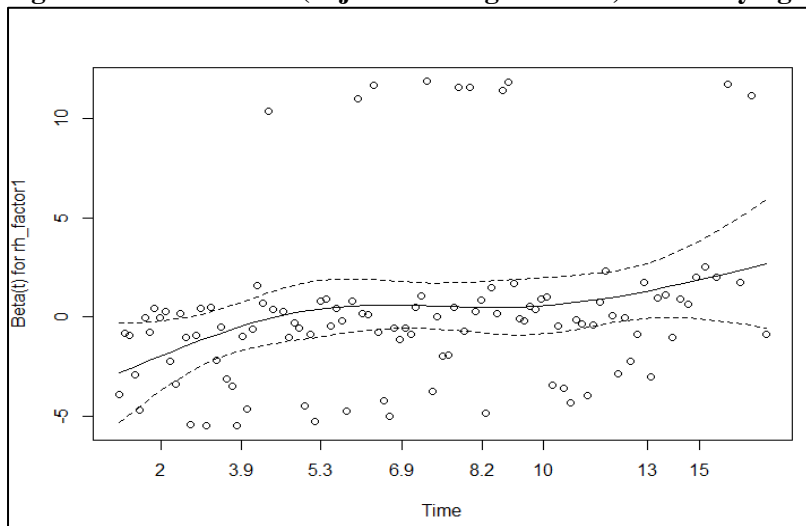
Follow-up (years)	< 5.3	5.3 – 10.0	> 10.0
RH	0.20 (0.03, 1.56), 0.1	3.54 (1.19, 10.53), 0.02	1.11 (0.23, 5.34), 0.9
No RH	0.70 (0.36, 1.35), 0.3	1.91 (0.79, 4.62), 0.1	1.31 (0.56, 3.08), 0.5
Controlled BP	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

In individuals with eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> the risk of DN progression was higher in those with RH during the time-period of 5.3–10.0 years, but no differences were observed between the groups before and after that time period.



**Fig. 6B. In the Model 2 (adjusted for age and sex) time-varying effect of RH group 1 (RH)**



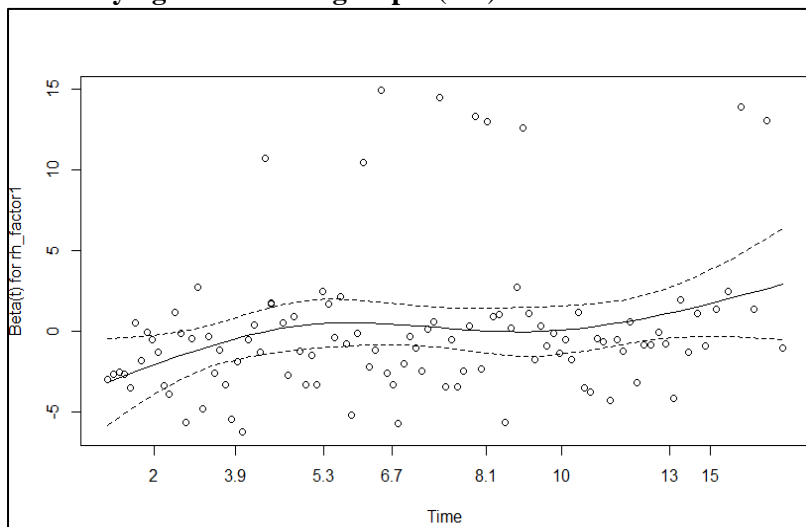
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 5.3	5.3 – 10.0	> 10.0
RH	1.00 (0.33, 3.08), 1.0	1.09 (0.22, 5.31), 0.9	1.08 (0.12, 9.74), 0.9
No RH	0.71 (0.37, 1.36), 0.3	1.38 (0.58, 3.24), 0.5	1.65 (0.54, 5.00), 0.4
Controlled BP	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The DN progression risk did not differ in those with RH or no RH, compared with those who had controlled BP during the follow-up.

**Fig. 6C. In the Model 3 (adjusted for age, sex, HBA<sub>1c</sub>, waist, triglycerides, smoking, previous CHD and stroke) time-varying effect of RH group 1 (RH)**



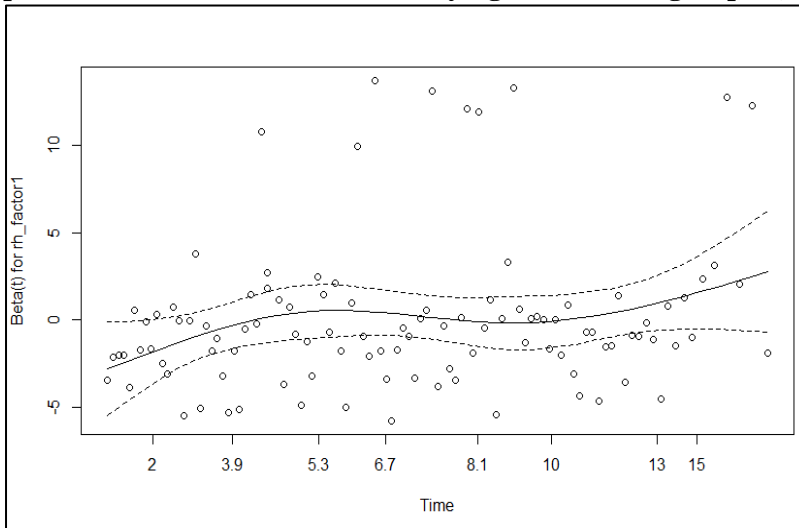
By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 5.5	5.5 – 10.0	> 10.0
RH	0.19 (0.02, 1.47), 0.1	2.49 (0.78, 7.91), 0.1	0.89 (0.18, 4.38), 0.9
No RH	0.67 (0.34, 1.32), 0.2	1.71(0.70, 4.17), 0.2	0.98 (0.41, 2.37), 1.0
Controlled BP	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The DN progression risk did not differ in those with RH or no RH, compared with those who had controlled BP during the follow-up.

**Fig. 6D. In the Model 4 (adjusted for age, sex, HBA<sub>1c</sub>, waist, triglycerides, smoking, nephropathy status, previous CHD and stroke) time-varying effect of RH group 1 (RH)**



By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

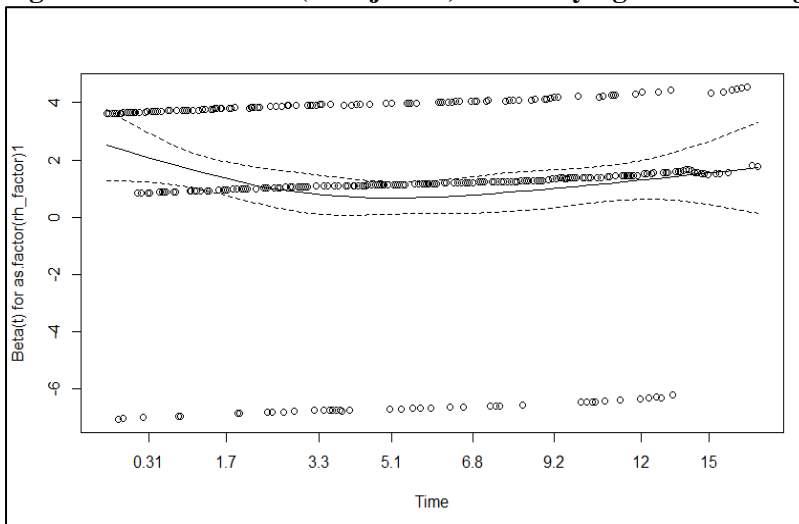
Follow-up (years)	< 5.5	5.5 – 10.0	> 10.0
RH	0.19 (0.02, 1.52), 0.1	2.54 (0.80, 8.10), 0.1	0.91 (0.18, 4.46), 0.9
No RH	0.66 (0.34, 1.32), 0.2	1.71 (0.70, 4.16), 0.2	0.98 (0.40, 2.36), 1.0
Controlled BP	Reference	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The DN progression risk did not differ in those with RH or no RH, compared with those who had controlled BP during the follow-up.

## 7. The Risk of DN progression in all individuals with the BP threshold of < 130/80 mmHg (Suppl. Table 7.)

**Fig. 7A. In the Model 1 (unadjusted) time-varying effect of RH group 1 (RH)**



By splitting the follow-up, the proportional hazard assumption was fulfilled in each time-interval.

Follow-up (years)	< 5.1	≥ 5.1
RH	3.44 (2.09, 5.65), <0.0001	2.91 (1.73, 4.89), <0.0001
No RH	0.75 (0.46, 1.24), 0.3	1.11 (0.69, 1.77), 0.7
Controlled BP	Reference	Reference

Data are HR (95% CI) and p-values (Controlled BP reference group).

The risk of DN progression was higher in individuals with RH during the both time periods, while the risk did not differ in those with no RH compared with those who had controlled BP.