Resting heart rate is associated with renal disease outcomes in patients with vascular disease: results of the ONTARGET and TRANSCEND studies

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Running title: Heart rate and renal outcomes

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Abstract

Background. Resting heart rate (RHR) is associated with cardiovascular disease outcomes in high-risk patients. It is not known whether RHR is predictive of renal outcomes such as albuminuria, end-stage renal disease (ESRD) or doubling of creatinine. We evaluated whether RHR could predict renal endpoints in patients at a
Methods. We analysed data from 28,757 patients in the ONTARGET and TRANSCEND trials. RHR and SBP were available for a mean of 4.9 ± 0.4 visits (range 3–5) within the first 2 years of the studies. Albuminuria was determined at baseline, at 2 years and at study end.

Results. Mean RHR was predictive of incident microalbuminuria [hazard ratio (HR) for RHR ≥80 vs. <60 beats/min 1.49, 95% confidence interval (CI) 1.29–1.71, P < 0.0001], incident macroalbuminuria (HR 1.84, 95% CI 1.39–2.42, P < 0.0001), doubling of creatinine (HR 1.47, 95% CI 1.00–2.17, P = 0.050) and ESRD (HR 1.78, 95% CI 1.00–3.16, P = 0.050), and the combined renal endpoint (HR 1.51, 95% CI 1.32–1.74, P < 0.0001). Associations were robust at SBPs from <120 to ≥150 mmHg, with the lowest risk at a SBP of 130–140 mmHg.

Conclusion. RHR is a potent predictor of these renal outcomes, as well as their combination, in patients with cardiovascular disease. RHR at all SBP levels should be considered as a possible renal disease risk predictor and should be investigated as a treatment target with RHR-reducing agents.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00153101.

Keywords: cardiovascular prevention, heart rate, high cardiovascular disease risk, hypertension, renal function.

Introduction

Elevated blood pressure and diabetes mellitus are associated with worse cardiovascular and renal disease outcomes including proteinuria [1, 2], which in turn is predictive of deterioration of renal function [3, 4]. Proteinuria also represents an early marker for cardiovascular disease outcomes in the general population [5] and
in high-risk patients [6–8]. High blood pressure and blood pressure variability are associated with cardiovascular death [9] and stroke [9, 10]. In addition to blood pressure and its variability [9, 10], high resting heart rate (RHR) has been associated with cardiovascular disease outcomes in patients with hypertension [11], myocardial infarction [12] and heart failure [13]. Data are not available for renal disease outcomes. Of interest, the prevalence of microalbuminuria in hypertensive individuals is correlated cross-sectionally with RHR in sinus rhythm [14] or atrial fibrillation [15].

Patients in the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) were randomly assigned to single renin–angiotensin system (RAS) blockade with telmisartan or ramipril or to double RAS blockade with the combination thereof. In the Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND), patients were randomly allocated to telmisartan or placebo. Similar major cardiovascular disease outcomes [composite of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure (time to first event)] were seen in the three treatment arms of ONTARGET. A lower event rate was observed in the telmisartan group of TRANSCEND; however, this finding was not significant [16, 17]. The effect of telmisartan on renal disease outcomes was similar to that of ramipril [18], whereas the combination therapy reduced albuminuria to a greater extent than the monotherapies, but increased major renal disease outcomes [19, 20]. ONTARGET/TRANSCEND are a suitable database to address the question of whether on-treatment heart rate is associated with the occurrence of renal events.
Herein, we tested the hypothesis that average in trial RHR (RHR mean) is related to renal outcomes, the progression of albuminuria and incident renal failure in high risk cardiovascular patients.

Methods

Population

All participants of the ONTARGET and TRANSCEND trials gave written informed consent and the protocols were reviewed and approved by the research ethics committee at each of the participating centres. Participants who provided sufficient urinary samples were eligible for inclusion in the current exploratory post hoc analysis. In total, 25,620 participants from 733 centres in 40 countries were included in ONTARGET. The parallel study TRANSCEND included 5926 patients with the same eligibility criteria as ONTARGET, but who were intolerant to angiotensin-converting enzyme inhibitors. In ONTARGET and TRANSCEND randomized high risk cardiovascular patients of 55 years or older with coronary artery, peripheral vascular or cerebrovascular disease or high risk diabetes with end organ damage. After a recruitment period of 2 years, patients were followed for a median time of 56 months [16, 17]. For the present analysis, we combined the data from patients in both studies with complete information on serum creatinine, urinary albumin/creatinine ratio, RHR, blood pressure and important baseline characteristics. The structure of the analysis groups and treatment assignment are shown in Fig. 1.

Biochemical analyses

Serum creatinine level was measured locally at the study sites before the run-in phase, as well as after 6 weeks, 2 years and at the final visit. Urinary samples were
collected in a subset of patients at the same time points (except at 6 weeks). Urinary albumin and creatinine levels were measured centrally using a turbidimetric method (Unicel DxC600 Synchron Systems, Beckman Coulter, Brea, CA, USA) and a specific Jaffe method (Unicel DxC600 Synchron Systems). Microalbuminuria was defined as a urinary albumin/creatinine ratio of between $30 \leq$ and $<300$ mg albumin/g creatinine, and macroalbuminuria as $\geq300$ mg albumin/g creatinine. Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease formula [21].

**Data analyses**

The primary objective of this analysis was to evaluate the role of RHR in renal outcomes, such as end-stage renal disease (ESRD; defined as initiation of dialysis, need for renal transplantation or eGFR $<15$ mL/min/1.73 m$^2$), doubling of serum creatinine concentration, new microalbuminuria or macroalbuminuria and the combined endpoint of ESRD, doubling of creatinine and new albuminuria. At each visit (at 6 weeks, 6 months and then every 6 months), RHR and systolic blood pressure (SBP) were measured in the sitting position after resting for 3 min using an automated validated device (Omron model HEM 757, Omron Corporation, Kyoto, Japan). In-trial RHR and SBP from all visits during the first 2 years of the studies were used to calculate RHR-mean and the average SBP (SBP-mean) as well the respective coefficients of variation. Complete data from at least three visits (mean 4.9 + 0.4, range 3–5) were required for inclusion in the analysis (averaged from all visits). Multiple measurements were used to calculate the intra-subject mean and variability of RHR and SBP. In-trial RHR-mean was related to renal disease outcomes during the subsequent study period (i.e. from 2 years). Of note, new
albuminuria and the majority of other renal outcomes could be detected before 2 years, because of the schedule of albuminuria and serum creatinine measurements.

Statistical analysis

Patients were divided into subgroups according to common cut-off levels of RHR-mean [<60, 60 to <65, 65 to <70, 70 to <75, 75 to <80 and ≥80 beats/min (bpm)], allowing statistical evaluations for the cohort with adequate group sizes. Baseline characteristics were presented by group separations, continuous data as means and standard deviations, and categorical data as percentages. RHR-mean groups were tested for differences using ANOVA for continuous data and the chi-squared test for categorical data. Event rates and Kaplan–Meier curves of renal disease outcomes were presented by RHR-mean categories, and tested for differences using Cox regression. In addition, we developed a multivariate model that included RHR-mean categories and all potential predictors of renal disease outcomes including age, body mass index, eGFR, sex, ethnicity, physical activity, education, smoking, alcohol consumption, concomitant diagnoses of hypertension, diabetes, atrial fibrillation, previous myocardial infarction or stroke, regular medication with aspirin, beta-blockers, diuretics, nitrates, calcium channel blockers, statins or oral hypoglycaemic agents, study, study treatment, adherence to study treatment and non-fatal cardiovascular events during the first 2 years. In a model selection procedure, only factors with a $P$-value of <0.25 were entered into the model and a $P$-value of <0.15 was required to remain in the model. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The association between RHR-mean as a continuous variable and renal disease outcomes was also analysed non-parametrically with restricted cubic splines, allowing for a potentially non-linear
relationship [22]. The likelihood ratio test was used to test for non-linearity, by comparing the model with the linear term alone to the model with the linear and cubic spline terms. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results
A total of 31,546 patients were enrolled in ONTARGET and TRANSCEND. There was no follow-up beyond 2 years for 1349 patients. Of the remaining 30,197 patients, 1259 had no or fewer than three values of RHR and SBP, and significant covariates were missing for 148. Due to the occurrence of an outcome event within the first 2 years, 33 patients had to be excluded from the ESRD analysis and 105 from the doubling of creatinine analysis. As urine samples were only collected in a subset of patients, the number of available patients was further reduced for all albuminuria-related endpoints. Fig. 1 provides an overview of the available number of patients for all endpoints as well as the treatment allocation in ONTARGET and TRANSCEND. RHR and SBP measurements were available from a mean of 4.9 ± 0.4 visits (range 3–5).

Demographic characteristics
Table 1 shows the demographic and clinical characteristics for RHR-mean categories in the most comprehensive dataset, i.e. the group for the analysis of ESRD. Due to the large sample size, most of the characteristics were significantly different between RHR-mean groups, but the clinical importance of this is uncertain. Of note, SBP-mean was relatively stable across the various RHR-mean groups. Diabetes was more common in groups with higher RHR-mean, and there were some
differences in cardiovascular medication (e.g. beta blockers were more common in participants with slower RHR). Regular physical activity and alcohol consumption were associated with a lower RHR-mean, whereas current smoking was related to a higher RHR-mean.

*Rates of renal events according to RHR-mean*

In Fig. 2, Kaplan–Meier curves summarize the development of new microalbuminuria (Fig. 2A), new macroalbuminuria (Fig. 2B) or doubling of serum creatinine (Fig. 2C). Incident microalbuminuria and macroalbuminuria gradually increased across RHR ranges from <60 to ≥80 bpm (P < 0.0001). The incidence of doubling of creatinine was small, but an association with RHR was clearly visible and statistically significant (P < 0.0001, Fig. 2C) with the lowest incidence rates in patients with RHR values of <60 bpm. ESRD was less common, but was also linked to RHR with the highest incidence observed at RHR values ≥80 bpm (P < 0.0001, Fig. 2D). The combined renal endpoint was observed in about 20% of patients with RHR ≥80 bpm and was significantly less common at lower RHR values (P < 0.0001, Fig. 2E). There was a regression from microalbuminuria and macroalbuminuria to normo-albuminuria in some patients. The lowest normalization rate was observed in patients with RHR above 80 bpm, but the relationship was not significant (P = 0.16, Fig. 2F).

Calculated yearly event rates for the renal outcomes and the adjusted HRs are shown in Fig. 3. Predictors of renal disease outcomes, which were identified in a model selection process (P < 0.15) and used for adjustments, are shown in Supplementary Table 1. SBP-mean, eGFR at baseline, diabetes and use of diuretics
were the most common predictors, and were included in the multivariate models for all endpoints.

The group with the lowest risk, i.e. RHR <60 bpm, was used as the referent (HR = 1). RHR-mean in the highest group (≥80 bpm) compared to the reference group was associated with increases in new microalbuminuria (HR 1.49, 95% CI 1.29–1.71, \( P < 0.0001 \)) and new macroalbuminuria (HR 1.84, 95% CI 1.39–2.42, \( P < 0.0001 \), Fig. 3A and B). The association with RHR-mean was not significant after adjustment for other predictors for doubling of creatinine (\( P = 0.21 \), Fig. 3C) or for ESRD (\( P = 0.20 \), Fig. 3D), although the HR values for the groups with the highest RHR indicated nominally increased risks (doubling of creatinine: HR 1.47, 95% CI 1.00–2.17, \( P = 0.050 \); ESRD: HR 1.78, 1.00–3.16, \( P = 0.050 \)). For the combined renal endpoints, a significant association was established (HR 1.51, 95% CI 1.32–1.74, \( P < 0.0001 \), Fig. 3E). There was no significant association between normalization to normoalbuminuria and RHR after adjustment (\( P = 0.66 \), Fig. 3F). The adjusted HRs showed that the threshold for development of new microalbuminuria (Fig. 3A) and new macroalbuminuria (Fig. 3B), as well as for the combined renal endpoint (Fig. 3E), was approximately 65–70 bpm. The event rates for ESRD were too small in this patient group with no particular risk of renal failure and, consequently, the power was not high enough to establish any significant association.

**Relationship between renal outcomes and RHR-mean as a continuous variable**

A non-parametric analysis using RHR-mean as a continuous variable revealed that the relationship between RHR-mean and renal disease outcomes was linear; the test for non-linearity could not be rejected (\( P > 0.5 \) for all endpoints) but a linear
relationship could be established \([P < 0.0001\) for all outcomes, except normalization to normoalbuminuria \([P = 0.0083\)\]. The HR values (with 95\% CIs) as a linear function of RHR-mean are shown in Fig. 4. Using as the reference RHR-mean of 60 bpm, formally believed to represent bradycardia, it can be seen that patients with values below 60 bpm have a reduced risk whereas those with values above 60 bpm have an increased risk. The relationship was reversed for normalization to normoalbuminuria. This supplementary analysis was not adjusted for other predictors.

**The effect of the interaction between RHR-mean and SBP-mean on renal outcomes**

In order to test whether there is an interaction between RHR-mean and SBP-mean, the respective interaction term was added to the multivariate models. The respective \(P\)-values were high (always >0.7) for all outcomes, indicating that RHR and SBP levels have additive effects. Fig. 5 shows the HRs and \(P\)-values for combinations of SBP-mean from \(<120\) to \(\geq150\) mmHg and RHR-mean from \(<60\) to \(\geq80\) bpm for new microalbuminuria and macroalbuminuria (with SBP 130–140 mmHg and RHR <60 bpm as references).

Incident micro- and macro-albuminuria (Figure 5A, 5B) were related to RHR at all SBP levels. SBP between 130–<140 mmHg appeared to be the nadir of the risk relationship of SBP (Figure 5B). The combined effects of RHR and SBP are summarized in the Table 2 supplement. On all endpoints there was a risk increase with RHR above 60 bpm independent of SBP levels and the nadir of mean SBP relationship was observed at SBP levels of 130–<140 mmHg. The strongest association was seen with the combined renal endpoint (ESRD, doubling of creatinine and new albuminuria). For example, patients with RHR \(\geq80\) bpm and SBP
≥150 mmHg have approximately a 3.5-fold increased risk compared to patients with RHR <60 bpm and SBP between 130 and 140 mmHg (HR 3.48, 95% CI 2.84–4.26).

Discussion

In this analysis in a high-risk population of contemporary treatment including RAS blockade we demonstrated that high RHR is predictive of renal outcomes defined as incident microalbuminuria, macroalbuminuria, doubling of creatinine or development of ESRD. A high RHR was associated with poor renal outcomes and the effects of HRH and elevated SBP were additive and remained robust after adjustment for comorbidities, RHR-modifying drugs at baseline and other classical cardiovascular disease risk factors.

Previous studies have focused on the effect of RHR on cardiovascular disease outcomes in patients with hypertension [11], ischaemic heart disease [12] or heart failure [13]. In patients with diabetes, elevated RHRs are associated with microvascular disease, (i.e. retinopathy or macroalbuminuria [23]), as well as with cardiovascular mortality and low eGFR in diabetic patients with pre-existing cardiovascular disease [24]. In patients without known cardiovascular disease there were associations between RHR and both cardiovascular and all-cause mortality [24], but not incident ischaemic heart disease [25]. In the ONTARGET population, there were associations between RHR and cardiovascular death, stroke and heart failure, but no significant correlation with myocardial infarction incidence after adjustment [26]. Herein, we extended our previous findings to a population with cardiovascular disease, or its risk factors, for renal endpoints. Microalbuminuria and macroalbuminuria were associated with high resting RHR, and the effects of high or
uncontrolled SBP were additive. The renal endpoints, as well as early renal damage such as microalbuminuria [5–8], were associated with elevated cardiovascular disease risk. Thus, the interactions between RHR and microalbuminuria and cardiovascular disease risk could act as a vicious circle to increase cardiovascular complications in patients with pre-existing cardiovascular disease [26] including heart failure [27]. It is interesting that all stages of renal damage from microalbuminuria to incident ESRD were associated with RHR. Moreover, the association between RHR and renal disease appears to be present in patients with hypertension [14], hypertension and atrial fibrillation [15], diabetes [24], known vascular disease [26] and heart failure [27]. Thus, RHR might influence renal pathophysiology throughout the cardiovascular and renovascular continuum.

Several mechanisms may underlie these effects such as progression of atherosclerosis, and thus nephrosclerosis, due to changes in endothelial oxidative stress [28], which is sensitive to RHR reduction [28, 29]. Furthermore, RHR is associated with increased aortic stiffness [30], which in turn is linked to cardiovascular disease outcomes such as stroke [31], coronary events [32] and heart failure [33]. High RHR is associated experimentally with endothelial dysfunction and impaired corpora cavernosa relaxation [34] and clinically with erectile dysfunction [35]. An increase in RHR appears to be associated with microvascular disease in general [23] and also with complications of renal failure [36, 37]. Furthermore, increased RHR is associated with psychosocial stress which is sensitive to RHR reduction and increased stroke size in mice [38]; in humans it is related to an accelerated decline in cognitive function after stroke [39]. In the kidney, myogenic autoregulation, i.e. vasoconstriction of the afferent arteriole in response to high
perfusion pressures to prevent hyperperfusion [40], is impaired in hypertension [41], ageing [42] and diabetes [43], making the kidney more prone to pulsatile stress [44]. To date, direct experimental data on heart rate or studies providing information on the relevance of RHR in humans have been lacking. However, it has been reported that increased RHR could also be a sign of increased sympathetic activation [45], and increased sympathetic activation has been observed in patients with renal failure [46].

**Study limitations**

Some limitations of the present study should be acknowledged. This was a *post hoc* exploratory analysis, therefore the allocation of individuals was not subject to randomization. Nevertheless, the large study population ensures statistical power to allow reliable correction for confounders. Furthermore, the measurement of in-trial RHR-mean is reliable, because it is an average of five measurements during the course of the trials. Using in-trial RHR-mean has provided more accurate results than investigating only associations with RHR at baseline [26].

**Conclusions**

The results of this *post hoc* analysis of a large study in a well-treated population with chronic stable cardiovascular disease show that RHR is associated with renal disease risk, and suggest that a reduction in RHR might be protective for kidney function. If this suggestion is proven to be correct, HRH could qualify not only as a risk marker but also as a risk factor, as previously shown in patients with chronic heart failure [13, 47]. Future studies of RHR reduction may provide evidence for a

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new therapeutic approach in patients with a high cardiovascular/renovascular disease risk, to halt (or reduce?) the progression of kidney disease.

Disclosures

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Legends

Fig. 1 Study flow of ONTARGET and TRANSCEND for the analysis of resting heart rate (RHR) and renal outcomes. Patients for whom there was no follow-up after 2 years or for whom less than three values for RHR and SBP were available were excluded from the analysis, resulting in a final study population of 28,790 patients.

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Fig. 2 Kaplan–Meier cumulative event curves for new microalbuminuria (A), new macroalbuminuria (B), doubling of creatinine (C), end-stage renal disease (D), combined renal endpoint (E) and normalization to normoalbuminuria (F) according to mean resting heart rate [(RHR) categories <60, 60 to <65, 65 to <70, 70 to <75, 75 to <80 and ≥80 beats/min (bpm)].

Fig. 3 Associations between heart rate and new microalbuminuria (A), new macroalbuminuria (B), doubling of creatinine (C), end-stage renal disease (D), combined renal endpoint (E) and normalization to normoalbuminuria (F), according to heart rate categories.

Fig. 4 Associations between heart rate [in beats/min (bpm)] and hazard ratio of new microalbuminuria (A), new macroalbuminuria (B), doubling of creatinine (C), end-stage renal disease (ESRD) (D), combined renal endpoint (E) and normalization to normoalbuminuria (F). Histograms of the resting heart rate distributions are shown below each graph.

Fig. 5 Interaction between heart rate [in beats/min (bpm)] and systolic blood pressure (in mmHg) on new microalbuminuria (A) and new macroalbuminuria (B).

Table 1 Demographic characteristics according to mean resting heart rate (RHR-mean) for all patients in the renal endpoint analysis.

SBP, systolic blood pressure; CV, cumulative variability (i.e. standard deviation/mean); MI, myocardial infarction; ASA, aspirin; eGFR, estimated glomerular filtration rate.

Supplementary Table 1 Effect of categories of mean resting heart rate (RHR) on new microalbuminuria, new macroalbuminuria, doubling of creatinine, end-stage renal disease (ESRD), combined renal endpoint and normalization to normoalbuminuria, adjusted for other predictors (results of multivariate Cox regression model selection).

For significant predictors \(P < 0.05\), hazard ratios (HRs) are given with 95% confidence intervals (CIs) (in the case of age and eGFR deciles, the most extreme comparisons are displayed). BMI, body mass index; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; ECG, electrocardiogram; CV, cardiovascular; AF, atrial fibrillation; CCB, calcium channel blocker.

Supplementary Table 2 Hazard ratios and 95% confidence intervals for the mean resting heart rate (RHR-mean) and mean systolic blood pressure (SBP-mean) categories. ESRD, end-stage renal disease.
<table>
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<th>5637</th>
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<td>Mean (SD)</td>
<td>55.5 (3.5)</td>
<td>62.5 (1.4)</td>
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<td>&lt;.0001</td>
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<td>Current</td>
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<td>%</td>
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<td>Hypertension</td>
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<td>67.5</td>
<td>69.8</td>
<td>72.7</td>
<td>73.5</td>
<td>74.8</td>
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<td>39.9</td>
<td>47.4</td>
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<td>46.4</td>
<td>40.0</td>
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<td>14.8</td>
<td>17.4</td>
<td>19.8</td>
<td>23.5</td>
<td>25.6</td>
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<td>2.1</td>
<td>2.8</td>
<td>3.3</td>
<td>4.4</td>
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<td>67.4</td>
<td>66.2</td>
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<td>40.9</td>
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<tr>
<td>Calcium channel blockers</td>
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<td>23.6</td>
<td>25.6</td>
<td>24.3</td>
<td>26.6</td>
<td>26.2</td>
<td>26.1</td>
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<td>26.8</td>
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<td>%</td>
<td>13.7</td>
<td>18.6</td>
<td>23.0</td>
<td>27.2</td>
<td>32.5</td>
<td>38.1</td>
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<tr>
<td>Statins</td>
<td>%</td>
<td>74.5</td>
<td>67.6</td>
<td>62.8</td>
<td>56.0</td>
<td>51.1</td>
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<td>ONTARGET</td>
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<td>%</td>
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<td>9.5</td>
<td>9.5</td>
<td>10.3</td>
<td>10.2</td>
<td>8.5</td>
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<tr>
<td>Ramipril</td>
<td>%</td>
<td>27.9</td>
<td>28.1</td>
<td>27.0</td>
<td>27.1</td>
<td>26.1</td>
<td>27.5</td>
</tr>
<tr>
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<td>%</td>
<td>36.3</td>
<td>36.5</td>
<td>36.8</td>
<td>37.0</td>
<td>37.8</td>
<td>37.0</td>
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<tr>
<td>Telmisartan/Ramipril</td>
<td>%</td>
<td>27.5</td>
<td>27.0</td>
<td>26.7</td>
<td>25.8</td>
<td>25.9</td>
<td>27.0</td>
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<tr>
<td>&lt;50 %</td>
<td>%</td>
<td>5.2</td>
<td>5.4</td>
<td>5.0</td>
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<td>50–100%</td>
<td>%</td>
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<td>8.0</td>
<td>9.0</td>
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<td>9.4</td>
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<tr>
<td>100%</td>
<td>%</td>
<td>87.3</td>
<td>86.6</td>
<td>86.0</td>
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<td>84.9</td>
<td>83.5</td>
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<tr>
<td>Non-fatal CV event</td>
<td>%</td>
<td>3.6</td>
<td>4.3</td>
<td>4.4</td>
<td>5.1</td>
<td>5.4</td>
<td>6.3</td>
</tr>
</tbody>
</table>
31,546 patients randomized

No follow-up beyond 2 years (n=1361)

30,197 patients left

Less than 3 values for heart rate (n=1259)

28,938 patients left

ESRD in 1st 2 years (n=33)
Doubling creatinine in 1st 2 years (n=105)
No urinary albumin at baseline (n=2568)
Micro-albuminuria at baseline (n=4043)
Macro-albuminuria at baseline (n=844)

Missing values in important covariates (n=148)

Patients analyzed
ESRD: 28,757
Doubling creatinine: 28,685
New micro-albuminuria: 22,338
New macro-albuminuria: 25,519
ESRD / doubl. Crea / new album: 22,253

Treatment Allocation (for ESRD analysis)

- Ramipril (R) (n=7849)
- Telmisartan (T) (n=7829)
- R + T (n=7852)
- T (n=2708)
- Placebo (n=2719)

ONTARGET

TRANSCEND

Figure 1

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Figure 4

A: New micro-albuminuria

B: New macro-albuminuria

C: Doubling of serum creatinine

D: ESRD

E: Combined renal endpoint

F: Normalization to normo-albuminuria

Resting heart rate (bpm)
A  New Microalbuminuria

B  New Macroalbuminuria

Figure 5