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GFR STUDY ORGANIZATION

Members of the Study Organization were as follows (all in Italy unless otherwise noted): Principal investigator — G. Remuzzi (Bergamo); Study coordinator — P. Ruggenenti (Bergamo); Coordinating center — Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Villa Camozzi, Ranica (Bergamo); Participating centers — G. Nastasi, A. Ongaro, F. Querci, A. Anabaya (Alzano Lombardo); R. Trevisan, A.R. Dodesini, G. Lepore, I. Nosari, C. A. Aros Espinoza, A. Fassi (Bergamo); A. Belviso, A. Parvanova, I.P. Iliev (Ponte San Pietro, Villa d'Almè); C. Chiurchiu, F. Arnoldi, L. Mosconi, M. Monducci (Ranica); A. Bossi, A. Parvanova, I.P. Iliev, M. Facchetti, V. Brusegan (Romano di Lombardia, Treviglio); F. Inversi, V. Bertone, R. Mangili, S. Bruno (Seriate); J: Zaletel, Ljubljana, Slovenia; Monitoring and Drug Distribution (Mario Negri Institute) — N. Rubis, G. Gherardi, W. Calini, O. Diadei, M. Lesti, G. Noris, K. Pagani, D. Rossoni, D. Villa (Ranica); Carriers (Mario Negri Institute) — G. Gaspari, S. Gelmi, G. Gervasoni (Ranica); Database and Data Validation (Mario Negri Institute) — A. Remuzzi, B. Ene-Iordache, V. Gambara (Ranica); Data Analysis (Mario Negri Institute) — A. Perna, N. Motterlini, M. Ganeva, J. Zamora, E. Porrini (Ranica); Laboratory Measurements (Mario Negri Institute) — F. Gaspari, F. Carrara, E. Centemeri, S. Ferrari, M. Pellegrino, N. Stucchi, C. Petrò, C. Locatelli, A. Cannata, E. Savoldelli (Ranica); Regulatory Affairs (Mario Negri Institute) — P. Boccardo (Ranica).

Subjects and Study Design

This cohort study included subjects from two randomized, double-blind, placebo-controlled clinical trials, BENEDICT-B (10) and DEMAND (11) both designed to evaluate the effect of ACE inhibitor therapy on onset and progression of nephropathy in subjects with type 2 diabetes. The two study populations were considered together since they were selected, monitored and treated according to similar pre-defined guidelines. Major similarities included:

1. Selection criteria:
    i. type 2 diabetes (WHO criteria),
    ii. arterial hypertension (systolic >130 mmHg and/or diastolic BP >85 mmHg, or concomitant antihypertensive therapy)
    iii. normo- or micro-albuminuria [urinary albumin excretion (UAE) in at least two of three consecutive overnight urine collections <20μg/min or ≥20 and <200μg/min, respectively],
    iv. serum creatinine <1.5mg/dl and HbA_{1C} <11%,
2. Enrollment period (from February 10, 1998 to June 22, 2005) and follow-up duration (up to progression to an end-point or completion of pre-planned treatment period by the last randomized patient)
3. Treatment targets (systolic/diastolic BP<120/80 mmHg and HbA_{1C}<7%)
4. Clinical outcomes, including six monthly measurements of GFR and albuminuria by gold-standard procedures
5. Approaches used to assess the main outcomes:
    i. GFR decline by linear regression analysis
    ii. progression to persistent microalbuminuria or macroalbuminuria defined as at least two out of three consecutive overnight UAE >20 μg/min or >200 μg/min, respectively, confirmed in two consecutive visits two months apart
6. Efficacy and safety variables recorded according to the same timetable by case record forms and databases with a similar frame
7. Study treatments including an ACE inhibitor alone or in combination with a calcium channel blocker (CCB), or placebo.

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Both studies were coordinated and monitored by the Mario Negri Institute for Pharmacological Research and were run by the same network of investigators. They conformed to the Declaration of Helsinki guidelines and were approved by the Ethical Committees of participating Centers. All patients provided written consent. Data were handled in respect of anonymity and confidentiality.

Measurements, Estimates and Definitions

BLOOD PRESSURE - The blood pressure was measured at the brachial artery of the non-dominant arm in the morning, before study drug administration and after five minutes rest in the sitting position, by using a validated oscillometric device (Omron 705IT®) and a standard cuff. The mean of 3 measurements taken 2 min apart was recorded for statistical analyses.

GLOMERULAR FILTRATION RATE – In all patients the GFR was centrally measured at the Coordinating Center with the iohexol (Omnipaque 300, GE Healthcare, Milan, Italy) plasma clearance technique (13) at baseline and every six months throughout the whole observation period. Iohexol plasma levels were measured by high-performance-liquid chromatography (HPLC) and the clearance was calculated according to a one-compartment model with Bröchner-Mortensen adjustment (15) and normalized to 1.73m^2 of body surface area.

GLUCOSE DISPOSAL RATE - Glucose disposal rate (GDR) was assessed at inclusion and at 1 year in a subgroup by the hyperinsulinemic euglycemic clamp (16). GDR was calculated as the mean of the glucose infusion rate per kilogram of body weight required to maintain steady-state euglycemia during the last 30 minutes of the clamp.

LABORATORY EVALUATIONS - Urinary albumin was measured by nephelometry (Beckman Array System) in three timed overnight urine samples collected in bottles with a preservative. HbA_{1c} was centrally measured by ion-exchange HPLC (normal range: 3.53 to 5.21%). Other parameters were evaluated with a Beckman Synchron CX5 instrument and a Coulter MaxM (Beckman Coulter).

Definitions

HYPERFILTRATION - Patients who had a measured GFR at inclusion exceeding the upper limit of the normal range (120 ml/min/1.73m^2) were *a priori* categorized as “hyperfiltering” and those with lower GFRs as “non-hyperfiltering”. Since the reproducibility range of GFR measurement by the iohexol plasma clearance technique is ±6.28% ((13,15)), a pre-defined cut-off 10% GFR reduction largely exceeding the reproducibility range of the measurement was expected to univocally identify patients with true GFR reductions from those with random data fluctuations related to the variability of the method. Thus, among patients who were hyperfiltering at baseline, those with a GFR reduction >10% at month six were considered as patients with ameliorated hyperfiltration. Those with smaller reductions were categorized as “persistently hyperfiltering”.

END POINTS - Pre-defined end points were: a.- the rate of GFR decline over time (GFR slope) defined as the regression line between repeated GFR measurements and time (17,18), and b.- time to onset of persistent micro- or macro albuminuria defined as UAE ≥20 and <200 μg/min or ≥200 μg/min, respectively (10,11).

Statistical Analysis

Analyses were performed at the Laboratory of Biostatistics of the Clinical Research Center by SPSS 14.0.1 (Chicago, IL), STATA 11.0 and SAS 9.1 (Institute Inc, Cary, North Carolina). Data were

expressed as mean ± standard deviation (SD), median and interquartile range (IQR) or number and percent as appropriate. P<0.05 indicated statistical significance.

COMPARATIVE AND CORRELATION ANALYSES - Baseline and follow-up characteristics were compared by paired or unpaired t-test, Wilcoxon rank sum test, chi-square or Fisher's exact test. Correlations between variables were evaluated using Pearson r or Spearman rho correlation coefficients.

GFR SLOPE ANALYSES – These analyses were pre-planned for a subgroup of patients from the BENEDICT Study (19) and for all patients from DEMAND (11) who had at least 3 follow-up GFR measurements in addition to baseline GFR. GFR changes over time were initially evaluated by a single slope linear model (14). However, on the basis of previous evidence that patients included in randomized trials may have a bi-modal rate of GFR decline (8,17,20) we also *a priori* used a two-phase model in which GFR changes from baseline to month six and GFR slope from month six to study end were assessed separately. To test the possibility that GFR reduction at six months could be affected by GFR at baseline (regression to the mean), GFR changes at six months were *a posteriori* compared between hyperfiltering and non-hyperfiltering patients after adjusting for baseline GFR values by using an analysis of covariance (ANCOVA) (21).

MULTIVARIABLE REGRESSION ANALYSES: The relationships between baseline GFR, or GFR changes from baseline to month six, and subsequent GFR decline were evaluated by two multivariable models considering as outcomes the GFR slopes calculated throughout the whole follow-up period (Model 1) or from month six to study end (Model 2), respectively. To account for possible heterogeneity between studies, we developed a meta-analysis of individual patient continuous outcome data using a random trial effect with patient-level covariates in which the original study and the observation from an individual patient were at the highest and lowest level, respectively (22). The possibility of including treatments as a random instead of a fixed effect was eventually assessed by the likelihood ratio test. Continuous explanatory variables were approximately centered to the mean for every analysis. Baseline GFR was introduced as a covariate in both Models 1 and 2. Then the analyses in Model 2 were repeated by considering GFR changes at six months instead of baseline GFR. The models included covariates *a priori* considered to be potentially associated with the outcomes (age; gender; smoking habit; baseline systolic BP, HbA1C, GFR, and albuminuria; previous inclusion in BENEDICT-B or DEMAND; randomization to ACE inhibitor therapy yes or no, and treatment arms) or found *a posteriori* to be significantly associated (p<0.05) with the outcome at univariable analyses. Systolic was considered instead of diastolic BP to avoid co-linearity. Independent variables that were non-normally distributed were log-transformed before analyses. In additional sensitivity analyses we further evaluated the bi-modal GFR change over time by considering repeated GFR measures as the outcome in a spline function with a knot at six months (23). Finally, we analyzed the slope of GFR in patients with persistent hyperfiltration as compared to those who had their initial hyperfiltration ameliorated at six months considered alone or together with those who were non hyperfiltering since inclusion.

PROGRESSION TO MICRO OR MACRO ALBUMINURIA - In subjects with at least one follow-up measurement of albuminuria, we *a priori* evaluated the association between baseline GFR, or hyperfiltration at inclusion, and the development of micro- or macro- albuminuria by Kaplan-Meier analysis and log-rank test, and by a multivariate proportional hazard model considering time to micro- or-macro- albuminuria as the dependent variable. We included in the model also potential confounders with a proven or expected relationship with the outcome such as age, gender, baseline albuminuria, baseline HbA_{1C} and systolic or diastolic BP, randomization to an ACE inhibitor yes or no, and inclusion in the DEMAND or

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BENEDICT-B trial. The same approach was used in *post-hoc* analyses evaluating progression to micro-or-macro-albuminuria in patients with hyperfiltration at inclusion who were persistently hyperfiltering at six months as compared to patients who had their hyperfiltration at inclusion ameliorated at six months considered alone or in combination with those who were persistently non-hyperfiltering since inclusion. The assumption of proportionality was assessed by the log-minus-log procedure.

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Supplementary Table 1. Baseline characteristics of patients with or without GFR slope data and of patients who were persistently hyperfiltering at month 6 compared to all other patients who were normofiltering or had their hyperfiltration at baseline ameliorated at month 6 (Others).

	With GFR slope	Without GFR slope	Persistent Hyperfiltration	Others
N	449	151	45	502
Demography / Clinical				
Age – yr	60.7 ± 7.6	62.9 ± 8.3*	55.8 ± 6.7	61.6 ± 7.7°
Male sex – no. (%)	306 (68.9)	107 (70.1)	34 (72.3)	350 (69.7)
Body Mass Index †	29.5 ± 4.5	28.8 ± 4.0	30.1 ± 4.9	29.2 ± 4.4
Know duration of diabetes – yr	7 (3-13)	7 (4-15)	7 (4-14)	8 (3-13)
Smoking habit – no. (%)				
Never smoked	203 (45.2)	69 (45.7)	20 (42.5)	225 (44.8)
Former smoker	174 (38.8)	66 (43.7)	19 (40.4)	200 (39.8)
Current smoker	72 (16.0)	16 (10.6)	8 (17.0)	77 (15.3)
Trough blood pressure				
Systolic	149.4 ± 15.1	151.0 ± 9.6	148.6 ± 14.9	149.5 ± 15.1
Diastolic	87.8 ± 9.3	87.7 ± 10.2	88.2 ± 8.0	87.7 ± 9.6
Laboratory				
Glycosilated hemoglobin - % ǂ	6.2 ± 1.6	6.1 ± 1.6	6.6 ± 1.4	6.2 ± 1.6
Glucose – mg/dL	170.7 ± 47.9	170.8 ± 48.0	181.5 ± 47.1	169.5 ± 49.4
Triglycerides - mg/dL ‖	123.0 (88.0-171.5)	121.0 (88.0-168.3)	123.5 (94.0-166.2)	120.0 (87.0-184.0)
Cholesterol - mg/dL **				
Total	197.4 ±35.6	198.8 ±34.7*	194.4 ± 42	198.3 ± 34.8
Low-density lipoprotein	151.6 ± 34.4	157.6 ± 34.8	150.2 ± 37.2	152.3 ± 34.2
High-density lipoprotein	45.7 ± 11.3	45.6 ± 11.3	44.2 ± 14.1	45.6 ± 11.6
Uric acid - mg/dL	5.3 ± 1.2	5.2 ± 1.4	4.8 ± 0.9	5.4 ± 1.3°

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	With GFR	Without GFR	Persistent	Others
Serum creatinine - mg/dL ∫	0.9 ± 0.2	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1°
GFR - mL/min/1.73m^2	101.5 ± 19.4	99.6 ± 20.3	130.3 ± 10.8	98.5 ± 17.9°
Hyperfiltration-no. (%)	67 (14.9)	23 (15.2)		
Albuminuria - µg/min	8.6 (4.0-26.5)	15.3 (4.0-26.6)*	10.5 (5.5-30.1)	9.5 (4.2-29.0)
Microalbuminuria - no. (%)	139 (31.0)	71 (47.0)*	17 (36.2)	169 (33.7)
Randomisation to ACEi-n**. (%)**	329 (73.3)	107 (71.0)	38 (80.9)	365 (72.7)
Antihypertensive drugs - no.				
Baseline	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Follow-up	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)
Antidiabetic Treatments				
Baseline (Diet / Oral /	17.4 / 64.4 /	20.0 / 60.0 / 10.6 /	12.7 / 72.3 / 10.6 / 4.2	18.1 / 63.1 /
Follow-up (Diet / Oral /	20.3 / 48.0 /	39.0 /36.0 / 18.0 /	21.2 / 44.6 / 19.0 / 14.8	23.3 / 47 / 15.

* $p<0.05$ vs. Patients with GFR slope; ° $p<0.05$ vs. Persistently Hyperfiltering. Data are means ± SD or median (IQR).

†: The body mass index is the weight in kilograms divided by the square of the height in meters.

Ŧ Glycosilated haemoglobin was measured by ion-exchange high-performance liquid chromatography (normal range, 3.5 to 5.2 percent). To convert percent HbA1C values to International Federation of Clinical Laboratory Medicine (IFCC) units (mmol/mol), use the formula: (Present HbA1C – 0.956) x 11.145.

∫: To convert values for serum creatinine to micromoles per liter, multiply by 88.4

‖ To convert values for triglycerides to millimoles per liter, multiply by 0.01129

** To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

φ Measured in 219 (178 non-hyperfiltering and 41 hyperfiltering) subjects.

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Supplementary Table 2. Baseline characteristics of patients with persistent or ameliorated hyperfiltration.

	Persistent Hyperfiltration	**Ameliorated Hyperfiltration**
Number of patients	45	37
Demography / Clinical		
Age – yr	55.7 ± 6.8	58.2 ± 7.3
Male sex – no. (%)	32 (71.1)	28 (75.7)
Body Mass Index †	30.05 ± 5.06	30.4 ± 4.3
Know duration of diabetes – yr	6 (4-12)	5 (3-13)
Smoking habit – no. (%)		
Never smoked	19 (42.2)	15 (40.5)
Former smoker	18 (40.0)	15 (40.5)
Current smoker	8 (17.8)	8 (18.9)
Trough blood pressure – mmHg		
Systolic	148.7 ± 15.1	150.8 ± 13.5
Diastolic	88.0 ± 8.0	88.6 ± 7.8
Mean arterial Pressure	108.2 ± 9.4	109.3 ± 8.6
Laboratory		
Glycosilated hemoglobin - % Ŧ	6.6 ± 1.4	6.7 ± 1.8
Glucose – mg/dL	183.4 ± 47.0	200.5 ± 56.6
Triglycerides - mg/dL ‖	140 (102-233)	167 (96 -290)
Cholesterol - mg/dL		
Total	196.6 ± 42.2	204.0 ± 40.0
Low-density lipoprotein	152.0 ± 37.1	161.1 ± 38.8
High-density lipoprotein	44.01 ± 14.1	42.8 ± 12.7
Uric acid - mg/dL	4.9 ± 0.94	4.9 ± 0.97
Serum creatinine - mg/dL ∫	0.78 ± 0.13	0.86 ± 0.14
GFR - mL/min/1.73m^2	130.5 ± 11.0	134.3 ± 12.4
Urinary albumin excretion - µg/min	9.14 (5.4-30)	9.08 (4.6-42.6)
Microalbuminuria - no. (%)	15 (33.3)	13 (35.1)
Glucose Disposal Rate φ - mg/kg/min	5.07 ± 2.86	5.11 ± 2.30
Therapy		
Randomisation to ACEi - no. (%)	36 (80.0)	28 (75.7)
Antihypertensive drugs - no.		
Baseline	2 (1-3)	2 (1-3)
Follow-up	3 (2.5-4)	4 (2-4)
Antidiabetic Treatments (%)		
Baseline (Diet / Oral / Oral+Ins / Ins)	12.7 / 72.3 / 10.6 / 4.2	16.2 / 64.9 / 16.2 /2.7
Follow-up (Diet / Oral / Oral+Ins / Ins)	21.2 / 44.6 / 19.0 / 14.8	16.2 / 51.4 / 18.9 / 13.5

Data are means ± SD or median (IQR). No difference between groups is significant

†: The body mass index is the weight in kilograms divided by the square of the height in meters. Ŧ Glycosilated haemoglobin was measured by ion-exchange high-performance liquid chromatography (normal range, 3.5 to 5.2 percent). To convert percent HbA1C values to International Federation of Clinical Laboratory Medicine (IFCC) units (mmol/mol), use the formula: (Present HbA1C – 0.956) x 11.145.

∫: To convert values for serum creatinine to micromoles per liter, multiply by 88.4

‖ To convert values for triglycerides to millimoles per liter, multiply by 0.01129

** To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

φ Measured in 39 (21 with ameliorated hyperfiltration and 18 with persistent hyperfiltration) subjects.

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Supplementary Table 3. Univariable results of fixed effects meta-analysis with patient-level covariates and random trial effects considering GFR decline from baseline (Model 1) and from month 6 (Model 2) to study end as dependent variables

	GFR Decline from baseline^		**GFR Decline from mo. 6**	
	(Model 1)		*(Model 2)*	
Fixed-effects Parameters	***Coefficient (SE)***	***P***	***Coefficient (SE)***	***p***
Age	- 0.0046 (0.002)	0.004	-0.004 (0.002)	0.01
Male gender	0.029 (0.026)	0.28	0.04 (0.03)	0.172
Smoking habit º	-0.008 (0.025)	0.74	-0.01 (0.03)	0.722
Known duration of Diabetes♦	-0.032 (0.014)	0.021	-0.03 (0.015)	0.07
Body Mass Index♦	-0.042 (0.08)	0.62	-0.03 (0.09)	0.72
Systolic Blood Pressure	-0.002 (0.0008)	0.005	-0.08(0.054)	0.14
HbA1c (%)♦	-0.08 (0.05)	0.10	-0.08 (0.05)	0.14
Serum Triglyceride levels♦	0.015 (0.025)	0.55	0.03 (0.03)	0.26
Serum Uric acid levels	0.009 (0.01)	0.35	0.007 (0.011)	0.56
Urinary albumin excretion♦	-0.022 (0.01)	0.050	-0.023 (0.013)	0.71
GFR	-0.0035 (0.006)	< 0.0001	-0.0002 (0.0007)	< 0.72
GFR change (baseline to mo-6)	------	------	-0.0055 (0.0009)	<0.0001
Use of ACEi (y/n)Ø	-0.012 (0.03)	0.66	-0.014 (0.03)	0.66

The estimates and SE for the intercept and the trial as a random effect for ear single covariate are not shown in order to simplify the table.

º active + former smokers vs. never smokers; ♦Ln transformed data; Ø Similar findings are observed if treatment arms are considered instead of use of ACEi; § Trial (0 = BENEDICT-B, 1 = DEMAND).The coefficient reflects the relationship between independent and dependent variables (GFR slope). A negative coefficient indicates that an increase in the independent variable is associated with a decrease of GFR slope. For the particular case of GFR change, a negative coefficient of a negative change indicates that a decrease in this variable is associated with a positive of GFR slope.

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Supplementary Table 4. Multivariable results of fixed effects meta-analysis with patient-level covariates and random trial effects considering GFR decline from baseline (Model 1) and from month 6 (Model 2) to study end as dependent variables

	GFR slope from baseline		**GFR slope from mo. 6**			
	(Model 1)		*(Model 2)*			
Fixed-effects Parameters						
	Coefficient (SE)	***p***	***Coefficient (SE)***	***p***	***Coefficient (SE)***	***p***
Intercept	-0.307 (0.038)	< 0.0001	-0.285 (0.056)	< 0.0001	-0.288 (0.055)	< 0.0001
Age	-0.0084 (0.0018)	< 0.0001	-0.005 (0.002)	0.02	-0.0038 (0.002)	0.01
Male gender	0.039 (0.027)	0.15	-0.031 (0.033)	0.35	-0.012 (0.032)	0.44
Smoking habit º	-0.021 (0.024)	0.38	- 0.023 (0.023)	0.43	- 0.015 (0.029)	0.68
Known duration of Diabetes♦	-0.019 (0.014)	0.18	-0.014 (0.017)	0.43	-0.013 (0.017)	0.13
Body Mass Index♦	-0.050 (0.086)	0.56	-0.11 (0.104)	0.29	-0.137 (0.10)	0.23
Systolic Blood Pressure	-0.0023 (0.00082)	0.005	-0.001 (0.001)	0.28	-0.0013 (0.001)	0.10
HbA1c (%)♦	-0.063 (0.050)	0.21	-0.051 (0.061)	0.41	-0.041 (0.06)	0.32
Serum Triglyceride levels♦	0.043 (0.025)	0.09	0.043 (0.03)	0.16	0.028 (0.029)	0.28
Serum Uric acid levels	-0.014 (0.010)	0.19	-0.003 (0.013)	0.83	0.006 (0.012)	0.61
Urinary albumin excretion♦	-0.017 (0.011)	0.11	-0.021(0.013)	0.11	-0.023 (0.013)	0.06
GFR	-0.006 (0.0007)	<0.0001	-0.0016 (0.0008)	0.050	-------	-----
GFR change (baseline to mo-6)#	------	----	----	------	-0.0054 (0.0009)	< 0.0001
Use of ACEi (y/n)Ø	0.00005 (0.026)	0.99	0.0032 (0.32)	0.92	0.0009 (0.03)	0.81
Random-effects Parameters						
Variances	***Estimate (SE)***		***Estimate (SE)***		***Estimate (SE)***	
Between-trial	0.0011 (0.0014)		0.0036 (0.004)		0.0037 (0.004)	
Within-trial-between-patient	0.056 (0.04)	-----	0.082 (0.005)	-----	0.071 (0.054)	----

SE = standard error.

º active + former smokers vs. never smokers; ♦Ln transformed data; Ø Similar findings are observed if treatment arms are considered instead of use of ACEi; § Trial (0 = BENEDICT-B, 1 = DEMAND).The coefficient reflects the relationship between independent and dependent variables (GFR slope). A negative coefficient indicates that an increase in the independent variable is associated with a decrease of GFR slope. For the particular case of GFR change, a negative coefficient of a negative change indicates that a decrease in this variable is associated with a positive of GFR slope. **# replacing GFR change for the change (baseline to mo-6) of HbA1c [-0.0066 (0.012), p= 0.6] or of systolic blood pressure [-0.00065 (0.0009), p= 0.50] or including both covariates lead to non-significant results.**

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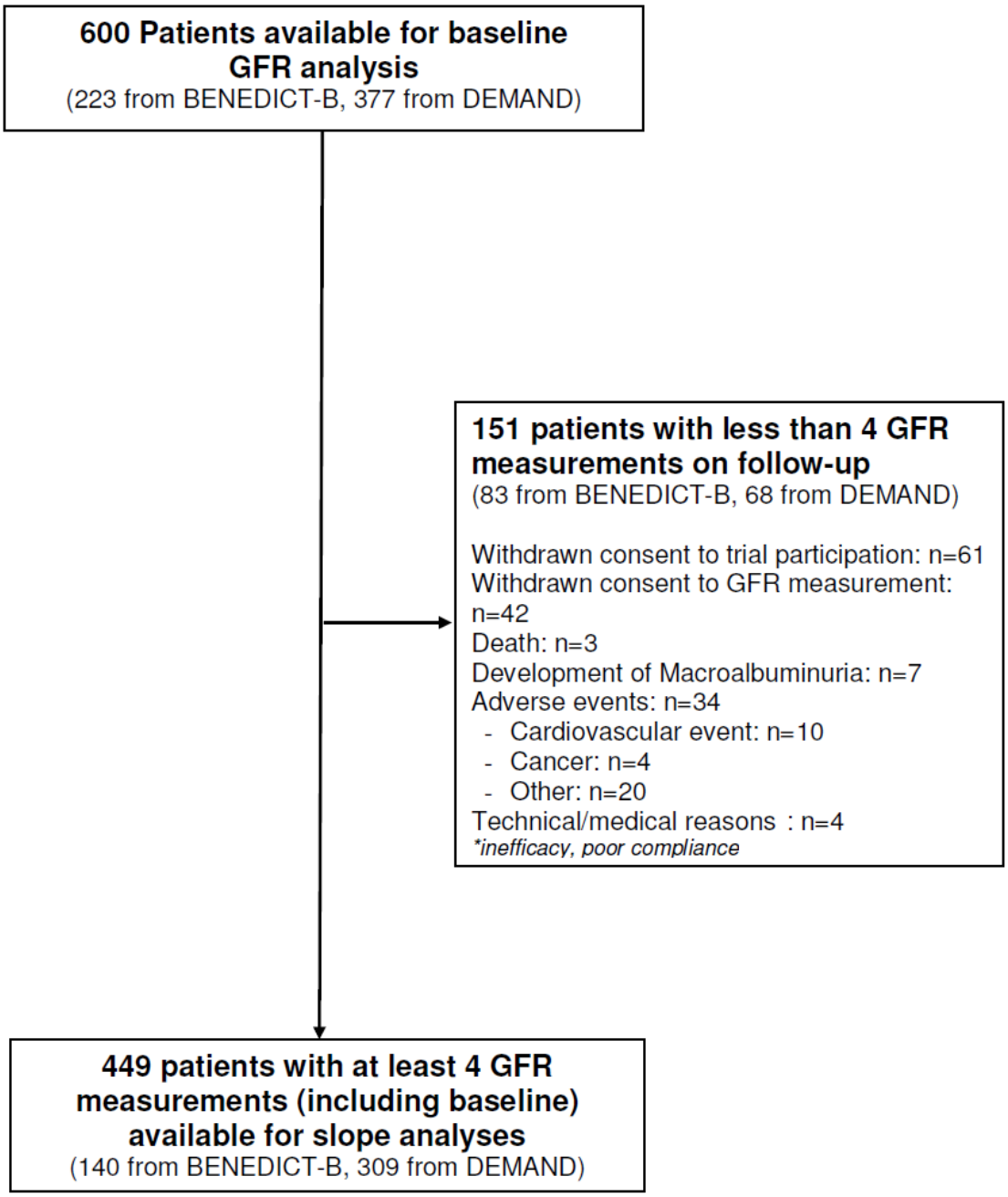
Supplementary Figure 1. Flow-chart of the Study



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Supplementary Figure 2. GFR at baseline (panel A), rate of GFR decline from baseline to study end (panel B), GFR changes from baseline to month six (panel C), rate of GFR decline from month six to study end (Panel D) all subjects considered as a whole (Overall) and in subgroups with or without hyperfiltration or microalbuminuria at inclusion or subsequent allocation to treatment with or without ACE inhibitors. Unpaired t-test for comparisons. Data are means and standard errors (Panels A and C) or medians and interquartile ranges (Panels B and D).