Supplemental Materials

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# *Sites and investigators in the CANVAS trial*

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## **Supplemental Table 1:** Effect of prognostic enrichment with TNFR-1 or TNFR-2 on sample size, number of screenings and costs for a future trial in the normoalbuminuria population.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Percent of Patients Screened from Trial | Event Rate Among Biomarker-Positive Patients | Sample Size | NNS | Total Screened | Total Costs for Screening and Patients in Trial  (million dollars) | Percent Reduction in Total Cost |
| **TNFR-1** |  |  |  |  |  |  |
| 0% | 0.05 | 3,692 | 1 | 3,692 | 184.6 | 0% |
| 25% | 0.06 | 3,200 | 1.3 | 4,267 | 164.3 | 11% |
| 50% | 0.07 | 2,769 | 2 | 5,538 | 144.0 | 22% |
| 75% | 0.09 | 2,280 | 4 | 9,121 | 123.1 | 33.30% |
| 95% | 0.12 | 1,618 | 20 | 32,367 | 113.3 | 38.60% |
| **TNFR-2** |  |  |  |  |  |  |
| 0% | 0.05 | 3,692 | 1 | 3,692 | 184.6 | 0% |
| 25% | 0.06 | 3,286 | 1.3 | 4,381 | 168.7 | 8.60% |
| 50% | 0.07 | 2,758 | 2 | 5,516 | 143.4 | 22.30% |
| 75% | 0.09 | 2,046 | 4 | 8,183 | 110.5 | 40.20% |
| 95% | 0.18 | 1,020 | 20 | 20,402 | 71.4 | 61.30% |

TNFR-1, tumor necrosis factor receptor-1; TNFR-2, tumor necrosis factor receptor-2; NNS, number needed to screen.

## **Supplemental Table 2:** Treatment effect of canagliflozin in patients with normoalbuminuria and TNFR-1 or TNFR-2 biomarker level above or below the 4th quartile compared to micro- or macroalbuminuria. P for interaction was calculated across the three subgroups: micro- or macroalbuminuria, TNFR-1/2 <4th quartile and normoalbuminuria and TNFR-1/2 ≥4th quartile and normoalbuminuria.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Number of patients** | **Number of events** | **Hazard ratio (95% CI)** | **P value** | **P for interaction** |
| **40% decrease in eGFR, kidney failure, or kidney death** |  |  |  |  |  |
| Micro- or macroalbuminuria | 979 | 86 | 0.64 (0.42 to 0.98) | 0.040 |  |
| TNFR-1 < 4th quartile and normoalbuminuria | 1,915 | 31 | 0.41 (0.20 to 0.82) | 0.012 | 0.546 |
| TNFR-1 ≥ 4th quartile and normoalbuminuria | 638 | 20 | 0.52 (0.22 to 1.27) | 0.152 |  |
| TNFR-2 < 4th quartile and normoalbuminuria | 1,915 | 26 | 0.35 (0.16 to 0.76) | 0.008 | 0.391 |
| TNFR-2 ≥ 4th quartile and normoalbuminuria | 638 | 25 | 0.61 (0.28 to 1.35) | 0.222 |  |
| **Hospitalization for heart failure** |  |  |  |  |  |
| Micro- or macroalbuminuria | 979 | 61 | 0.95 (0.56 to 1.62) | 0.858 |  |
| TNFR-1 < 4th quartile and normoalbuminuria | 1,915 | 49 | 0.72 (0.41 to 1.27) | 0.259 | 0.764 |
| TNFR-1 ≥ 4th quartile and normoalbuminuria | 638 | 19 | 0.75 (0.29 to 1.90) | 0.541 |  |
| TNFR-2 < 4th quartile and normoalbuminuria | 1,915 | 42 | 0.70 (0.38 to 1.30) | 0.259 | 0.758 |
| TNFR-2 ≥ 4th quartile and normoalbuminuria | 638 | 26 | 0.79 (0.36 to 1.75) | 0.563 |  |

eGFR, estimated glomerular filtration rate; TNFR-1, tumor necrosis factor receptor-1; TNFR-2: tumor necrosis factor receptor-2.

## **Supplemental Figure 1:** Histograms of TNFR-1, TNFR-2, KIM-1, UACR and eGFR in patients with normoalbuminuria. TNFR-1, UACR and eGFR are not truncated, TNFR-2 is truncated at 30,000 pg/ml and KIM-1 is truncated at 800 pg/ml.Y:\FAR\Medewerkers\AIO\Simke Waijer\2. Research\7. CANVAS\Data Analysis\Figures\histogram.emf

eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; TNFR-1, tumor necrosis factor receptor-1; TNFR-2, tumor necrosis factor receptor-2; KIM-1, kidney injury molecule-1.

## **Supplemental Figure 2:** Hazard ratios per quartile of TNFR-1 (panel a) and TNFR-2 (panel b) for the kidney outcome in patients with normoalbuminuria. The number above each circle represents the number of outcomes and the number of patients in each quartile. On the x-axis is the median biomarker value of each quartile.

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Models are adjusted for treatment allocation, age, sex, race, BMI, history of cardiovascular disease, systolic blood pressure, diastolic blood pressure, LDL cholesterol, HbA1c, UACR, and eGFR.

eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; TNFR-1, tumor necrosis factor receptor-1; TNFR-2, tumor necrosis factor receptor-2; UACR urinary albumin:creatinine ratio

## **Supplemental Figure 3:** Kaplan-Meier curve for the kidney outcome in patients with normoalbuminuria below or above the 4th quartile for TNFR-1 and TNFR-2.

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TNFR-1, tumor necrosis factor receptor-1; TNFR-2, tumor necrosis factor receptor-2.

## **Supplemental Figure 4:** Associations between TNFR-1 and TNFR-2 in patients with normoalbuminuria. TNFR-1 is not truncated and TNFR-2 is truncated at 30.000

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TNFR-1, tumor necrosis factor receptor-1; TNFR-2, tumor necrosis factor receptor-2.

## **Supplemental Figure 5:** Effect of prognostic enrichment with UACR or KIM-1 on sample size, number of screenings, and costs for a future trial in the normoalbuminuria population.

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UACR, urinary albumin: creatinine ratio; KIM-1, kidney injury molecule-1.