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Citizen Petition to FDA

Subject: Serious adverse effects including death associated with angiotensin converting enzyme inhibitor and angiotensin receptor blocker drug therapy

By

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CP1

Action requested:

Restriction or withdrawal of the use of angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) therapy in the following conditions.

1) Diabetes mellitus with uncontrolled hyperglycemia. Random blood glucose $\geq$ 200 mg/dl
2) Patients with diuretic therapy.
3) Diabetes mellitus with gastroparesis giving rise to vomiting.
4) Diabetic autonomic neuropathy with diarrhea.
5) Stable chronic renal failure in diabetic, hypertensive or congestive heart failure patients.
6) Elderly patients.
7) Debilitated patients with tube feeding.

Volume depletion in all of the above conditions potentiates ACEI or ARB induced acute renal failure (ARF).

Statement of grounds: Factual and legal grounds for petition

1. We did a study to examine whether ACEI alone induces ARF or whether it does so when used in combination with a diuretic. The purpose was to determine if diuretics potentiate ACEI-induced ARF. The medical records of patients taking ACEI without or with diuretics were reviewed. Complete data from 74 patients were obtained and the data were analyzed. These 74 patients had a diagnosis of hypertension, congestive heart failure (CHF) or diabetes mellitus. Blood urea nitrogen (BUN) and serum creatinine (Scr) values before, during and after discontinuation of ACEI therapy for a mean period of 8.7

months were collected. Seventy four patients were divided into two groups: Group A patients (n = 41) who received ACEI alone. Group B patients (n = 33) who received a combination of ACEI and a diuretic. ARF was defined by rise of Scr level of $\geq$ 0.5 mg/dl from the baseline level. ARF developed in 1 of 41 (2.4%) Group A patients compared to 11 of 33 (33%) Group B patients. This group difference was highly significant (P <.001). In Group A mean Scr before (1.24 $\pm$ .34 mg/dl) was identical to that (1.23 $\pm$ .33 mg/dl) after 8.7 of ACE therapy. Whereas in Group B post-therapy mean Scr (3.11 $\pm$ 2.27 mg/dl) was significantly higher (P < .01) than pre therapy mean Scr (1.65 $\pm$ 85 mg/dl). CHF patients had a higher rate of ARF than patients with other diagnoses. Renal function recovered to baseline upon discontinuation of combination therapy; saline infusion enhanced recovery. This study indicated that diuretics through sodium-volume depletion potentate the effect of ACEI to cause ARF (1).

2. For the past several years, increased numbers of patients are seen in consultation in the offices or hospitals who developed ARF or progression of chronic renal failure associated with use of ACEI or ARB. The prevalent underlying conditions are inadequately treated diabetes mellitus and hypertension. A total of 21 reports to that effect were faxed to MedWatch, thereafter to Dr. Mehul Desai in FDA. ACEI or ARB has the greatest impact in patients with uncontrolled hyperglycemia and in those treated with large doses of diuretics. Volume depletion is the underlying mechanism of the adverse effects of ACEI or ARB. Few patients are presented here to illustrate the problem of renal failure associated with ACEI or ARB. They may or may not have been included in the reports submitted to Med-Watch and Dr. Mehul Desai.

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Citizens Petition to FDA
An Addendum Serious side effects including death associated with angiotensin converting enzyme inhibitor and angiotensin receptor blockers drug therapy

C. Environmental Impact

There is no environmental impact in this petition

D. Economic Impact

Economic impact of the adverse effects of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) is very high. The economic impact is mainly due to hospital admissions for acute renal failure, hyperkalemia, metabolic acidosis and anemia. Hyperkalemia is the most dangerous one of all the complications of ACEI and or ARBs frequently requiring intensive care unit (ICU) admission.

Medicare pays on DRG basis between US $ 30,000 to 39,000 for each admission for acute renal failure. For each ICU admission, payment goes up to US $ 100,000 or more.

A patient not included in the petition had eleven hospital admissions in the ICU extending from February 21, 2000 to April 14, 2001 (total period = 14 months) for congestive heart failure (CHF) and progressive renal failure. Progressive renal failure and hyperkalemia was precipitated mainly by the excessive use of ACEI. He initially refused hemodialysis but later on agreed. In his final days, hemodialysis could not be preformed because of extremely low blood pressure which could not be revived. The total payments to the hospital for 11 admissions were US $ 474,000. Doctors fees, laboratory test, radiologic procedure and hemodialysis were not included in the hospital payments. Estimated total cost was US $ 1 million. In the United States alone, over 10 billion dollars are spent annually for CHF patients, two-thirds of which go to pay for hospitalization. Excessive use of ACEI and or ARB in CHF patients make them worse because of concomitant deterioration

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of renal function with the use of these agents resulting in repeated hospitalizations. Therefore it all comes down to hospitalization which is the most expensive part of health care. Who pays for these costs; taxpayers like you and me. These hospital admissions could have been largely prevented if ACEI or ARB was not used at all.

Petitioner finds no benefit from the use of these drugs in diabetes and CHF patients. These agents make the above patients only worse and force them to go to hospital for symptomatic relief. Why then use these drugs? As the petitioner understands that the main motive of the use of these drugs is to make pharmaceutical companies to become from rich to richer at the expense of tax payers money and patients health and life.

It is time that FDA acts on the above soon and save patients from further calamity.

Dr Anil K. Mandal

PATIENT ILLUSTRATIONS

PATIENT #1

DW, a 46-year-old African-American female, full-time employee, gave a history of hypertension of three years duration. As of July 10, 2001, her serum chemistry and hemoglobin were normal. On September 27, 2001, her primary care physician prescribed lisinopril (prinivil ®) 20 mg PO daily and hydrochlorothiazide 25 mg daily. Her other medications included premarin 0.625 mg PO daily and synthroid 175 mcg PO daily. On December 30, 2001, she was admitted to a hospital for nausea, vomiting, dizziness and low urine output. The results of serial laboratory studies are presented below. She developed ARF. Her BUN and serum creatinine increased by 5-6 times above normal levels. She also became anemic (Hb = 10.5 g/dl)A renal consultation was taken. Lisinopril and hydrocholorothiazide were discontinued. She was treated with normal saline infusion. Clonidine 0.1 mg PO TID was prescribed for blood pressure control. Her symptoms remitted with improvement of renal function. As of January 1, 2002 she was discharged from the hospital and followed up in the petitioner's office. Her renal function and hemoglobin returned to normal within six weeks. She underwent coronary arteriogram and renal arteriogram. Coronary arteries and renal arteries were normal.

Serial Serum Chemistry During and After ACE Inhibitor Therapy

Date	**BUN** mg/dl	**Cr** mg/dl	**Na** mEq/L	**K** mEq/L	**C1** mEq/L	**Co2** mEq/L	**Glu** mg/dl	**Hb** g/dL
Jul 10/01	*11*	*0.8*	140	3.5	106	23	116	11.9
	Lisinopril and hydrochlorothiazide started							
Dec 30/01	*67*	*5.6*	130	4.5	97	19	103	10.9

Lisinopril and hydrochlorothiazide discontinued

Dec 31/01	*46*	*2.6*	135	4.5	103	NA	NA	NA
Jan 01/02	*32*	*1.5*	135	4.6	105	19	110	10.5
Feb 18/02	*16*	*0.9*	134	3.7	100	24	97	12.9

BUN = blood urea nitrogen, Cr =Serum creatinine, Glu = Serum glucose, Hb = Hemoglobin, NA = Not availaible

PATIENT #2

A 67-year-old African-American female was admitted to a local hospital on January 29, 2002, for severe shortness of breath and weakness. Her significant medical history included diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and chronic renal failure. Medications at the time of hospital admission included: synthroid 50 mcg PO daily, actos 45mg PO daily. Novolin 70/30, 30 units am and 20 units pm, neurontin 600 mg PO BID, irbesartan (Avapro ®) 150 mg PO BID, furosemide 80 mg am and 40 mg pm, metolazone 2.5 mg PO daily, vioxx 25 mg PO daily, premarin 0.625 mg PO daily, albuterol inhalation as needed. A serum chemistry showed marked elevation of glucose, BUN, and serum creatinine. A renal consultation was taken. Irbesartan, lasix and metolazone were discontinued. Vioxx was continued for her arthritis. She was treated with normal saline infusion and potassium supplements. Clonidine 0.05 mg PO BID was prescribed for blood pressure control. On February 02, 2002 she was discharged from the hospital. On February 05, 2002, irbesartan, furosemide and metolazone were restarted. On February 18, 2002, they were discontinued. A comprehensive summary of serum chemistry is presented below.

Serial Serum Chemistry During and After ACE inhibitor or ARB Therapy

Date	BUN mg/dl	Cr mg/dl	Na mEq/L	K mEq/L	Cl mEq/L	CO2 mEq/L	Glu (F) mg/dl
Jan 05/01	*35*	2.6	137	3.7	102	30	151
	Irbesartan, lasix and metolazone started						
Jan 29/02	*86*	5.8	134	3.3	89	35	800
	Irbesartan, lasix and metolazone discontinued						
Jan 30/02	91	5.6	132	3.3	88	34	288
Jan 31/02	*73*	4.8	137	3.6	97	34	111
Feb 02/02	*52*	4.2	136	4.9	102	27	101
	Irbesartan, lasix and metolazone restarted						
Feb 11/02	*69*	4.4	139	5.0	102	27	95
Feb 18/02	Irbesartan, lasix and metolazone discontinued						
Mar 11/02	*36*	2.8	136	4.7	102	26	109
May 07/02	*44*	2.9	139	4.0	103	31	111
Apr 14/03	35	2.8	138	4.2	99	34	236
Nov 17/03	37	2.7	141	3.9	102	27	139
Feb 06/06	30	3.1	142	4.9	104	30	209

Cr = serum creatinine, F = fasting

Her 24-h proteinuria, creatinine clearance and serum creatinine before and after irbesartan are presented next.

Date 2000	**Proteinuira (g/24h)**	**Ccl (ml/min)**	**Serum Cr (mg/dl)**
2000	>4 g	37	NA
	Irbesartan started		

Mar 01/01	NA	23	2.6
Jan 29/02	Irbesartan discontinued		
Feb 01/02	2.4	25.7	4.2
Feb 27/02	2.7	37.4	2.8
Jan 19/03	1.8	25	2.8
Nov 17/03	2.6	29	2.7

Ccl = creatinine clearance , Serum Cr = serum creatinine, NA= Not available

ANALYSIS

Patient has had chronic renal failure with stable renal function, normal serum potassium and elevated fasting glucose. By taking irbesartan along with high does of diuretics her renal function markedly deteriorated. Her glucose was markedly elevated and serum potassium decreased. Upon discontinuation of irbesartan and diuretics, her renal function rapidly improved. Upon restarting irbesartan and diuretics, her BUN increased by 17 mg/dl in 5 days. Renal function returned to almost baseline within 3 weeks of discontinuation of irbesartan and diuretics. Since then her renal function has remained essentially unchanged from the baseline level despite proteinuria. Her blood glucose control is optimum to less than optinum

Patient #3

A 54-year-old African-American female, gives history of hypertension of one-year duration, history of borderline diabetes, and history of congestive heart failure. She was seen in consultation in petitioner's office in late December 2001. Physical examination was negative except for obesity. Her blood pressures were 130/70 mmHg. Her medication included furosemide 40 mg PO daily, sertraline (Zoloft ®) 100mg PO daily,

atrovastatin (lipitor ®) 10 mg PO daily, carvedilol (coreg ®) 3.1 mg PO daily, nitroglycerin sublingually PRN. Her BUN, serum creatinine and electrolytes serially are shown next.

Serial Serum Chemistry During and After ACE Inhibitor Therapy

Date	**BUN** mg/dl	**Cr** mg/dl	**Na** mEq/L	**K** mEq/L	**C1** mEq/L	**CO2** mEq/L
	Enalapril. spironolactone started					
Oct 29/01	*84*	*2.5*	137	7.2	110	15
	Enalapril. spironolactone discontinued					
Nov 09/01	*76*	*2.3*	138	5.7	112	19
Jan 10/02	*23*	*1.3*	141	4.2	104	29
	Ramipril and atacand started					
Feb 27/02	*55*	*1.7*	142	5.4	109	24
	Ramipril and atacand discontinued					
May 24/02	*43*	*1.6*	137	4.2	103	21
Aug 26/02	*35*	*1.5*	140	4.5	106	27
Jul 21/03	*25*	*1.4*	137	3.9	104	24
Mar 22/04	*25*	*1.1*	135	4.0	100	26
July 17/06	*34*	*1.5*	140	3.7	103	26

Cr = serum creatinine

ANALYSIS

It was intriguing to find markedly elevated BUN, serum creatinine and serum potassium and reduced CO_2 (metabolic acidosis) which could not be explained by the current therapy at the time of office visit in December 2001. Therefore, the patient was asked if she was taking one of these medicines previously: enalapril, lisinopril, or ramipril, which might have been discontinued by the primary care physician after noting the abnormal laboratory values in October and November 2001. Patient went home, looked at her discontinued medicine list, and informed petitoner's office that prior to October 29, 2001, she was taking enalapril 5 mg PO BID, spironolactone 25 mg PO TID, micro K 10 mEq PO daily, but they had been discontinued. As of January 10, 2002 her renal function and serum potassium were normal. Since patient couldn't afford to buy prescription blood pressure medicine, such as clonidine and amlodipine, she received samples of ramipril (altace ®) 5 mg PO daily and atacand 32 mg PO daily from the primary care physician's office in late January 2002. As of February 27, 2002 she showed elevation of BUN, and serum creatinine and potassium levels. At an office visit on March 6, 2002, ramipril and atacand were discontinued. In May 2002, she received Medicaid which permitted her to obtain prescription medicine of amlodipine and dyazide (triamterene hydrochlorothiazide 37.5/25) for blood pressure control . Since then her renal function and serum potassium level have remained at normal or near normal levels. It should be noted that her renal function in terms of BUN and serum creatinine on July 17, 2006 is no different from that three years ago on August 26, 2002.

PATIENT # 4

A 75-year-old white male gives history of diabetes and hypertension for many years. On March 27, 2002 he was admitted to a local hospital for gastrointestinal bleeding. Medication included lisinopril 10 mg PO BID, furosemide 40 mg PO daily, and insulin as required. He was previously admitted to a hospital for renal insufficiency. At that time, medication included lisinopril 5 mg PO daily and furosemide 20 mg PO daily. His BUN was 33 mg/dl and serum creatinine 1.9 mg/dl. Nephrology consultation was taken when lisinopril was discontinued. Lisinopril 10 mg PO BID was restarted by primary care physician. Lisinopril and furosemide were discontinued upon hospital admission. Serial laboratory results are presented next.

Serial Serum Chemistry During and After ACE Inhibitor Therapy

Date	**BUN** mg/dl	**Cr** mg/dl	**Na** mEq/L	**K** mEq/L	**C1** mEq/L	**Co_2** mEq/L	**Glu** mg/dl	**Hb** g/dL	**Hct** %
Mar 27/02	*128*	*3.9*	139	7.4	107	19	341	8.4	26.4
	Lisinopril and furosemide discontinued								
Mar 28/02	*110*	*3.1*	147	5.0	112	23	141	9.2	28.4
Mar 29/02	*92*	*2.2*	148	4.1	114	20	152	8.9	28.4
Mar 30/02	*68*	*1.8*	144	4.3	NA	NA	NA	9.3	29.0

Cr =Serum creatinine, Hct = Hematocrit, NA = Not availaible , Hb = hemoglobin

Endoscopy showed bleeding duodenal ulcer. Markedly elevated BUN most likely precipitated bleeding from duodenal ulcer. He received packed cell transfusion, normal saline infusion, and sliding-scale Humulin N coverage. Kayexalate and 9 alpha

fluorohydrocortisone (Florinef)were prescribed for hyperkalemia. His renal function improved and hyperkalemia resolved. He was discharged from the hospital with the advice for office follow up by the consulting nephrologist.

PATIENT # 5

A 70 years white male was admitted to a local hospital not feeling well. Past medical history included blackout spells and chest pain, right upper lobe pneumonectomy in 1992, and removal of $4/5^{th}$ stomach in 1969. Heart catheterization in 2003 was normal. His blood pressures were in the range of 93/57 mmHg sitting and 78/45 mmHg lying. Medication included irbesartan, nitroglycerine, furosemide, minoxidil, and K-dur.

Serial Serum Chemistry During and After ACE Inhibitor Therapy

Date	**BUN** mg/dl	**Cr** mg/dl	**Na** mEq/L	**K** mEq/L	**C1** mEq/L	**Co_2** mEq/L	**Glu** mg/dl	**Hb** g/dL	**Hct** %
Apr 26/03	*58*	*3.1*	132	5.6	99	20	252	12.3	37.5
Apr 28/03	*71*	*3.1*	128	3.4	101	23	34	NA	NA
May 28/03	*21*	*1.3*	141	4.9	101	24	109	11.1	34.3

Cr = serum creatinine, NA = not available Hb = hemoglobin, Hct = hematocrit

All of the above medications except nitroglycerine were discontinued. 5% dextrose in half-normal saline infusion was given at 60 ml/h for 48 hours. On May 2, 2003, he was discharged from the hospital and asked to follow up in petitioner's office. A serum chemistry on May 28, 2006 showed normal renal function and electrolytes, and normal glucose. Anemia is noted. On June 6, 2003, in an office visit, he denied any complaint and felt very well. His medication at the time of office visit included verapamil 260 mg

PO daily, bicitra 20 ml PO TID for metabolic acidosis, and procrit injection, 6,000 units once a week for anemia.

PATIENT # 6

68 years white female was first seen in the petitioner's office on October 21, 1999. She gave a long history of diabetes and hypertension. Her weight ranged from 250-260 lb. Her blood pressure was 240/140 mmHg. Her medication consisted of novolin, clonidine patch and furosemide. Her serum creatinine was 1.2 mg/dl, creatinine clearance was 76 ml/min and 24 h proteinuria 7060 mg. Enalapril 10 mg PO daily was prescribed. On November 22, 1999 she was admitted to a local hospital with extreme dizziness and perspiration. Her blood pressure was 180/100 mmHg. Her medication consisted of clonidine 0.2 mg PO BID, amlodipine 5 mg PO BID, enalapril 10 mg PO daily, furosemide 20 mg PO daily, metolazone 5 mg PO daily and novolin 45 units in the morning and 40 units in the evening. Laboratory studies revealed serum creatinine 1.5 mg/dl, creatinine clearance 20.4 ml/min, 24 h proteinuria 3133 mg, fasting serum glucose was 190 mg/dl. On January 14, 2000, patient had a office visit. She felt well, her blood pressure was 150/90 mmHg. Her laboratory studies consisted of fasting glucose 103 mg/dl, serum creatinine 1.1 mg/dl, creatinine clearance 88 ml/min and 24 h proteinuria 4095 mg. As of March 24, 2004, she felt fine, her blood pressure was under good control. Laboratory studies showed BUN 23 mg/dl, serum creatinine 1.3 mg/dl, fasting glucose 76 mg/dl, creatinine clearance 59 ml/min and 24 h proteinuria 647 mg.

Analysis of findings

This patient illustrates that intensive blood pressure (BP) control in diabetic patients is of paramount importance in reducing proteinuria and preserving renal function. She takes

enalapril, an ACEI concurrently with other antihypertensive drugs to keep her BP under tight control. Her renal function as of 2004 has decreased compared to that in 2000 showing negative effect of enalapril. Blood pressure control is the target goal in this patient therefore enalapril is continued. Several studies have shown that intensive blood pressure control reduces proteinuria and protects renal function independent of agents used (2,3).

Patient #7

A patient who was seriously ill due to intake of lisinopril is presented here. This is a 51 years white female who was admitted to a local hospital on May 20, 2006 through emergency room with the complaints of increased shortness of breath and anuria (no urine output). Her renal function was normal in the past. She is obese and exhibits gross pitting edema in the lower extremity bilaterally. Her medication consisted of 1) Plavix, 2) Imdur, 3) Simvastatin, 4) Lisinopril. She showed metabolic acidosis. Her arterial blood pH was 7.27, HCO_3 17.4 mEq/L and anion gag 23. She developed anuric acute renal failure with a BUN of 97 mg/dl and serum creatinine of 4 mg/dl. Lisinopril was discontinued. All other medications continued. She was treated with lasix rip and bicarbonate infusion for several days. She made full recovery of kidney function and was discharged from the hospital to a nursing home. Here are here serial serum chemistry.

Date 2006	**BUN (mg/dl)**	**Cr (mg/dl)**	**Ccl (GFR) (ml/min)**	**Na (mEq/L)**	**K (mEq/L)**	**CO_2 (mEq/L)**
5/20	97	4.0	13	137	4.8	16
Lisinopril discontinued. Lasix and bicarbonate infusion started-Prompt increase in urine output-reached several liters daily.						
5/21	75	1.9	30	141	4.1	22

5/22	58	1.2	NA	142	3.0	27
5/23	49	1.2	50	144	3.3	34
5/24	27	1.0	62	143	3.1	38
Lasix and bicarbonate infusion discontinued.						
6/02	22	0.9	118	137	4.2	24

Cr = serum creatinine, Ccl = creatinine clearance, GFR = Glomerular filtration rate, Na = serum sodium, K = serum potassium

Patient # 8

NC 47 years white male was admitted to a hospital for Groshong Catheter malfunction on June 23, 2006. He was found to have acute renal failure. His medication consisted of lisinopril 5 mg PO daily, Coreg, Lasix, Lipitor, Tricor. Lisinopril and lasix were discontinued by the primary care physicians. Two days later, his renal function returned to normal. Serum K decreased indicating spurious elevation of K by lisinopril.

DATE 2006	**BUN (mg/dl)**	**Cr (mg/dl)**	**Na (mEq/L)**	**K (mEg/L)**	**CO_2 (mEq/L)**	**Glu (mg/dl)**
6/18	15	0.6	NA	NA	NA	NA
6/23	52	2.2	132	4.6	19	237
Lisinopril and lasix were discontinued. Normal saline infusion given						
6/25	22	1.0	132	3.5	26	157

Cr = serum creatinine, Glu = serum glucose.

The adverse effect events associated with employment of ACEI and ARB have continued to grow and reached an epidemic proportion. To that effect, it is important to note that the petitioner saw ACEI/ARB adverse effects in three patients in a single day July 19, 2006 and four patients on August 12, 2006.

Several patients are presented here to reveal the magnitude of the problem.

Patient # 9

A 68 years white female was referred by a cardiologist to a nephrologist for renal problem. She gave history of hypertension and developed stroke with right sided hemiparesis in 2003. Her first visit with the petitioner was on June 19, 2006 and the second visit was on July 18, 2006. Her medication at the time of first visit were plavix 75 mg PO daily, aspirin, hydrochlorothiazide 12.5 mg PO daily, prevacid 20 mg PO daily, avapro (ARB) 150 mg PO twice daily, metoprolol 50 mg daily, clonidine patch once weekly, caduet (combination of amlodipine and lipitor) 5/10 daily. Her blood pressure was 130/80 mmHg. She is wheelchair bound, difficult to examine for abdominal bruit for renal artery stenosis. A bruit was heard in the carotid artery bilaterally. Her laboratory are shown below. She developed ARF as shown by elevation of BUN and Scr from baseline values on 12/19/04

Date	**BUN (mg/dl)**	**Scr (mg/dl)**	**Na (mEq/L)**	**K (mEq/L)**	**CO_2 (mEq/L)**	**Glucose (mg/dl)**	**GFR (ml/min)**
12/19/04	16	1.1	138	4.0	23	112	
4/25/06	40	2.1	138	4.7	22	101	26

Avapro was discontinued on 6/19/06 Hydrochlorothiazide 12.5 mg changed from daily intake to Monday, Wednesday, Friday regimen. Returned to office 7/18/06 BP was 140/80mmHg.

7/18/06	12	0.9	145	3.9	25	111	NA

Her renal function recovered to normal range after discontinuation of avapro.

Scr = serum creatinine , NA = not available

Life threatening hyperkalemia with cardiotoxicity caused by ACEI ramipril requiring immediate hemodialysis is presented here.

Patient # 11

JC, 79 years African American male was admitted to a local hospital on August 7, 2006 through the emergency room. He went to a clinic of another hospital in Jacksonville, Florida for aranesp injection for chronic anemia, when he was found to be very weak. A blood sample was drawn for serum chemistry which showed severe renal failure and hyperkalemia. He was sent to the emergency room. He has a long history of hypertension, peripheral vascular disease and chronic metabolic acidosis.

Medication:

1) Flomax 0.4 mg P.O. Daily
2) Doxazosin 4 mg P.O. B.I.D.
3) Colchicine 0.6 mg P.O. Daily
4) Lopressor 50 mg P.O. B.I.D.
5) Altace (Ramipril) 10 mg P.O. B.I.D.
6) Sodium bicarbonate 2 tablets B.I.D.

7) Chromagen forte (iron) 1 tablet daily

8) Aranesp as per schedule

Blood pressure 158/62 mmHg. He also gave history of recent diarrhea x 3-4 days.

Laboratory

Date 2006	**BUN** (mg/dl)	**Cr** (mg/dl)	**Na** (mEq/L)	**K** (mEq/L)	**CO_2** (mEq/L)	**Hb** (g/dl)
8/07	115	5.6	NA	6.4	NA	
8/07	96	5.6	138	7.3	9	14.3

Alltace was discontinued. Heparin 5000 units subcutaneously every 12 h was added.

Hemodialysis x 1 was done

8/13	30	1.7	136	3.9	23	10.5

NA= Not available

Analysis of the findings

Patient developed progressive renal failure accompanied by severe hyperkalemia and severe metabolic acidosis. Hyperkalemia was associated with cardiotoxic effect as shown by peaked T wave in the electrocardiogram. Emergency hemodialysis x 1 was done to avert severe adverse effects of hyperkalemia and metabolic acidosis.

All these adverse effects are common to ACEI. Therefore ramipril caused slowly progressive renal failure shown in his medical record. Then volume depletion from recent onset of diarrhea probably caused by colochicine aggravated renal failure and metabolic acidosis. However, severe hyperkalemia is unique to ACEI, (ramipril). Hyperkalemia is further aggravated by metabolic acidosis. Severe renal failure, metabolic acidosis and life

threatening hyperkalemia abated upon discontinuation of ramipril assisted by hemodialysis treatment.

Patient # 12

HT, 81 years white female was admitted to a local hospital on August 8, 2006 with an admitting diagnosis of acute renal failure (ARF). Her medication consisted of lopressor 50 mg P O daily, plavix 75 mg daily and diovan 20 mg daily. Patient was seen by the petitioner on August 12, 2006. Patient was not symptomatic but very frightened and asked me if she had to go to dialysis. She had a history of diarrhea for 3 months prior to hospital admission. Her laboratory studies showed that she had acute renal failure, hyperkalemia and severe anemia. Diovan was discontinued on 08/12/06 and she was treated with bicarbonate infusion at 60 ml/h and epogen 10,000 units subcutaneously every other day. Petitioner assured her that it is very unlikely that she has to go to dialysis. Details of the laboratory studies are shown below.

Date 2006	**BUN (mg/dl)**	**Cr (mg/dl)**	**Na (mEq/L)**	**K (mEq/L)**	**CO_2 (mEq/L)**	**GFR (ml/min)**	**Hb (g/dl)**
08/08	58	2.3	132	5.7	23	21.6	7.8
08/09	57	2.2	134	5.6	24	23	NA
08/11	49	2.1	134	5.0	30	24	N
08/12	53	2.5	138	5.7	30	20	8.6
Diovan discontinued, bicarbonate infusion and epogen started							
08/13	60	3.1	135	5.8	29	15	9.3
Florinef (9, alpha fluorohydrocortisone) for hyperkalemia started							
08/14	52	2.4	140	5.0	31	21	8.1
08/15	41	2.0	138	5.1	29	25	9.3

08/16	27	1.5	138	4.3	27	35	10.2

NA = Not available, GFR = Glomerular filtration rate

Here is 81 years woman who developed severe acute renal failure rapidly reaching GFR of 15 ml/min, accompanied by moderately severe hyperkalemia and severe anemia. Volume depletion as a result of diarrhea potentiated ARB induced ARF (1). Discontinuation of diovan accompanied by bicarbonate infusion resulted in recovery of renal function and assurance of no dialysis treatment. GFR is still low but is likely to increase further. Severe anemia is due to decreased erythropoietin production caused by diovan.

Analysis of the observations

The patients profile presented here indicate that ACEI or ARB or a combination of both causes ARF or progression of stable chronic renal failure. The onset of ARF related to these agents can be traced in some cases but not in others. However, one thing is certain that discontinuation of these agents invariably results in recovery of renal function to baseline levels in two to 4 weeks. Fluid therapy in the form of normal saline infusion with sodium bicarbonate at a rate of 50 to 60 ml/hr for a few days hastens recovery. This recovery of renal function without the use of ACEI or ARB constitutes an unequivocal evidence that ARF was caused by ACEI or ARB or a combination of both.

Most of these patients illustrated here were taking a diuretic in addition to ACEI or ARB. supporting further that a diuretic potentiates ACEI-induced ARF which was reported by petitioner earlier (1).

It will be interesting for FDA to know that none of the consultation requests for ARF associated with ACEI or ARB ever state as such. Consultation requests show

hemodynamic-ARF or ARF caused by dehydration. However, the requesting physician in a private conversation agree that ARF was due to ARB or ACEI.

The petitioner has been told by the requesting physicians that they feel nervous by putting in record about ACEI or ARB as a probable cause of ARF for fear of malpractice

ARF is commonly associated with hyperkalemia, metabolic acidosis and anemia. The target population of these complications are patients with diabetes mellitus, hypertension and congestive heart failure.The risk of ARF is very high in diabetic patients with uncontrolled hyperglycemia, in patients treated with one or more diuretics for hypertension, CHF and in patients with preexisting chronic renal failure. A common feature is loss of body fluid from osmotic diuresis as in uncontrolled hyperglycemia, from diuretic therapy, or from inability to concentrate urine as in chronic renal failure. Loss of body fluid is associated with low to very low blood pressure as in patient #5. Blood pressure is directly related to renal blood flow (RBF) and glomerular filtration rate (GFR). Low BP gives rise to low RBF and low GFR. Hypotension triggers angiotensin II production which helps to maintain BP, and hence RBF and GFR. ACEI or ARB reduces angiotensin II thereby reduces BP further with reduction of RBF and GFR and resulting in azotemia. Normal saline infusion expands intravascular volume, increases BP and consequently increases RBF and GFR. Increase in GFR promotes excretion of urea and creatinine thereby normalizing BUN and serum creatinine levels. In these situations BUN rises much more than serum creatinine. This above scenario is illustrated in this patient presentation.

Patient # 13

A 68 years old white female was seen in petitioner's office on March 31, 2006 after consultation in a hospital. She was admitted for edema and low serum albumin. She was treated with lasix and albumin infusion. She did well and discharged from the hospital. Her medications were 1) potassium chloride 10 mEq P.O. twice daily, 2) bumetaride (Bumex) 1 mg P.O. twice daily, 3) metolazone 2.5 mg P.O. once daily, 4) enalapril 10 mg P.O. once daily.

Laboratory

Date 2006	**BUN (mg/dl)**	**Cr (mg/dl)**	**Na (mEq/L)**	**K (mEq/L)**	**CO_2 (mEq/L)**	**Glucose (mg/dl)**
5/12	32	0.9	134	4.2	32	88
enalapril discontinued for elevated BUN Norvasc 5 mg P.O. daily started for BP control						
7/09	20	0.7	138	4.0	35	79

She had elevated BUN but normal serum creatinine level. In less than two months, her BUN decreased to normal level and serum creatinine decreased further. BUN elevations were disproportionately higher than serum creatinine elevations in patients #3 and #4. BUN data were not presented in any clinical studies. BUN and serum creatinine levels together provide a better estimation of overall renal function than serum creatinine alone. Diabetic patients who have developed diabetic nephropathy manifest proteinuria, low serum albumin and peripheral edema. They are the target candidates for ACEI or ARB therapy. Clinical trials claim that these agents retard the progression of nephropathy to end stage renal disease ESRD (4). Many large studies have shown that intensive glucose control with insulin is fundamental to prevention of diabetic microvascular complications including nephropathy (5-7). Most clinical trials on ACEI or ARB have omitted data on

glucose control (4,8,9) to hide the truth that glucose control is fundamental to renal protection as well help pharmaceutical companies to sell their products. (see attachment). Without information on glucose control either by fasting blood glucose, 2h postpradial blood glucose or HbA1c levels, it is difficult to validate if ACEI or ARB is beneficial in diabetes. For instance data in a study which brought the wave of benefit of ACEI or ARB can be challenged. In that study, both placebo and captopril treated groups had initial HbA1c level of 11.6% suggesting severe uncontrolled hyperglycemia. Thereafter during 4 years of trial, no further information was provided as to how were these two groups treated: insulin, oral agents or both. No information was provided about their glycemic control throughout the trial period. How can one not be suspicious that surreptitious good glycemic control in the selective captorpil group compared to poor glycemic control in the placebo group made the two groups different (4). Further the statistical difference, between the two groups was marginal. It appears that the trial was intended to help Bristol-Myers to sell their product.

Variable degree of proteinuria is common in diabetic nephropathy. Proteinuria is related to glycemic control. The Stockholm study has shown that intensive insulin therapy significantly reduces proteinuria compared to low dose or conventional insulin therapy (10).

ACEI or ARB or a combination of both is almost invariably prescribed to reduce proteinuria without little or no attention to glycemic control. ACEI or ARB reduces proteinuria but it does so only at the expense of reduction of creatinine clearance (Ccl) or GFR. Figure 1 illustrates this scenario, ND a 65 years white male gives a history of diabetes mellitus for 23 years and is treated with Humulin N insulin. Glucose control was

inadequate. In October 2001, his fasting glucose was 203 mg/dl and showed hard exudates and microaneurysm in left eye. He was placed on enalapril orally 10 mg daily for heavy proteinuria in October 2001. Proteinuria decreased to 8324 mg/24h as well as Ccl to 87 m/min as of December 2001. Discontinuation of enalapril resulted in increase of proteinuria to 13476 mg/24h and Ccl to 105 ml/min as of January 2002. Serum creatinine (Scr) was 2.0 mg/dl. Enalapril 5 mg orally daily was reinstituted which was subsequently increased to 20 mg daily. On November 2002 proteinuria decreased to 6443 mg/24h and Ccl to 59 ml/min. Serum creatinine was 2.5 mg/dl. Enalapril was discontinued. Again proteinuria increased to 13813 mg/24h but Ccl increased only modestly to 76 ml/min Scr decreased slightly to 2.4 mg/dl. Enalapril of 10 mg/day was reinstituted. On February 28, 2003 proteinuria decreased again to 6048 mg/24h, so did Ccl to 46.2 ml/min. Scr increased to 2.8 mg/dl. Enalapril was discontinued. Since March 2003, he refused to take enalapril any further. He controls his glucose adequately with insulin injections several times daily and keeps blood pressure under adequate control by medication as prescribed. As of April 19. 2005 proteinuria has spontaneously decreased to 2209 mg/24h, Ccl has remained unchanged at 46 ml/min. Scr decreased slightly to 2.5 mg/dl. As of March 27, 2006 proteinuria has decreased further to 2070 mg/24h and Ccl increased to 50 ml/min. Scr is essentially unchanged at 2.6. mg/dl. His fasting glucose was 102 mg/dl and 2 h postprandial glucose was 143 mg/dl. HbAlc was 7.9%. He feels fine and engergetic and works full time in his business. This patient illustrates that good glycemic control reduces proteinuria and preserves renal function as opposed to ACEI or ARB which reduces proteinuria at the expense of GFR.

Overall assessment and justification of request for restriction of use or withdrawal of use of ACEI or ARB in diabetic nephropathy

The representative sample of patients presented here provides an unequivocal evidence that ACEI or ARB causes acute renal failure and progressive culmination of stable chronic renal failure into ESRD. The risk of renal failure is high when glucose control is poor or associated with diuretic therapy. ARF is often accompanied by hyperkalemia, metabolic acidosis and anemia. All of these complications require hospital admission for aggressive management with escalating cost of health care. Further, hyperkalemia and metabolic acidosis have a high risk of causing pulmonary edema and cardiac arrest with sudden death. Severe hyperkalemia including death is not unknown in dialysis patients treated with ACEI or ARB drugs. A patient is presented here to demonstrate just that.

Patient # 14

A 26 years African American female was admitted to a local hospital on July 28, 2006 with a history of markedly elevated blood glucose and rectal bleeding after a maintenance hemodialysis treatment. She gave history of diabetes mellitus since age 13 and was treated with 70/30 insulin 30 units subcutaneously in the morning and 20 units subcutaneously in the evening. Her glucose control had been poor all the time requiring frequent hospitalization. She developed nephrotic syndrome with 24 hours proteinuria of 11 g. She was prescribed enalapril 20 mg P.O. twice daily and Cozaar (losartan) 50 mg P.O. daily which she was taking as per medication list till the day of last hospital admission. Other medication consisted of diltiazem 240 mg P.O. daily, labetalol 300 mg

P.O. daily, zocor 80 mg daily, catapres patch 3 once a week. In emergency room she was alert but poorly conversed. Her blood pressure was 154/55 mmHg. Her serum chemistry at 14:30 hrs showed sodium 123 mEq/L, **potassium** 6.8 mEq/L, chloride 89 mEq/L, carbon dioxide 20 mEq/L, glucose 1010 mg/dl, BUN 88 mg/dl, serum creatinine 8.3 mg/dl, calcium 7.8 mg/dl, magnesium 2.2 mg/dl, hemoglobin 7.7 g/dl, hematocrit 25.3%. She was treated with insulin infusion in the emergency room. At 16:30 hrs, instant hemodialysis was ordered but it took approximately 3 hours to initiate hemodialysis with 0 (zero) potassium in the bath. Within 45 minutes of hemodialysis, she had tonic-clonic convulsion followed by cardiac arrest. She was resuscitated with return of pulse and blood pressure but lasted only for a few minutes. Second resuscitation was unsuccessful. **She expired 10 pm on July 28, 2006**. A blood sample drawn for serum chemistry just before cardiac arrest showed sodium 141 mEq/L, potassium 4.3 mEq/L, chloride 97 mEq/L, carbon dioxide 25 mEq/L, glucose 569 mg/dl, BUN 90 mg/dl, serum creatinine 6.4 mg/dl, calcium 8.5 mg/dl.

In the emergency room, enalapril and cozaar were discontinued but it was too late to avert the serious consequence of severe hyperkalemia attributed to these agents. Serum potassium could have been much higher should she not hemodialyzed the day before. **Therefore death in this young woman is related to severe hyperkalemia which was caused by ACEI and ARB drugs.**

The real issue is why are these agents used? What is the benefit? The petitioner cares for patients intensively and tenaciously and has found no renal protection with use of ACEI or ARB in diabetic or hypertensive patients. He has encountered no diabetic patient who has shown an improvement or stability of renal function with the use of these agents.

Deteriorating renal function is unique to these agents. Discontinuation of these agents almost invariably results in recovery of renal function, whereas their continuation results in progressive renal failure ultimately ending in dialysis program.

Several studies are in agreement with the petitioner's observation and have found no importance of ACEI or ARB in diabetes or hypertension.

1. Notable among these studies is the large scale ALLHAT study which has found no advantage of lisinopril (ACEI) over other antihypertensive drugs, such as amlodipine (calcium channel blocker) or chlorthalidone (diuretic) for most cardiovascular disease and renal outcomes (11).

2. A study similar to ALLHAT study examined the effect of amlodipine or lisinopril compared to chlorthalidone in hypertensive patients with reduced GFR and found neither amlodipine nor lisinopril superior to chlortholidone in reducing the rate of development of ESRD.

3. A metaanalysis of controlled doubled-blinded randomized trials has not found ARB to be superior to standard antihypertensive treatment in diabetic patients (13).

4. Other investigators have tried combined ACEI and ARB and have noted profound fall in urinary protein only at the expense of an increase in serum potassium and a greater fall in hematocrit (14).

5. In another study one month following discontinuation of ARB, GFR increased by a mean of 45%, mean Scr decreased from 2.9 mg/dl to 1.8 mg/dl and required less erythropoietin for anemia (15)

6. Patient in Figure 1 confirms that tight control of glucose with multiple insulin injections per day can reduce proteinuria and protects renal function. This finding is

consistent with Stockholm study in which intensive insulin therapy reduced proteinuria more than conventional insulin therapy (10).

The greatest pitfall of assessment of renal protection in clinical trials or similar studies is the employment of only Scr to define renal protection. Ccl or other measures of GFR such as inulin clearance or icthalamate clearance was not done or not presented. The importance of Scr alone to assess renal function changes can be questioned as it is affected by age, weight, muscle mass, race and medication (16). GFR in the form of Ccl is the best overall index of renal function in health and disease. However, in clinical practice Scr is the most widely used index but it demonstrates an inadequate sensitivity, particularly in early stages of renal impairment (17). Next patient (Patient # 15) and Figure 1 are supportive of the above. In both patients Ccl varied widely with use of these agents but Scr changes were small. **This small Scr changes without Ccl or estimated GFR represents a misleading concept of renal protection.**

Patient # 15

67 Yr AAF, History of diabetes 12 years. Effect of fosinopril on proteinuria and renal function

Date 1999-2006	**24h Proteinuria** (mg)	**24h Ccl** (ml/min)	**Serum Creatinine** (mg/dl)
Oct 17, 99	160	125	0.8
	Fosinopril 20 mg daily started		
Nov 09,00	88	90	0.9
Dec 08, 02	142	81	1.0
Feb 18, 04	5	55	1.1
June 18, 04	**Fosinopril discontinued. Referred for decreased Ccl**		

July 15, 04	151	96	1.0
Jan 20, 05	417	76	1.0
Apr 07, 05	215	86	0.9
Mar 24, 06	NA	NA	0.8

NA = Not available
Ccl = creatinine clearance

This patient demonstrates that fosinopril (ACEI) decreased proteinuria to almost undetectable level, but it did so only by concomitant decrease of 56% Ccl. One month following discontinuation of fosinopril, proteinuria increased so did Ccl suggesting a link between proteinuria and Ccl. Scr changes are minimal and do not relate to Ccl changes.

Summary and conclusion

ACEI or ARB are preponderently used to treat diabetic nephropathy, hypertensive nephropathy and proteinuria due to non-diabetic renal disease. The reasons are: 1) Overwhelming publicity for renal protection by the above drugs in published articles and by pharmaceutical representatives. 2) Emphasis to follow guidelines introduced by the associations which emphasize use of ACEI or ARB in diabetes and hypertension. 3) Personal gain. For the latter, many investigators in the area are stock holders of pharmaceutical companies and do not wish to compromise their personal gain for the sake of the patients. Personal gain in the form of gifts, lunches, dinners, travels for the doctors and families highly influences the prescription habit of the doctors throughout the world. Nephrologists by using only Scr which changes slightly but with progressive decrease of Ccl assure the patients of the benefit of ACEI or ARB in preventing progression of diabetic nephropathy to ESRD which is not al all true. Then when patients become symptomatic and Ccl is found to be 15 ml/min or less they are informed of the

need for dialysis treatment. Many patients do not question the decision of their doctors. If the wishful thought of a nephrologist was intended for benefit of patients, progression into ESRD could have been averted by not using these agents and by, paying full attention into glycemic control which is fundamental to renal protection. Therefore, ACEI or ARB use has become instrumental in pushing patients into dialysis program which is a lucrative source of income from Medicare. Most primary care physicians prescribe ACEI or ARB because of overwhelming publicity for renal protection but soon find that these agents cause renal failure. However, they are unable to stand up and speak for the truth.

If the petitioner's presumption is wrong, why are diabetic and hypertensive patients entering into dialysis programs at a steadily increasing rate (18), despite the preponderant use of ACEI or ARB which is intended to slow down the progression. Is this an intentional or oversight act? This can only be proved by withdrawing these agents from the market. The petitioner's presumptive evidence is consistent with actual data. Diabetes-related ESRD has increased from 143774 (42%) between 1980-1990 to 249997 (57%) between 1990-2000. Diabetics with chronic kidney disease (CKD) are three times more likely to progress to ESRD than non-diabetic patients with CKD indicating vulnerability of diabetic patients to the action of ACEI or ARB. The risk of developing ESRD and reaching renal replacement therapy among individuals with CKD was estimated to have increased between 1978 and 1991 by 60% among diabetics and by 40% among non diabetics. In year 2000 diabetes-ESRD incidence rate varied from -17% in 20-39 age group to 194% in 75+ age group (19). **Why is diabetes-ESRD increasing?** It has something to do with poor glycemic control and excessive use of ACEI or ARB. One

may argue that the incidence of diabetes-ESRD is increasing because not many patients are treated with ACEI or ARB drugs. However, a strong counterargument can be made in that regard. For instance in a single day in this month (August 06) the petitioner saw 28 nephrology patients. Of these 28 patients, 18 patients (64.2%) are on maintenance hemodialysis which is agreement with the above data.. All of them have history of diabetes and hypertension. Whether they were treated with ACEI or ARB could not be confirmed. However, some of the 18 patients are still receiving ACEI or ARB suggesting that they were treated with ACEI or ARB in the past. On the otherhand, five of the 10 remaining patients (50%) developed ARF including patient # 12. All five recovered renal function upon discontinuation of ACEI or ARB and fluid therapy. One patient required hemodialysis. Therefore it is evident that incidence of diabetes-ESRD is increasing concurrently with increase of adverse effects of the agents further suggesting that those drugs are the cause of increased incidence of diabetes-ESRD. If the petitioner was not involved in the care of these five patients and other patients reported herein and many other patients not reported, they have progressed into ESRD. As stated earlier, ACEI or ARB is continued despite rising BUN and Scr, permitting many patients unknowingly to enter into dialysis program**. This is a deceitful act**. Therefore the practice of deceiving patients by using ACEI or ARB for renal protection which is not true according to the petitioner must be stopped. This can be accomplished only if FDA puts a stop to the use of these drugs. Then only all or most physicians will focus full attention to glycemic control with insulin therapy and adequate blood pressure control with agents other than ACEI or ARB. ACEI or ARB confers no additional benefit in hypertensive patients (11,12).

It is the hope of petitioner that FDA will do something to that effect, and thereby determine if the incidence of diabetes-related ESRD is indeed declining. The petitioner is seeking an opportunity to make a PowerPoint presentation of this topic with a hope that the presentation will open up the eyes of FDA personnel that acute renal failure or progression of chronic renal failure associated with hyperkalemia, metabolic acidosis and anemia truly happen associated with the use of ACEI or ARB drug therapy and make FDA to do something to mitigate the suffering of the patients and reduce health care cost from dialysis treatments. It is understable that FDA does the best to carefully examine the safety and effectiveness of a drug before approval. However, FDA's decision is often weakened by too much force from the pharmaceutical companies making FDA to undermine its high standard to evaluate the safety and effectiveness of a drug (see attached)

Hope to hear from FDA with regard to petition.

Sincerely,

Anil Mandal, MD

Attachement

08-22-06

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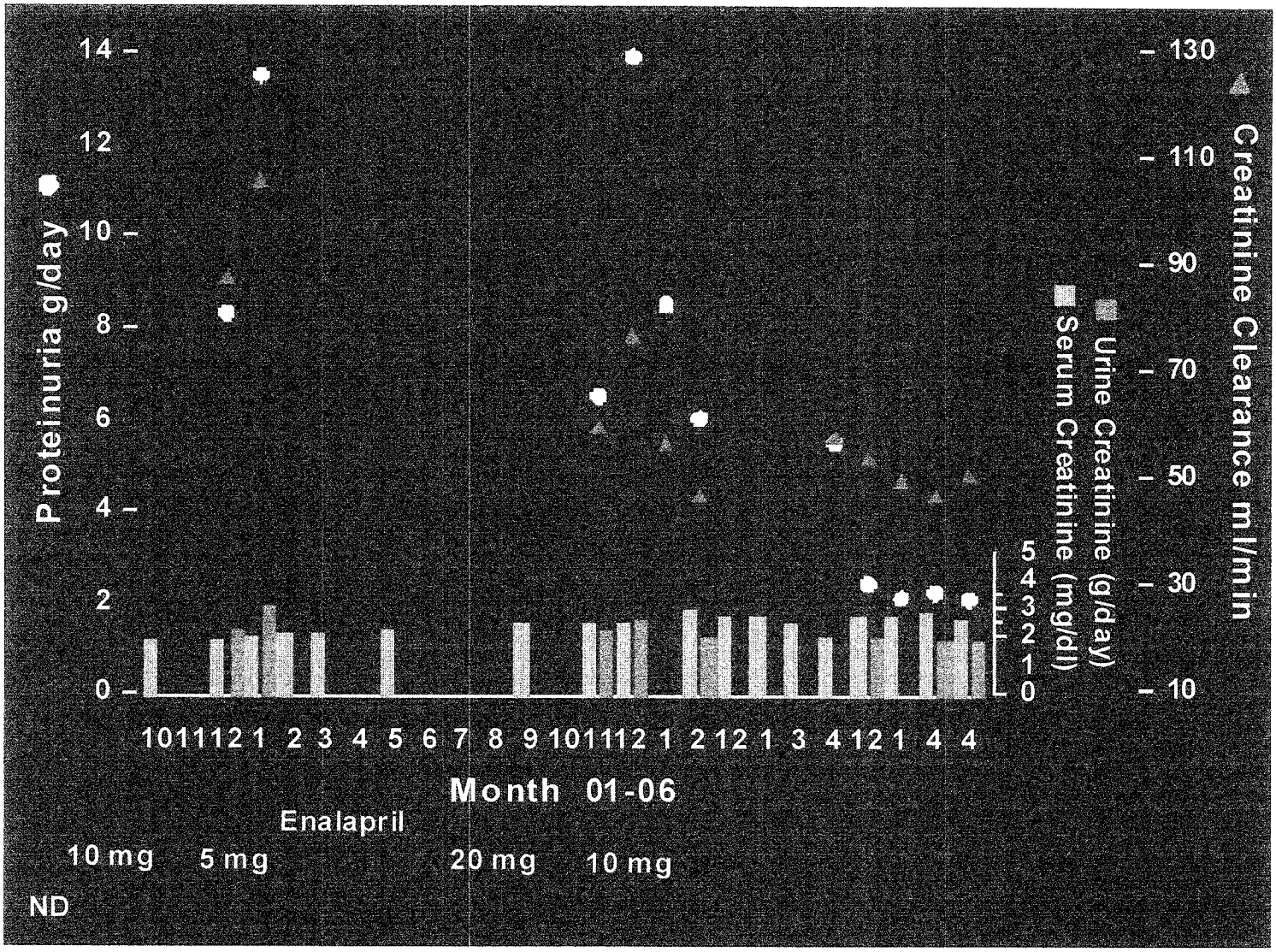

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