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Integrity Check for MDRD Analysis File

As a partial check of the integrity of the MDRD analysis dataset in the NIDDK Data Repository [Note 1], a set of tabulations was performed to verify that results reported in Tables 1 and 2 of Klahr et al's 1994 article in NEJM. (Note 1) can be reproduced using the archived dataset. Tables 1 and 2 from the NEJM article are included in Attachment 1; STATA 8/SE code and output for our tabulations are included in Attachment 2. The full text of the NEJM article can be found in Attachment 3.

The published NEJM Table 1 breaks down the MDRD study population's sample size by Study (1 or 2), Diet Group (Usual, Low Protein, or Very Low Protein), and Blood Pressure group (Usual or Low). Our first tabulation from the archived dataset (Table 1) produced counts that are identical to the published table.

NEJM Table 2 presents clinical characteristics of the MDRD study population *at the time of randomization.* As a check of this table, we generated the overall means and standard deviations for these characteristics using NIDDK archive data for: glomerular filtration rate, creatinine clearance rate, serum creatinine, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and reported intake of protein, phosphorous, and total calories. These values were calculated separately for Study 1 and 2. To identify the record for the subject visit that would provide the measurement of these variables "at the time of randomization", we:

1. Sorted the 25,963 records in the analysis file by ID and Visit Date

2. Deleted records for all visits for which the date of visit was later than the date of randomization or for which a glomerular filtration measurement was absent.

3. Within each subject ID, we then eliminated all visits except the most recent one (i.e., the record of the last visit that occurred prior to randomization).

The calculated and published means and standard deviations are shown in Table 2. The values we obtained are identical to the published version with some quite minor deviations (highlighted in yellow in Table 2). In some instances — especially for creatinine clearance — measurements were missing on the record for the most recent visit prior to randomization (73 of 585 cases for Study 1 and 13 of 255 cases for Study 2 were missing creatinine clearance measurements).

Abbreviated Check of Baseline and Event Data (Note 4)

Baseline File. The baseline file was examined to insure that: (1) the file structure conformed to the description provided by the study's data center, and (2) summary statistics on a small number of variables for the 840 *randomized subjects* in the baseline file were equivalent to statistics obtained from the analysis file and/or the NEJM publication.

1. As described by the study data center, the baseline file contains a total of 5,338 records for visits numbered (visn) 0, 1, 2, and 3. The file includes: 2,340 records for Study 1 (4 baseline visit records each for 585 subjects), 1,020 records for Study 2 (4 baseline visit records each for 255 subjects); and 1,978 records for cases that were not assigned to a study [Note 2] (955 records for baseline visit 0; 435 for visit 1; 350 for visit 2; and 238 for visit 3).

2. Selecting records for subjects assigned to either Study 1 or Study 2, we found that

- For both the Analysis and the Baseline files, we calculated identical means and standard deviations for subject's age at Baseline visit 3 (51.75, s.d. = 12.37) . This agrees with the text of the NEJM article which says that "average age was 52 years".

- For both the Analysis and Baseline files, we found that 508 of 840 study subjects (60.48%) were males. This agrees with the NEJM article which states that "sixty percent of patients were men".

- Race is recorded only in the Baseline file. Our tabulation found that 714 of the 840 study subjects (85.0%) were classified as white. This agrees with the NEJM statement that "85 percent [of patients] were white."

- Somewhat different renal diagnoses are recorded in the Analysis and Baseline files. The Analysis file records a 9-category code labeled "final dx after reclassification". Tabulation of this variable classifies 200 of the 840 study participants (23.8 percent) as having a primary diagnosis of polycystic kidney disease, 208 (24.8 percent) with glomerular diseases, and 26 (3.1 percent) with Type II diabetes with nephropathy. This agrees with the NEJM statement that "The most common renal diagnoses were glomerular diseases (25 percent) and polycystic kidney diseases (24 percent); 3 percent of patients had non-insulin-dependent diabetes." The Baseline file records responses for a 24-category diagnosis variable presumably coded from Question 5a on MDRD Form 7. This variable coding would logically predate the collapsing and "reclassification" of diagnoses reflected in the Analysis file. This variable (dxform7) had non-missing codes for 797 of the 840 subjects [Note 3]. 200 of these cases were coded "polycystic kidney disease" and 26 were coded "Type II diabetes with nephropathy".

Event File. Repository and study staff have not reviewed the events file. They are aware that the STOP variable in this dataset has some puzzling aspects. DCC staff indicate that there was some noise in the definitions of these variables mostly related to events that occurred after the patient's scheduled close out visit. This issue will require further research by NIDDK Repository and DCC staff if it is important to data users.

NOTES.

1. Analysis was done using a CD file supplied by NIDDK Data Repository on May 6, 2005. The file is: \mdrd_cd\MDRD_Transport_Files \MDRD_c_dcc_TRA_file\analysis.sas7bdat".
For analysis, this file was transformed into a STATA 8/SE dataset using Stat/Transfer version 7. Similar procedures were used with the baseline and event data files ("base.sas7bdat" and "events.sas7bdat").

2. That is, "study" variable had a missing value.

3. These "non-missing" codes included 31 cases coded "other" and 8 coded "unknown".

4. The variable *DXCAT* in BASE file and *RENALDX* in ANALYSIS file both use the 9-category SAS label format identified as *RENALCAT* (1 "Polycystic Kidney Dis"; 2 "Hereditary Nephritis"; 3 "Tubulointerstit Dis"; 4 "Urinary Tract Dis" ; 5 "Hypertensive Neph"; 6 "Type II Diab with Neph"; 7 "Glomerular Dis"; 8 "One Kidney"; 9 "Other or Unknown").

This yields the following tabulation from the BASE FILE for Study 1 and 2 subjects' at visit number 0:

```
. tab dxcat if visn==0 & ((study==1) | (study==2))

      initial dx after |
      recategorization |      Freq.     Percent        Cum.
-----------------------+-----------------------------------
 Polycystic Kidney Dis |        200       23.81       23.81
  Hereditary Nephritis |         22        2.62       26.43
   Tubulointerstit Dis |         73        8.69       35.12
     Urinary Tract Dis |         30        3.57       38.69
     Hypertensive Neph |        144       17.14       55.83
Type II Diab with Neph |         26        3.10       58.93
        Glomerular Dis |        216       25.71       84.64
            One Kidney |         27        3.21       87.86
      Other or Unknown |        102       12.14      100.00
-----------------------+-----------------------------------
                 Total |        840      100.00
```

And it yields the following tabulation from the ANALYSIS FILE at visit number 0:

```
. tab renaldx if visn==0

        final dx after |
      reclassification |      Freq.     Percent        Cum.
-----------------------+-----------------------------------
 Polycystic Kidney Dis |        200       23.81       23.81
  Hereditary Nephritis |         22        2.62       26.43
   Tubulointerstit Dis |         39        4.64       31.07
     Urinary Tract Dis |         33        3.93       35.00
     Hypertensive Neph |         55        6.55       41.55
Type II Diab with Neph |         26        3.10       44.64
        Glomerular Dis |        208       24.76       69.40
            One Kidney |         27        3.21       72.62
      Other or Unknown |        230       27.38      100.00
-----------------------+-----------------------------------
                 Total |        840      100.00
```

Given the non-equivalence of these tabulations, we were concerned as to whether the same category values were appropriate for both variables (*dxcat* and *renaldx*).

MDRD DCC staff (T Greene, e-mail, October 13, 2005) indicated that the same format statement applies to both *dxcat* and *renaldx.* The difference between these variables is that *dxcat* was based on the original renal diagnosis information in the database, and *renaldx* is a revised classification based on a review process of a committee formed to look into the renal diagnoses during the trial. *Renaldx* required data obtained later during the baseline period that was not available at the screening visit, and thus is available for all randomized patients but not for all enrolled patients. Hence, studies involving all enrolled patients must use *dxcat*, but both *dxcat* and *renealdx* are available for studies of randomized patients only. The main distinction is that cases with insufficient documentation were reclassified as "other or unknown" in *renaldx* instead of being classified as one of the designated diagnoses. Thus, the other or unknown category has a greater frequency for *renaldx*, but specific diagnoses (such as hypertensive nephropathy) have lower frequencies. *Renaldx* is the "official" renal diagnosis variable for the randomized patients, but sometimes authors have opted to present results for randomized patients based on *dxcat* instead in cases where they wanted to compare the renal diagnoses of MDRD patients to diagnoses of other studies that did not have a review process.

REFERENCES.

Saulo Klahr, Andrew S. Levey, Gerald J. Beck, Arlene W. Caggiula, Lawrence Hunsicker, John W. Kusek, Gary Striker, for The Modification of Diet in Renal Disease Study Group. Effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. NEJM, 330:877-884, 1994

Table 1. Tabulation from Repository "Analysis" File exactly matches published tabulation.

DIET (a,b)	STUDY 1 Ns Moderate BP (b)	Low BP	STUDY 2 Ns Moderate BP (b)	BP Low
Moderate Protein	145	149	0	0
Low Protein	140	151	62	67
Very Low Protein	0	0	61	65

(a) Assumes diets labelled K, L, and M in archive file are very low protein, low protein, and moderate protein respectively, as described in Table 2 of Beck et al. (1991, cited below).

(b) There is some variation between Beck et al. (1991, cited below) and Klahr et al. (1991, cited below) in the terminology used to describe the experimental conditions . Beck et al. (1991, p.569) describe the diet conditions as: M: Moderate protein and phosphorous, L: Low protein and phosphorous, and K: Very Low protein and phosphorous; the BP goals are decribed as "moderate" and "low" mean arterial blood pressure goals. Klahr et al. (1991, abstract) use the terms "usual protein [diet]" and "usual-blood-pressure group" in place of the two "moderate" conditions described by Beck et al.

REFERENCES.

Beck GJ, Berg RL, Coggins CH, et al. The Modification of Diet in Renal Disease Study Group. Design and statistical issues of the Modification of Diet in Renal Disease Trial. Control Clin Trials. 12:566-86, 1991.

Klahr S, Levey AS, Beck GJ, et al. Effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. NEJM, 330:877-884, 1994.

Table 2. Comparison of NEJM Table 2 and tabulation from NIDDK Depository Analysis File of overall means and standard devisions by study .

	ARCHIVE DATA			PUBLISHED	
Measurement	**Mean**	**Std.Dev.**	**Obs**	**Mean**	**Std.Dev.**
Study 1					
Glomerular filtration rate	38.6	8.9	585	38.6	8.9
Creatinine clearance rate	50.3	13.1	512	50.4	13.1
serum creatinine	1.9	0.5	584	1.9	0.5
Systolic BP	131	18	585	131	18
Diastolic BP	81	10	585	81	10
Mean Arterial BP	98	11	585	98	11
Protein	1.17	0.29	584	1.12	0.19
Phosphorous	17.8	5.1	584	17.8	5.1
Total calories	27.2	7.1	584	27.2	7.1
Study 2					
Glomerular filtration rate	18.5	3.4	255	18.5	3.4
Creatinine clearance rate	24.6	7.1	242	24.6	7.1
serum creatinine	3.4	0.9	255	3.4	0.9
Systolic BP	133	18	255	133	18
Diastolic BP	81	10	255	81	10
Mean Arterial BP	98	11	255	98	11
Protein	0.90	0.28	255	0.87	0.19
Phosphorous	14.1	4.5	255	14.1	4.6
Total calories	24.9	6.7	255	24.9	6.7

ATTACHMENT 1

NEJM Tables 1 and 2

from

Saulo Klahr, Andrew S. Levey, Gerald J. Beck, Arlene W. Caggiula, Lawrence Hunsicker, John W. Kusek, Gary Striker, for The Modification of Diet in Renal Disease Study Group. Effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. NEJM, 330:877-884, 1994.

DIET†	STUDY 1 (N = 585)		STUDY 2 (N = 255)	
	MEAN ARTERIAL PRESSURE‡			
	usual	low	usual	low
	no. of patients			
Usual protein	145	149	—	—
Low protein	140	151	62	67
Very low protein	—	—	61	65

*Patients in study 1 had a glomerular filtration rate of 25 to 55 ml per minute per 1.73 m^2; patients in study 2 had a rate of 13 to 24 ml per minute per 1.73 m^2.

†The usual-protein diet consisted of 1.3 g of protein and 16 to 20 mg of phosphorus per kilogram (standard body weight) per day, the low-protein diet consisted of 0.58 g of protein (≥0.35 g of protein high in essential amino acids) and 5 to 10 mg of phosphorus per kilogram per day, and the very-low-protein diet consisted of 0.28 g of protein and 4 to 9 mg of phosphorus per kilogram per day, supplemented by a keto acid–amino acid mixture (0.28 g per kilogram per day) (Ross Laboratories, Columbus, Ohio).

‡Mean arterial pressure is defined in the Methods section. The usual mean arterial pressure was ≤107 mm Hg for patients 18 to 60 years old at entry (equivalent to 140/90 mm Hg) or ≤113 mm Hg for patients ≥61 years old at entry (equivalent to 160/90 mm Hg); low mean arterial pressure was ≤92 mm Hg for patients 18 to 60 years old at entry (equivalent to 125/75 mm Hg) or ≤98 mm Hg for patients ≥61 years old at entry (equivalent to 145/75 mm Hg).

Table 1. Assignment of Patients to Diet and Blood-Pressure Groups in Studies 1 and 2.

Variable	Usual Protein		Low Protein		Overall
	Usual Pressure	Low Pressure	Usual Pressure	Low Pressure	
			mean ±SD		
Study 1 (n = 585)					
Glomerular filtration rate (ml/min/1.73 m^2)	37.6±9.0	38.2±8.6	38.9±8.8	39.7±9.1	38.6±8.9
Creatinine clearance (ml/min/1.73 m^2)	49.2±12.6	49.2±11.6	51.3±14.4	51.9±13.7	50.4±13.1
Serum creatinine (mg/dl)†	2.0±0.5	2.0±0.5	1.9±0.5	1.9±0.5	1.9±0.5
Systolic pressure (mm Hg)	132±17	131±19	131±19	132±16	131±18
Diastolic pressure (mm Hg)	80±10	81±10	81±10	82±10	81±10
Mean arterial pressure (mm Hg)	97±10	98±11	98±11	98±10	98±11
Protein (g/kg/day)‡	1.12±0.18	1.12±0.18	1.13±0.21	1.11±0.20	1.12±0.19
Phosphorus (mg/kg/day)	17.5±5.4	17.7±4.8	17.9±5.4	17.9±4.9	17.8±5.1
Total calories (kcal/kg/day)	27.6±7.0	26.8±6.8	27.0±7.8	27.6±6.9	27.2±7.1
	Low Protein		Very Low Protein		Overall
	Usual Pressure	Low Pressure	Usual Pressure	Low Pressure	
Study 2 (n = 255)					
Glomerular filtration rate (ml/min/1.73 m^2)	18.7±3.1	18.8±3.3	18.3±3.7	18.4±3.5	18.5±3.4
Creatinine clearance (ml/min/1.73 m^2)	24.3±5.2	24.2±7.2	25.3±8.3	24.6±7.3	24.6±7.1
Serum creatinine (mg/dl)†	3.5±0.9	3.4±0.8	3.2±0.9	3.5±0.9	3.4±0.9
Systolic pressure (mm Hg)	131±17	134±20	135±16	132±17	133±18
Diastolic pressure (mm Hg)	80±11	80±10	81±11	82±9	81±10
Mean arterial pressure (mm Hg)	97±12	98±11	99±11	99±10	98±11
Protein (g/kg/day)‡	0.89±0.19	0.83±0.16	0.89±0.20	0.86±0.19	0.87±0.19
Phosphorus (mg/kg/day)	14.4±4.3	14.4±4.3	14.1±5.1	13.6±4.3	14.1±4.5
Total calories (kcal/kg/day)	24.8±6.9	24.9±6.3	24.6±6.6	25.0±7.2	24.9±6.7

*Usual pressure and low pressure refer to usual and low mean arterial pressure, respectively.

†To convert serum creatinine values to micromoles per liter, multiply by 88.4.

‡Protein was calculated on the basis of urinary excretion of urea nitrogen.

Table 2. Clinical Characteristics of the Study Population at the Time of Randomization.

ATTACHMENT 2

STATA 8/SE Code and Output for Tabulations from MDRD Data in NIDDK Repository

(Analysis, Base, and Event Datasets)

```
-------------------------------------------------------------------------------
      log:  P:\NIDDK\MDRD\AnalysisIntegrity.output.log
  log type:  text
 opened on:  13 Sep 2005, 07:53:45

. use "C:\mdrd_CD_Sept12\mdrd_cd\MDRD_Transport_Files\MDRD_c_dcc_TRA_file\analy
> sis.dta", clear

. generate Study_BP = (10*study) + bp

. label define s_bp 11"St1-ModBP" 12"St1-LoBP"  21"St2-ModBP" 22"St2-LoBP"

. label values Study_BP s_bp

. tab diet Study_BP if visn==0

diet group |
  (1=k 2=l |                  Study_BP
      3=m) | St1-ModBP   St1-LoBP  St2-ModBP   St2-LoBP |     Total
-----------+--------------------------------------------+----------
         1 |         0          0         61         65 |       126
         2 |       140        151         62         67 |       420
         3 |       145        149          0          0 |       294
-----------+--------------------------------------------+----------
     Total |       285        300        123        132 |       840


.
. sort id visdt

. drop if gfr==.
(17656 observations deleted)

. generate Rdiff = visdt - randomdt
(17 missing values generated)

. tab id if visdt==.

 patient id |      Freq.     Percent        Cum.
------------+-----------------------------------
      10283 |          1        5.88        5.88
      40044 |          1        5.88       11.76
      40045 |          1        5.88       17.65
      40084 |          1        5.88       23.53
      40125 |          1        5.88       29.41
      40232 |          1        5.88       35.29
      60062 |          1        5.88       41.18
      60112 |          1        5.88       47.06
      60124 |          1        5.88       52.94
      60218 |          1        5.88       58.82
      60265 |          1        5.88       64.71
      70191 |          1        5.88       70.59
      90102 |          1        5.88       76.47
     100328 |          1        5.88       82.35
     130275 |          1        5.88       88.24
     140200 |          1        5.88       94.12
     150068 |          1        5.88      100.00
------------+-----------------------------------
      Total |         17      100.00

. tab visn if visdt==.

      visit |
     number |      Freq.     Percent        Cum.
------------+-----------------------------------
          1 |         17      100.00      100.00
```

```
------------+-----------------------------------
      Total |         17      100.00

. drop if Rdiff > 0
(6627 observations deleted)

. tab visn

      visit |
     number |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |        840       50.00       50.00
          3 |        840       50.00      100.00
------------+-----------------------------------
      Total |      1,680      100.00

. generate IDnext = id[_n +1]
(1 missing value generated)

. replace IDnext = 999999 if _n ==_N
(1 real change made)

. drop if id == IDnext
(840 observations deleted)

. tab visn

      visit |
     number |      Freq.     Percent        Cum.
------------+-----------------------------------
          3 |        840      100.00      100.00
------------+-----------------------------------
      Total |        840      100.00

. tab Rdiff

      Rdiff |      Freq.     Percent        Cum.
------------+-----------------------------------
        -41 |          3        0.36        0.36
        -38 |          2        0.24        0.60
        -37 |          5        0.60        1.19
        -36 |          3        0.36        1.55
        -35 |          6        0.71        2.26
        -34 |          6        0.71        2.98
        -33 |          2        0.24        3.21
        -32 |          5        0.60        3.81
        -31 |          6        0.71        4.52
        -30 |          7        0.83        5.36
        -29 |         12        1.43        6.79
        -28 |         16        1.90        8.69
        -27 |         16        1.90       10.60
        -26 |          7        0.83       11.43
        -25 |         18        2.14       13.57
        -24 |         14        1.67       15.24
        -23 |         20        2.38       17.62
        -22 |         29        3.45       21.07
        -21 |         39        4.64       25.71
        -20 |         38        4.52       30.24
        -19 |         24        2.86       33.10
        -18 |         27        3.21       36.31
        -17 |         34        4.05       40.36
        -16 |         53        6.31       46.67
        -15 |         55        6.55       53.21
        -14 |         69        8.21       61.43
        -13 |         65        7.74       69.17
        -12 |         44        5.24       74.40
```

```
        -11 |         54        6.43       80.83
        -10 |         33        3.93       84.76
         -9 |         58        6.90       91.67
         -8 |         58        6.90       98.57
         -7 |         12        1.43      100.00
------------+-----------------------------------
      Total |        840      100.00

. sort study

. by study: summarize gfr ccr pcr sys dia map dpro dphos dcal

-------------------------------------------------------------------------------
-> study = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
         gfr |       585    38.61742    8.899193     24.506     55.395
         ccr |       512     50.2544     13.0543     24.547    110.512
         pcr |       584    1.930822    .5193432         .9        3.7
         sys |       585    131.4154     17.5431         89        206
         dia |       585    81.05641    10.03667         46        107
-------------+--------------------------------------------------------
         map |       585    97.84393    10.64731       69.7        123
        dpro |       584    1.165736    .2924724        .38        2.6
       dphos |       584    17.77098    5.113476       5.25      40.77
       dcals |       584    27.24913    7.102928      11.51      53.51

-------------------------------------------------------------------------------
-> study = 2

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
         gfr |       255     18.5279    3.382998     12.503     24.492
         ccr |       242    24.62541    7.051994      3.504     55.164
         pcr |       255     3.42549     .880015        1.6        6.6
         sys |       255    133.0882    17.57596         93        194
         dia |       255    80.81373    10.23857         52        107
-------------+--------------------------------------------------------
         map |       255    98.23726    10.85725       67.7        125
        dpro |       255    .8992549    .2828146        .33       1.71
       dphos |       255    14.10306    4.484659       5.65       31.6
       dcals |       255    24.85239    6.745475      10.29      49.88


. log close
      log:  P:\NIDDK\MDRD\AnalysisIntegrity.output.log
  log type:  text
 closed on:  13 Sep 2005, 07:53:46
-------------------------------------------------------------------------------
```

```
-------------------------------------------------------------------------------
      log:
C:\mdrd_CD_Sept12\mdrd_cd\MDRD_Transport_Files\MDRD_c_dcc_TRA_file\Base_Test.log
  log type:  text
 opened on:  13 Sep 2005, 13:55:47

. set more off

. use
"C:\mdrd_CD_Sept12\mdrd_cd\MDRD_Transport_Files\MDRD_c_dcc_TRA_file\analysis.dta"
, clear

. label define SEX 1 "Male" 2 "Female"

. label values sex SEX

. label define RENALDX 1 "Polycystic Kidney Disease" 2 "Hereditary Nephritis" 3 "Analgesic Nep
> hritis" 4 "Pyelonephritis" 5 "Other Interstitial Nephritis" 6 "Obstructive Uropathy-Acquired
> " 7 "Obstructive Uropathy-Congenital" 8 "Vesico-Ureteral Reflux" 9 "Urinary Tract Stones" 10
>  "Hypertensive Nephrosclerosis" 11 "Diabetic Nephropathy" 12 "Renal Artery Stenosis" 13 "Mem
> branous Nephropathy" 14 "Focal Sclerosis" 15 "Membranoproliferative Glomerulonephritis" 16 "
> Mesangial Proliferative Glomerulonephritis" 17 "Chronic Renal Failure With Proteinuria" 18 "
> Nephrotic Syndrome Without Biopsy" 19 "Absence Of One Kidney" 20 "Iga Nephropathy" 21 "Other
>  Glomerulonephritis" 22 "Other" 23 "Unknown"  24 "None"

. label define RENALCAT 1 "Polycystic Kidney Dis" 2 "Hereditary Nephritis" 3 "Tubulointerstit
> Dis" 4 "Urinary Tract Dis" 5 "Hypertensive Neph" 6 "Type II Diab with Neph" 7 "Glomerular Di
> s" 8 "One Kidney" 9 "Other or Unknown"

. label values renaldx RENALCAT

. summarize b3age if visn == 3

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
       b3age |      1621    51.79661    12.32663      19.05      71.24

. tab sex if visn == 3

     gender |
    (1=male |
  2=female) |      Freq.     Percent        Cum.
------------+-----------------------------------
       Male |        982       60.58       60.58
     Female |        639       39.42      100.00
------------+-----------------------------------
      Total |      1,621      100.00

. tab renaldx if visn == 3

        final dx after |
     reclassification |      Freq.     Percent        Cum.
----------------------+-----------------------------------
 Polycystic Kidney Dis |        392       24.18       24.18
  Hereditary Nephritis |         43        2.65       26.84
   Tubulointerstit Dis |         75        4.63       31.46
     Urinary Tract Dis |         65        4.01       35.47
     Hypertensive Neph |        104        6.42       41.89
Type II Diab with Neph |         49        3.02       44.91
        Glomerular Dis |        399       24.61       69.52
            One Kidney |         49        3.02       72.55
     Other or Unknown |        445       27.45      100.00
----------------------+-----------------------------------
                Total |      1,621      100.00

.
```

```
. use
"C:\mdrd_CD_Sept12\mdrd_cd\MDRD_Transport_Files\MDRD_c_dcc_TRA_file\base.dta",
clear

. label define SEX 1 "Male" 2 "Female"

. label define RACE 1 "White" 2 "Black" 3 "Hispanic" 4 "Asian" 5 "Native
American" 6 "Pacific
> Islander" 7 "Other" 8 "Arabic" 9 "Unknown"

. label values sex SEX

. label values race RACE

. label define RENALDX 1 "Polycystic Kidney Disease" 2 "Hereditary Nephritis" 3 "Analgesic Nep
> hritis" 4 "Pyelonephritis" 5 "Other Interstitial Nephritis" 6 "Obstructive Uropathy-Acquired
> " 7 "Obstructive Uropathy-Congenital" 8 "Vesico-Ureteral Reflux" 9 "Urinary Tract Stones" 10
>  "Hypertensive Nephrosclerosis" 11 "Diabetic Nephropathy" 12 "Renal Artery Stenosis" 13 "Mem
> branous Nephropathy" 14 "Focal Sclerosis" 15 "Membranoproliferative Glomerulonephritis" 16 "
> Mesangial Proliferative Glomerulonephritis" 17 "Chronic Renal Failure With Proteinuria" 18 "
> Nephrotic Syndrome Without Biopsy" 19 "Absence Of One Kidney" 20 "Iga Nephropathy" 21 "Other
>  Glomerulonephritis" 22 "Other" 23 "Unknown"  24 "None"

. label values dxform7 RENALDX

. sort study

. by study: tab visn

-------------------------------------------------------------------------------
-> study = 1

      visit |
     number |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |        585       25.00       25.00
          1 |        585       25.00       50.00
          2 |        585       25.00       75.00
          3 |        585       25.00      100.00
------------+-----------------------------------
      Total |      2,340      100.00

-------------------------------------------------------------------------------
-> study = 2

      visit |
     number |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |        255       25.00       25.00
          1 |        255       25.00       50.00
          2 |        255       25.00       75.00
          3 |        255       25.00      100.00
------------+-----------------------------------
      Total |      1,020      100.00

-------------------------------------------------------------------------------
-> study = .

      visit |
     number |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |        955       48.28       48.28
          1 |        435       21.99       70.27
          2 |        350       17.69       87.97
          3 |        238       12.03      100.00
------------+-----------------------------------
```

```
      Total |      1,978      100.00

. drop if study == .
(1978 observations deleted)

. tab study visn

     study |
  assigned |                visit number
        to |         0          1          2          3 |     Total
-----------+--------------------------------------------+----------
         1 |       585        585        585        585 |     2,340
         2 |       255        255        255        255 |     1,020
-----------+--------------------------------------------+----------
     Total |       840        840        840        840 |     3,360


. summarize b3age if visn == 3

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
       b3age |       840    51.74871    12.37359      19.05      71.24

. tab sex if visn ==3

        sex |      Freq.     Percent        Cum.
------------+-----------------------------------
       Male |        508       60.48       60.48
     Female |        332       39.52      100.00
------------+-----------------------------------
      Total |        840      100.00

. tab race if visn ==3

 race-population |
           group |      Freq.     Percent        Cum.
-----------------+-----------------------------------
           White |        714       85.00       85.00
           Black |         66        7.86       92.86
        Hispanic |         39        4.64       97.50
           Asian |         11        1.31       98.81
 Native American |          1        0.12       98.93
Pacific Islander |          3        0.36       99.29
           Other |          1        0.12       99.40
          Arabic |          5        0.60      100.00
-----------------+-----------------------------------
           Total |        840      100.00

. tab dxform7 if visn ==3

                    renal dx from form 7 |      Freq.     Percent        Cum.
-----------------------------------------+-----------------------------------
              Polycystic Kidney Disease |        200       25.09       25.09
                   Hereditary Nephritis |         19        2.38       27.48
                    Analgesic Nephritis |         13        1.63       29.11
                         Pyelonephritis |         25        3.14       32.25
            Other Interstitial Nephritis |         37        4.64       36.89
          Obstructive Uropathy-Acquired |          2        0.25       37.14
        Obstructive Uropathy-Congenital |          5        0.63       37.77
                  Vesico-Ureteral Reflux |         16        2.01       39.77
                    Urinary Tract Stones |          6        0.75       40.53
            Hypertensive Nephrosclerosis |        136       17.06       57.59
                    Diabetic Nephropathy |         26        3.26       60.85
```

```
                  Renal Artery Stenosis |          1        0.13       60.98
                 Membranous Nephropathy |         16        2.01       62.99
                        Focal Sclerosis |         70        8.78       71.77
Membranoproliferative Glomerulonephriti |         19        2.38       74.15
Mesangial Proliferative Glomerulonephri |          7        0.88       75.03
 Chronic Renal Failure With Proteinuria |         39        4.89       79.92
      Nephrotic Syndrome Without Biopsy |          6        0.75       80.68
                  Absence Of One Kidney |         26        3.26       83.94
                        Iga Nephropathy |         44        5.52       89.46
               Other Glomerulonephritis |         45        5.65       95.11
                                  Other |         31        3.89       99.00
                                Unknown |          8        1.00      100.00
----------------------------------------+-----------------------------------
                                  Total |        797      100.00

.
end of do-file

. log close
       log:
C:\mdrd_CD_Sept12\mdrd_cd\MDRD_Transport_Files\MDRD_c_dcc_TRA_file\Base_Test.log
  log type:  text
 closed on:  13 Sep 2005, 13:56:28
-------------------------------------------------------------------------------
```

ATTACHMENT 3

The full text of the article referenced will be provided to approved requestors along with the data archive.

Saulo Klahr, Andrew S. Levey, Gerald J. Beck, Arlene W. Caggiula, Lawrence Hunsicker, John W. Kusek, Gary Striker, for The Modification of Diet in Renal Disease Study Group. Effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. NEJM, 330:877-884, 1994.

DIET†	STUDY 1 (N = 585)		STUDY 2 (N = 255)	
	MEAN ARTERIAL PRESSURE‡			
	usual	low	usual	low
	no. of patients			
Usual protein	145	149	—	—
Low protein	140	151	62	67
Very low protein	—	—	61	65

*Patients in study 1 had a glomerular filtration rate of 25 to 55 ml per minute per 1.73 m^2; patients in study 2 had a rate of 13 to 24 ml per minute per 1.73 m^2.

†The usual-protein diet consisted of 1.3 g of protein and 16 to 20 mg of phosphorus per kilogram (standard body weight) per day, the low-protein diet consisted of 0.58 g of protein (≥0.35 g of protein high in essential amino acids) and 5 to 10 mg of phosphorus per kilogram per day, and the very-low-protein diet consisted of 0.28 g of protein and 4 to 9 mg of phosphorus per kilogram per day, supplemented by a keto acid–amino acid mixture (0.28 g per kilogram per day) (Ross Laboratories, Columbus, Ohio).

‡Mean arterial pressure is defined in the Methods section. The usual mean arterial pressure was ≤107 mm Hg for patients 18 to 60 years old at entry (equivalent to 140/90 mm Hg) or ≤113 mm Hg for patients ≥61 years old at entry (equivalent to 160/90 mm Hg); low mean arterial pressure was ≤92 mm Hg for patients 18 to 60 years old at entry (equivalent to 125/75 mm Hg) or ≤98 mm Hg for patients ≥61 years old at entry (equivalent to 145/75 mm Hg).

Table 1. Assignment of Patients to Diet and Blood-Pressure Groups in Studies 1 and 2.

Variable	Usual Protein		Low Protein		Overall
	Usual Pressure	Low Pressure	Usual Pressure	Low Pressure	
			mean ±SD		
Study 1 (n = 585)					
Glomerular filtration rate (ml/min/1.73 m^2)	37.6±9.0	38.2±8.6	38.9±8.8	39.7±9.1	38.6±8.9
Creatinine clearance (ml/min/1.73 m^2)	49.2±12.6	49.2±11.6	51.3±14.4	51.9±13.7	50.4±13.1
Serum creatinine (mg/dl)†	2.0±0.5	2.0±0.5	1.9±0.5	1.9±0.5	1.9±0.5
Systolic pressure (mm Hg)	132±17	131±19	131±19	132±16	131±18
Diastolic pressure (mm Hg)	80±10	81±10	81±10	82±10	81±10
Mean arterial pressure (mm Hg)	97±10	98±11	98±11	98±10	98±11
Protein (g/kg/day)‡	1.12±0.18	1.12±0.18	1.13±0.21	1.11±0.20	1.12±0.19
Phosphorus (mg/kg/day)	17.5±5.4	17.7±4.8	17.9±5.4	17.9±4.9	17.8±5.1
Total calories (kcal/kg/day)	27.6±7.0	26.8±6.8	27.0±7.8	27.6±6.9	27.2±7.1
	Low Protein		Very Low Protein		Overall
	Usual Pressure	Low Pressure	Usual Pressure	Low Pressure	
Study 2 (n = 255)					
Glomerular filtration rate (ml/min/1.73 m^2)	18.7±3.1	18.8±3.3	18.3±3.7	18.4±3.5	18.5±3.4
Creatinine clearance (ml/min/1.73 m^2)	24.3±5.2	24.2±7.2	25.3±8.3	24.6±7.3	24.6±7.1
Serum creatinine (mg/dl)†	3.5±0.9	3.4±0.8	3.2±0.9	3.5±0.9	3.4±0.9
Systolic pressure (mm Hg)	131±17	134±20	135±16	132±17	133±18
Diastolic pressure (mm Hg)	80±11	80±10	81±11	82±9	81±10
Mean arterial pressure (mm Hg)	97±12	98±11	99±11	99±10	98±11
Protein (g/kg/day)‡	0.89±0.19	0.83±0.16	0.89±0.20	0.86±0.19	0.87±0.19
Phosphorus (mg/kg/day)	14.4±4.3	14.4±4.3	14.1±5.1	13.6±4.3	14.1±4.5
Total calories (kcal/kg/day)	24.8±6.9	24.9±6.3	24.6±6.6	25.0±7.2	24.9±6.7

*Usual pressure and low pressure refer to usual and low mean arterial pressure, respectively.

†To convert serum creatinine values to micromoles per liter, multiply by 88.4.

‡Protein was calculated on the basis of urinary excretion of urea nitrogen.

Table 2. Clinical Characteristics of the Study Population at the Time of Randomization.

Study Period and Diet	Decline in Glomerular Filtration Rate		
	Usual Pressure	Low Pressure	Both
	milliliters per minute per 4 months		
Base line to 4 months			
Usual protein	1.2 (0.1–2.3)	2.4 (1.4–3.5)	1.8 (1.1–2.6)
Low protein	2.6 (1.5–3.7)	4.3 (3.2–5.3)	3.4 (2.7–4.2)
Both	1.9 (1.1–2.7)	3.4 (2.6–4.1)	2.6 (2.1–3.2)
	milliliters per minute per year		
4 Months to end			
Usual protein	4.5 (3.7–5.3)	3.3 (2.5–4.1)	3.9 (3.3–4.4)
Low protein	3.3 (2.5–4.2)	2.3 (1.5–3.0)	2.8 (2.2–3.4)
Both	3.9 (3.3–4.5)	2.8 (2.2–3.3)	3.3 (2.9–3.7)
	milliliters per minute per 3 years		
Base line to 3 years			
Usual protein	13.1 (10.8–15.4)	11.2 (8.8–13.5)	12.1 (10.5–13.8)
Low protein	11.5 (9.1–13.9)	10.3 (8.0–12.6)	10.9 (9.2–12.5)
Both	12.3 (10.6–14.0)	10.7 (9.1–12.4)	11.5 (10.3–12.7)

*The means were estimated with the maximum-likelihood method for the two-slope model (with separate slopes from the final base-line visit to the fourth month of follow-up and from the fourth month of follow-up to the end of follow-up) and for the projected decline in the glomerular filtration rate from base line to three years. There were no significant interactions between the diet and blood-pressure interventions. There were significant effects of dietary and blood-pressure interventions from the final base-line visit to the fourth month of follow-up ($P = 0.004$ and $P = 0.010$, respectively) and from the fourth month to the end of follow-up ($P = 0.009$ and $P = 0.006$, respectively). The estimated decline in the glomerular filtration rate over three years did not differ significantly between the diet groups or between the blood-pressure groups. Values in parentheses indicate 95 percent confidence intervals.

Table 3. Mean Rate of Decline in the Glomerular Filtration Rate in Study 1, According to Diet and Blood-Pressure Group.

Study Period and Diet	Decline in Glomerular Filtration Rate		
	Usual Pressure	Low Pressure	Both
	milliliters per minute per 4 months		
Base line to 4 months			
Usual protein	1.2 (0.1–2.3)	2.4 (1.4–3.5)	1.8 (1.1–2.6)
Low protein	2.6 (1.5–3.7)	4.3 (3.2–5.3)	3.4 (2.7–4.2)
Both	1.9 (1.1–2.7)	3.4 (2.6–4.1)	2.6 (2.1–3.2)
	milliliters per minute per year		
4 Months to end			
Usual protein	4.5 (3.7–5.3)	3.3 (2.5–4.1)	3.9 (3.3–4.4)
Low protein	3.3 (2.5–4.2)	2.3 (1.5–3.0)	2.8 (2.2–3.4)
Both	3.9 (3.3–4.5)	2.8 (2.2–3.3)	3.3 (2.9–3.7)
	milliliters per minute per 3 years		
Base line to 3 years			
Usual protein	13.1 (10.8–15.4)	11.2 (8.8–13.5)	12.1 (10.5–13.8)
Low protein	11.5 (9.1–13.9)	10.3 (8.0–12.6)	10.9 (9.2–12.5)
Both	12.3 (10.6–14.0)	10.7 (9.1–12.4)	11.5 (10.3–12.7)

*The means were estimated with the maximum-likelihood method for the two-slope model (with separate slopes from the final base-line visit to the fourth month of follow-up and from the fourth month of follow-up to the end of follow-up) and for the projected decline in the glomerular filtration rate from base line to three years. There were no significant interactions between the diet and blood-pressure interventions. There were significant effects of dietary and blood-pressure interventions from the final base-line visit to the fourth month of follow-up ($P = 0.004$ and $P = 0.010$, respectively) and from the fourth month to the end of follow-up ($P = 0.009$ and $P = 0.006$, respectively). The estimated decline in the glomerular filtration rate over three years did not differ significantly between the diet groups or between the blood-pressure groups. Values in parentheses indicate 95 percent confidence intervals.

Table 3. Mean Rate of Decline in the Glomerular Filtration Rate in Study 1, According to Diet and Blood-Pressure Group.

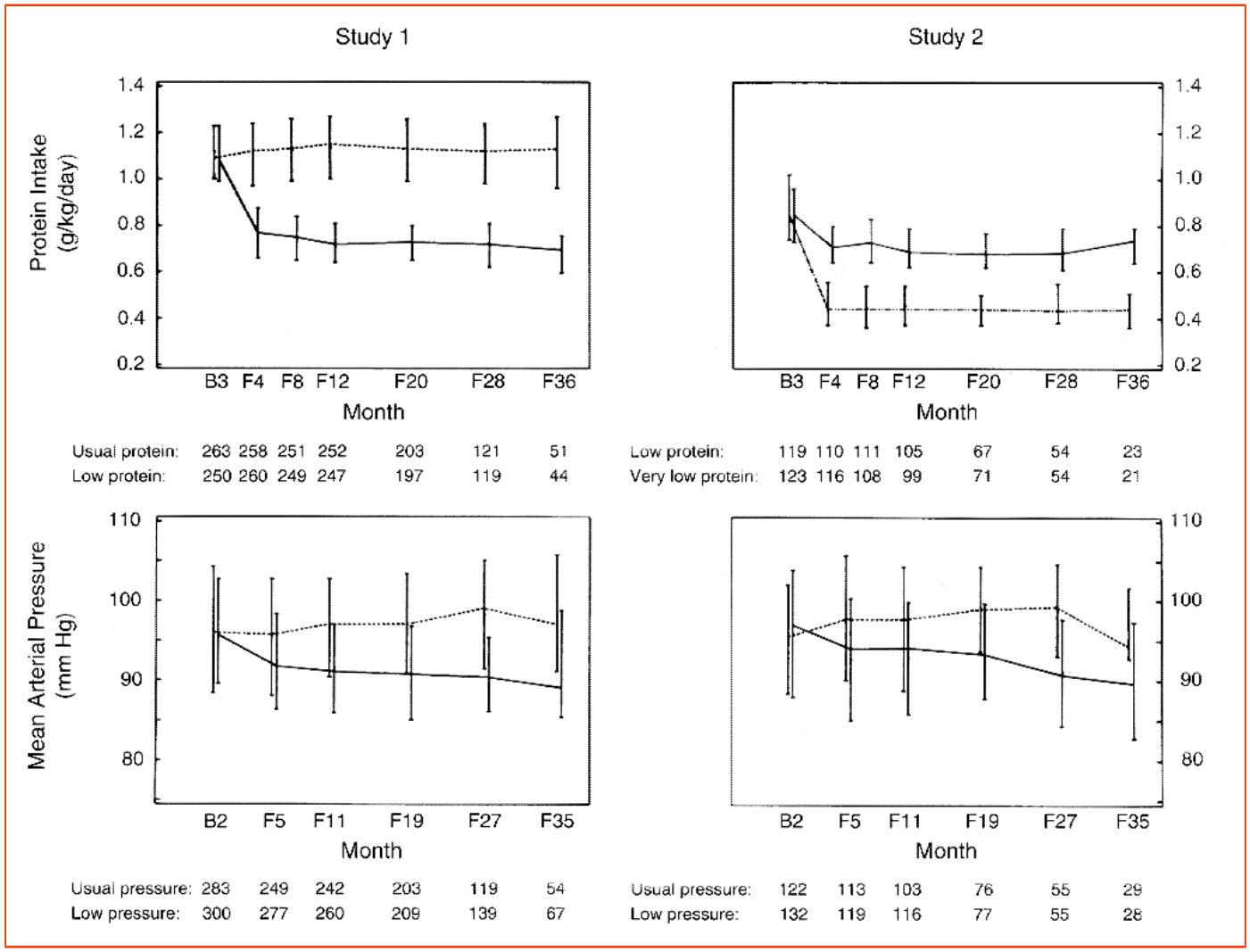

Figure 1. Estimated Protein Intake and Mean Arterial Pressure in Patients with Renal Disease Enrolled in Studies 1 and 2.

Protein intake was estimated from urinary excretion of urea nitrogen. The two diets in study 2 were designed to provide the same amount of nitrogen, but the nitrogen contained in the keto acid-amino acid mixture was subtracted from the urinary urea nitrogen in the very-low-protein group. The median values at each base-line (B) and follow-up (F) visit are given for the patients on the usual-protein diet (dashed line), the low-protein diet (solid line), and the very-low-protein diet (dashed-and-dotted line) and for those with usual blood pressure (dashed line) and low blood pressure (solid line). The bars show the 25th and 75th percentiles. The numbers of patients with estimated protein intake and blood-pressure measurements at each visit are shown below the panels. Urea nitrogen values are shown at selected times; mean arterial pressure is shown at selected visits when the glomerular filtration rate was not measured.

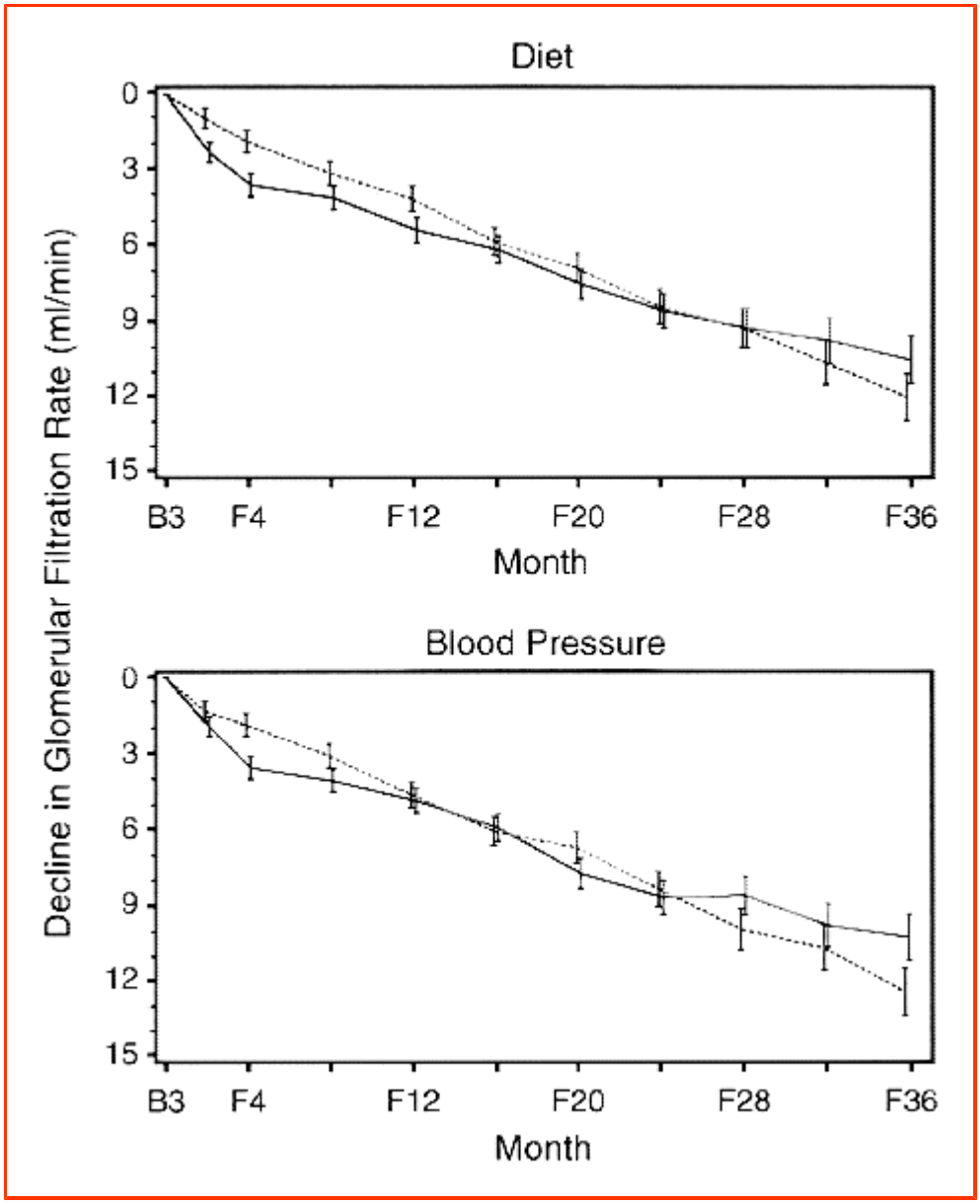

Figure 2. Estimated Mean (±SE) Decline in the Glomerular Filtration Rate from Base Line (B) to Selected Follow-up Times (F) in Study 1.

The upper panel compares the patients assigned to the usual-protein diet (dashed line) with those assigned to the low-protein diet (solid line). The lower panel compares the patients assigned to the usual-blood-pressure group (dashed line) with those assigned to the low-blood-pressure group (solid line). To correct for any bias introduced by stopping points, the mean declines were estimated by the maximum-likelihood method with a two-slope model for the covariance matrix of the serial measurements of the glomerular filtration rate.

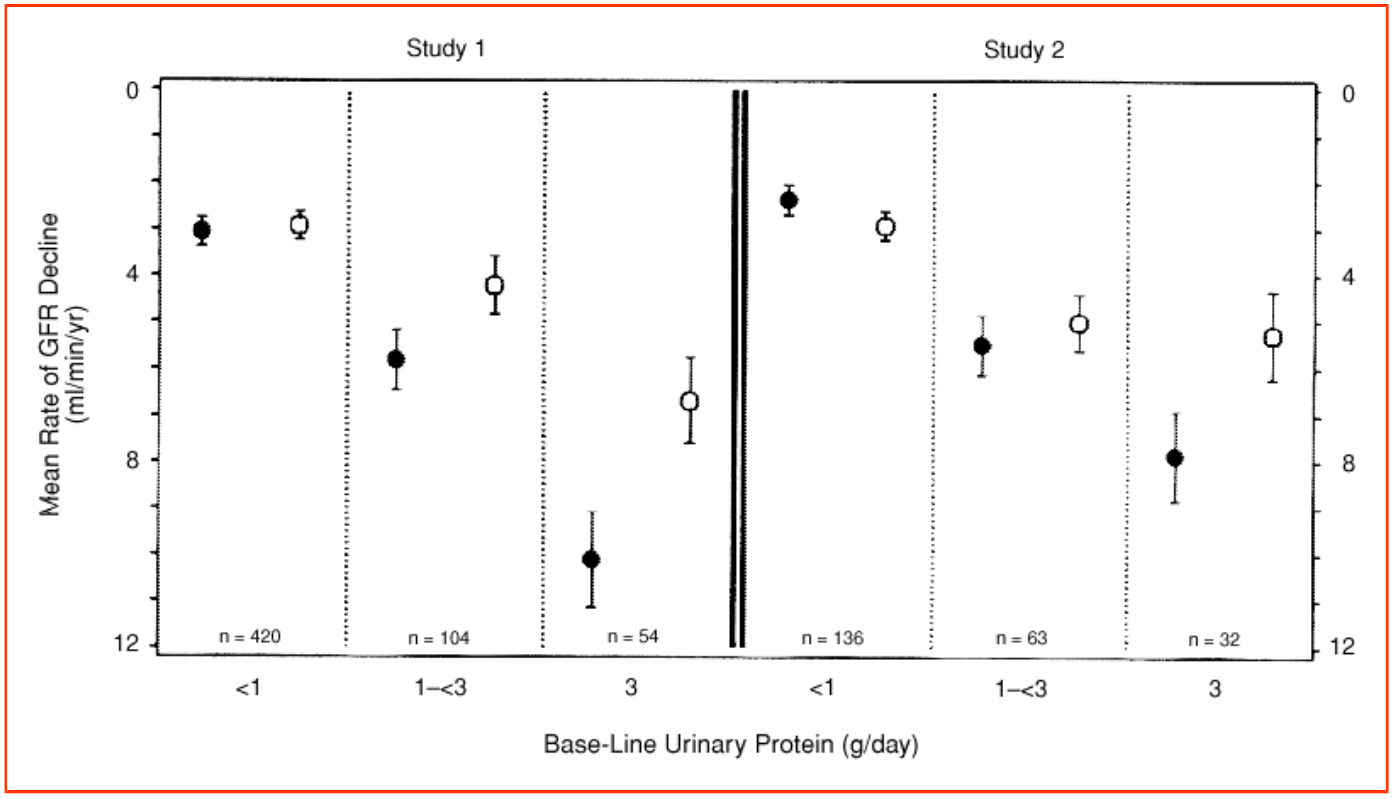

Figure 3. Decline in the Glomerular Filtration Rate (GFR) According to Base-Line Urinary Protein Excretion and Blood-Pressure Group in Studies 1 and 2.

The projected mean (±SE) rate of decline per year in the glomerular filtration rate from base line to three years, based on the two-slope model, is shown for study 1. The mean rate of decline in the glomerular filtration rate per year, estimated from the single-slope informative censoring model, is shown for study 2. The solid and open circles designate the patients with usual and low blood pressure, respectively. The number at the bottom of each panel indicates the total number of patients with follow-up glomerular filtration rate measurements in the two blood-pressure groups combined. A higher level of base-line urinary protein excretion was associated with a more rapid mean decline in the glomerular filtration rate and a larger difference in the mean rate of decline in the glomerular filtration rate between the two blood-pressure groups.

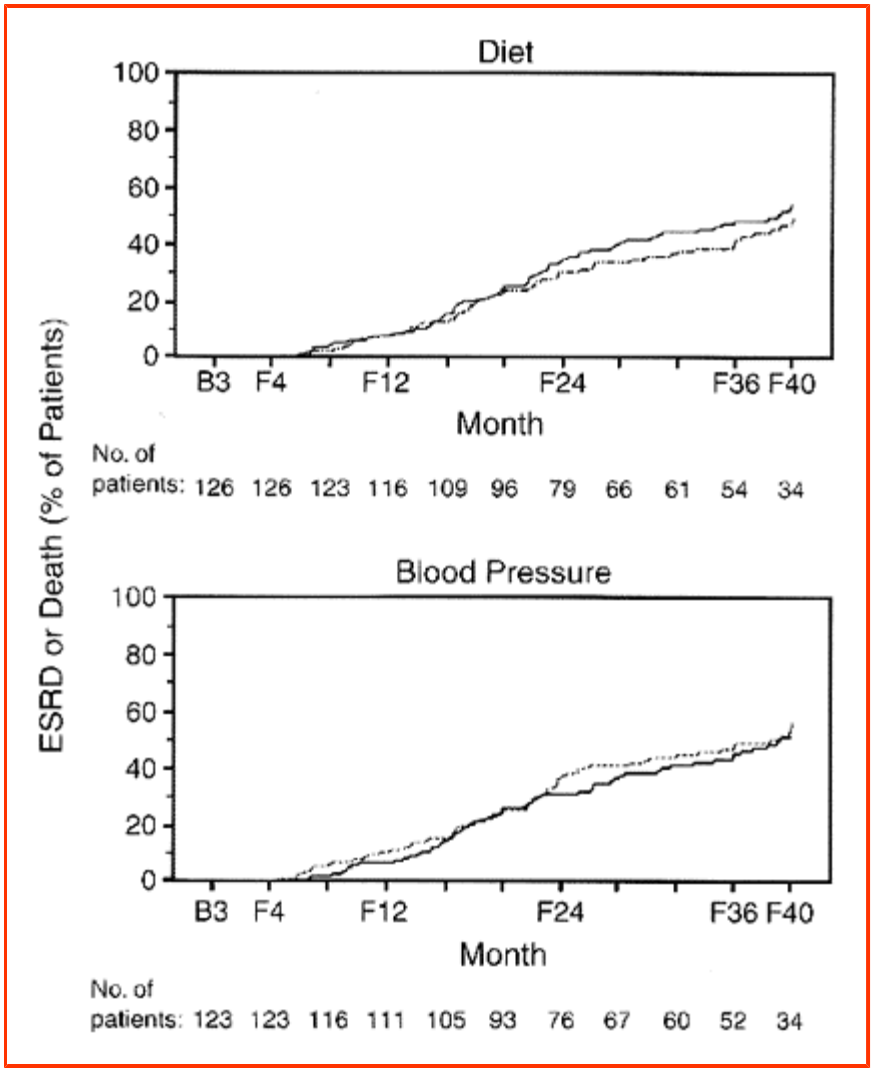

Figure 4. The Occurrence of End-Stage Renal Disease (ESRD) or Death in Patients in Study 2.

The upper panel compares the patients assigned to the low-protein diet (solid line) with those assigned to the very-low-protein diet (dashed-and-dotted line) (P = 0.62). The lower panel compares the patients in the usual-blood-pressure group (dashed line) and those in the low-blood-pressure group (solid line) (P = 0.33). The numbers below each panel indicate the total number of patients in the two groups being compared at each base-line (B) or follow-up (F) visit. The relative risk of ESRD or death was 0.93 (95 percent confidence interval, 0.65 to 1.33) for the patients assigned to the very-low-protein diet, as compared with those assigned to the low-protein diet and 0.85 (95 percent confidence interval, 0.60 to 1.22) for the patients in the low-blood-pressure group, as compared with those in the usual-blood-pressure group.