2006

Renal Dysfunction, Cardiovascular Risk, and the Response to Ace Inhibition in Patients After Myocardial Infarction

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RENAL DYSFUNCTION, CARDIOVASCULAR RISK, AND THE RESPONSE TO ACE INHIBITION IN PATIENTS AFTER MYOCARDIAL INFARCTION

A THESIS SUBMITTED TO THE
YALE UNIVERSITY SCHOOL OF MEDICINE
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF MEDICINE

By

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RENAL DYSFUNCTION, CARDIOVASCULAR RISK, AND THE RESPONSE TO ACE INHIBITION IN PATIENTS AFTER MYOCARDIAL INFARCTION.

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Background: Proteinuria is a known cardiovascular risk factor in hypertensive or diabetic patients as well as the general population. Worsening renal function (WRF) has been shown to influence outcomes in the heart failure population. The prognostic value of these markers for renal dysfunction in patients after myocardial infarction is unclear.
Methods: The Survival and Ventricular Enlargement trial (SAVE) randomized 2231 patients with left ventricular dysfunction between 3-16 days (average 11 days) post-MI to receive captopril or placebo; those with a serum creatinine above 2.5mg/dl were excluded from SAVE. WRF was defined as an increase in creatinine greater-than 0.3mg/dl measured from baseline to two weeks after randomization. A subset of 583 SAVE patients who underwent baseline dipstick urinalysis was also studied. We examined the predictive values of WRF and proteinuria on cardiovascular outcomes during 42 months of follow-up. We then explored the potential interaction between these markers of renal dysfunction and the response to angiotensin-converting enzyme (ACE) inhibition.
Results: Proteinuria was present in 20.9% of patients who were generally older, more often hypertensive, and who had lower ejection fractions and glomerular filtration rates. Proteinuria was associated with an increased risk of death (HR 1.84, 95%CI 1.20-2.82). In 1854 subjects with paired serum creatinine measurements, WRF occurred in 223 subjects (12.0%) and had no significant association with ACE inhibitor therapy (p=0.38). WRF was a stronger predictor of death (HR 1.55, 95%CI 1.15-2.11) than baseline serum creatinine (HR 1.47, 95%CI 1.05-2.05). The absolute benefit of captopril therapy was greatest for patients with proteinuria (p=0.02), but not for those with WRF (p=0.40).
Conclusions: Proteinuria and WRF were not uncommon in patients after myocardial infarction, and were strongly associated with increased risk for death and cardiovascular outcomes irrespective of baseline renal function. Patients randomized to captopril did not demonstrate more WRF than patients receiving placebo, and subjects with proteinuria who took captopril had the highest reduction in cardiovascular outcomes.

ACKNOWLEDGEMENTS

This project would not have come to fruition without the invaluable assistance and generosity of a number of people. Dr. Scott Solomon is the individual most responsible for my education during this research year, and has been an amazing mentor, providing me with the appropriate amount of guidance and independence in conducting this project. I am also greatly indebted to the mentorship provided by Dr. Marc Pfeffer, whose expertise has inspired me to pursue a career in clinical research. I truly appreciate his challenging me to ask the right clinical questions and demonstrating how to maintain the highest level of integrity in research methodology. I would like to extend my most sincere thanks to the other collaborators on this project and their knowledge of cardiology and nephrology as well as their statistical acumen: Dr. Charles Tomson, Dr. Hicham Skali, Dr. Marcello Tonelli, and Dr. Harlan Krumholz.

A research fellowship awarded by the Stanley J. Sarnoff Endowment for Cardiovascular Science allowed me to conduct this project at the Brigham & Women's Hospital in Boston, MA. To the Sarnoff Endowment as well as the Yale School of Medicine and the Office of Student Research, I owe tremendous gratitude. I am also grateful to Dr. Lawrence Young-without his guidance during medical school I would never have had the opportunity to learn about cardiovascular research or do the Sarnoff Fellowship. Finally, none of this would have been possible without the loving support of my parents, sister, and friends.

"To understand the heart and mind of a person, look not at what he has already achieved, but at what he aspires to do."

Kahlil Gibran (Lebanese poet 1883 - 1931)

Table of Contents

INTRODUCTION

Chronic kidney disease is an established cardiovascular risk factor. Renal function is considered as powerful an adverse prognostic factor for mortality as clinical variables such as ejection fraction and New York Heart Association function class (1). Individuals with renal dysfunction are more likely to die from cardiovascular disease than renal failure. Patients with end-stage renal disease are at a risk for cardiovascular outcomes that is 10-20 times greater than age and sex-matched controls in the general population (2). The increase in risk is partly due to nontraditional cardiovascular risk factors that are present in renal disease, such as anemia, disrupted calcium-phosphate metabolism, and microalbuminuria. In addition, the "cardiorenal syndrome" has been described as a pathophysiological condition in which combined cardiac and renal dysfunction accelerates the rate of cardiovascular morbidity and mortality due to distinct properties that do not occur in conditions affecting each organ independently (3).

Two markers of renal dysfunction, proteinuria and reduced glomerular filtration rate (GFR), are known clinical manifestations of kidney disease that have demonstrated separate associations to end-stage renal disease as well as cardiovascular morbidity and mortality. Proteinuria and reduced GFR have each been proven to increase risk in patients with chronic diseases as well as the general population. The Seventh Report of the Joint National Committee (JNC-7) has incorporated both albuminuria and decreased GFR into the group of major cardiovascular risk factors (4).

Proteinuria is a known predictor of morbidity and mortality, and has consistently been shown to influence outcomes in patients even after adjustment for GFR and irrespective of other cardiovascular risk factors such as diabetes or hypertension (5-11).

Microalbuminuria, which is below the limit of detection of albumin excretion in standard urine dipsticks, is now considered a target for treatment in diabetics. The Framingham Heart Study, Prevention of Renal and Vascular End-stage Disease Study (PREVEND), and other observational studies have suggested the utility of screening for microalbuminuria in the general population as a method of risk stratification for cardiovascular disease (12-14).

Reduced GFR is a strong independent predictor of cardiovascular outcomes and mortality in the general population (15) following myocardial infarction (16-20) and heart failure (21, 22). Worsening renal function (WRF), defined as small increases in creatinine over a specified period of time, has been assessed in heart failure patients as an independent prognostic marker (23, 24). In patients hospitalized for acute heart failure, WRF was a stronger predictor of death than the initial level of creatinine (25). WRF has been associated in these studies with in-hospital mortality, longer length of stay, higher rates of hospital readmission, and increased risk of death six months after discharge.

Medical therapies that have been explored in treating heart failure patients with renal dysfunction include diuretics, inotropic agents, vasodilators, and natruetic peptides, but data have remained largely inconclusive. Angiotensin converting enzyme (ACE) inhibitors have been shown to reduce cardiovascular morbidity and mortality in patients with heart failure or systolic dysfunction (26-28), following myocardial infarction (29-33), and in patients at high risk for vascular events (34, 35). Having also been proven as nephroprotective (36-38), the potential benefit of ACE inhibitors to both improve renal function and lower cardiovascular risk is an area that must be explored in more detail. Despite supportive evidence suggesting the renal benefits of ACE inhibition, cross-

sectional analyses have documented that patients with lower GFR do poorly because they are less likely to receive medications such as ACE inhibitors, B-blockers, aspirin or revascularization procedures such as PTCA and CABG (39). Fears of renal clearance, hypotension, or acute renal failure have led to a state of "therapeutic nihilism" in treating patients with renal dysfunction; this has also been suggested as an explanation for the increased cardiovascular risk seen in these patients (39). Large prospective clinical trials using ACE inhibitors generally do not include patients with advanced renal dysfunction. ACE inhibition has proven efficacy in reducing microalbuminuria in diabetic and hypertensive patients (5, 40). However, the impact of reducing proteinuria on cardiovascular outcomes, particularly in the post-MI population, is not yet clear. Furthermore, whether treatment of post-MI patients with ACE inhibitors is associated with WRF or affects outcomes in patients with WRF is unknown.

STATEMENT OF PURPOSE

The impact of proteinuria and WRF as risk factors for cardiovascular outcomes after acute myocardial infarction is not well characterized. We analyzed patients enrolled in the Survival and Ventricular Enlargement (SAVE) Trial to determine the prognostic importance of proteinuria and worsening renal function on cardiovascular outcomes. We also evaluated whether the response to ACE inhibition in reducing cardiovascular events is affected by the presence of these markers of renal dysfunction.

Most of the literature involving the cardiorenal syndrome stems from analyses done in heart failure patients. As patients are living longer with coronary artery disease

due to advancements in cardiac catheterization and surgery, the utilization of medical therapies, particularly ACE inhibition, in patients who develop the cardiorenal syndrome after myocardial infarction must be better understood. In addition to summarizing the analyses performed in SAVE, this thesis also aims to provide a comprehensive overview of the cardiorenal syndrome as it pertains to patients after myocardial infarction or who have established coronary artery disease. We conducted additional analyses using data from the Cholesterol and Recurrent Events (CARE) Study and the Prevention of Events with ACE Inhibition (PEACE) Trial to characterize the cardiovascular risk associated with having the combination of proteinuria and reduced GFR as well as the impact of ACE inhibition in lowering cardiovascular events for patients with reduced GFR.

METHODS

Subjects:

The SAVE trial was a randomized, double-blind placebo-controlled trial examining the use of the ACE inhibitor captopril in 2231 patients with acute myocardial infarction and left ventricular dysfunction (ejection fraction $\leq$ 40%), but without overt heart failure (29). Patients were randomized to receive captopril (50mg po tid) or placebo commencing between 3 and 16 days post-MI. The trial excluded patients with a serum creatinine above 2.5mg/dl. SAVE demonstrated that long-term administration of captopril to recent survivors of MI with left ventricular dysfunction resulted in improved survival and reduced morbidity and mortality. The reduction in risk was significant for all-cause mortality (19%, 95% confidence interval [CI] 3-32%), cardiovascular death (21%, 95%CI 5-35%), development of severe heart failure (37%, 95%CI 20-50%), hospitalization for congestive heart failure (22%, 95%CI 4-37%), and recurrent

myocardial infarction (25%, 95%CI 5-40%). The trial was conducted from 1988-1991 in Canada and the United States.

Proteinuria

All Canadian patients in SAVE were required to undergo dipstick urinalyses because of safety concerns during administration of study drug. Baseline dipstick urinalyses were performed on average 10 days post-MI. Typical dipstick classification of proteinuria included none, trace, 1+, 2+, 3+, 4+, corresponding to urinary protein concentrations of <10mg/dl, 10-30, 30-100, 100-300, and >1000mg/dl, respectively (41). The 4-variable Modification of Diet in Renal Disease equation:
$[186 \times \text{serum creatinine}^{-1.154} \times \text{age in years}^{-0.203} \times 1.210 \text{ (if black)} \times 0.742 \text{ (if female)}]$
was used to estimate GFR, which has been shown to agree with iothalamate measurements of GFR (42). From an initial 658 subjects enrolled in Canada, baseline dipstick measures were available in 598 patients; we excluded an additional 15 patients due to missing serum creatinine measurements, leaving 583 subjects for analysis.

Worsening Renal Function

All subjects received a captopril test dose of 6.25mg; patients who developed hypotensive symptoms or ischemia after initiation of study drug (n=23) were excluded from the trial. Subjects were randomized to receive captopril or placebo commencing between 3 and 16 days post-MI. The titration scheme involved an initial dose of 12.5mg which was advanced as tolerated up to 25mg TID prior to discharge. During an outpatient visit approximately two weeks later at the discretion of site investigators the dose was to be doubled. Serum creatinine was measured at baseline as well as during the

outpatient visit after two weeks. From the initial 2231 subjects, there were 356 subjects missing serum creatinine measurements at either baseline (n=31) or two weeks (n=325), and 21 subjects who had a cardiovascular event occur prior to two weeks, leaving for analysis 1854 randomized and consenting SAVE subjects with baseline and two week serum creatinine measurements who at the first outpatient visit had no cardiovascular events. When stratifying the risk of WRF by treatment, 41 additional subjects were not taking captopril due to dropout, leaving 1813 subjects with paired samples and no cardiovascular events who after two weeks were taking their assigned study medication.

Statistical Analysis:

Proteinuria

We considered trace or higher protein on dipstick as evidence of proteinuria. Multivariate analyses were performed to assess the predictive value of having any proteinuria and the degree of proteinuria (none, trace, greater-than-trace) after adjusting for known and suspected cardiovascular risk factors including age, gender, history of diabetes, history of hypertension, history of congestive heart failure, body mass index, previous infarction, left ventricular ejection fraction, systolic and diastolic blood pressure, baseline GFR, use of diuretics, and treatment assignment. Participants with GFR<60 ml/min/1.73m^2 body surface area were considered to have overtly impaired kidney function as per recent guidelines (42). Increased rates of adverse renal and cardiovascular events are generally seen below this threshold value, which has been utilized in many clinical trials to classify patients with renal dysfunction. Whether the combination of having reduced GFR and proteinuria has an additive impact on outcomes

was also tested. We finally evaluated whether proteinuria modified the effect of captopril on death or the composite endpoint by assessing the interaction between proteinuria and treatment with ACE inhibition.

Worsening Renal Function

WRF was defined as an increase in creatinine greater-than 0.3mg/dl from baseline, which was the threshold value based on receiver operator curve analyses from heart failure studies that demonstrated a clinically significant change in creatinine, and was less likely to be due to laboratory assay variability (43). We performed multivariable analyses using logistic and Cox regression to assess for independent predictors of WRF. The prognostic value of WRF was determined after adjusting for the same covariates as in the analysis of proteinuric subjects with the exception of body mass index, and systolic and diastolic blood pressure. We also examined the risk according to treatment assignment to see whether captopril is associated with WRF or modifies the relationship between WRF and cardiovascular risk.

In both analyses, Student's T-test and chi-square tests were used to compare continuous and categorical variables between groups. Cox Proportional Hazards models were used to derive univariate and multivariate estimates of risk for outcomes starting from baseline in the proteinuria cohort and from the two-week visit after randomization when the second creatinine was measured in the WRF cohort. All-cause mortality and cardiovascular mortality were considered primary endpoints. Stroke, recurrent MI, hospitalization for congestive heart failure, and a combination outcome of mortality and cardiovascular morbidity were also assessed during a follow-up period of approximately

42 months in both analyses. Deaths and cardiovascular endpoints were reviewed by the outcomes committee without knowledge of the individual's treatment assignment or laboratory values. Statistical analyses were performed with STATA software, version 8.2 (Stata Corp.)

RESULTS

Proteinuria

The baseline characteristics and outcomes of Canadian and U.S. subjects in SAVE were generally similar except for a lower incidence of diabetes, hypertension, and use of coronary revascularization procedures in Canada (44). Of the 583 patients with baseline creatinine and urine dipstick measures, 122 (20.9%) had proteinuria (trace, n=87 (14.9%); greater-than-trace, n=35, (6.0%)). The prevalence of diabetes did not significantly differ in patients with or without proteinuria (p=0.18). Subjects with proteinuria were older, more often hypertensive (p=0.03), had a higher baseline serum creatinine (p<.001) and Killip class (p<.001), a lower left ventricular ejection fraction (p<.001), and were more likely to be taking diuretics (p=0.05) compared to those without proteinuria (Table 1). The mean GFR was lower in subjects with proteinuria (60.9 vs. 69.9 ml/min/1.73m^2, p<0.001), and there was an increasing prevalence of proteinuria with decreasing GFR (Figure 1). Nevertheless, proteinuria was still present in 17.2% of patients with a GFR $\geq$ 60 ml/min/1.73m^2.

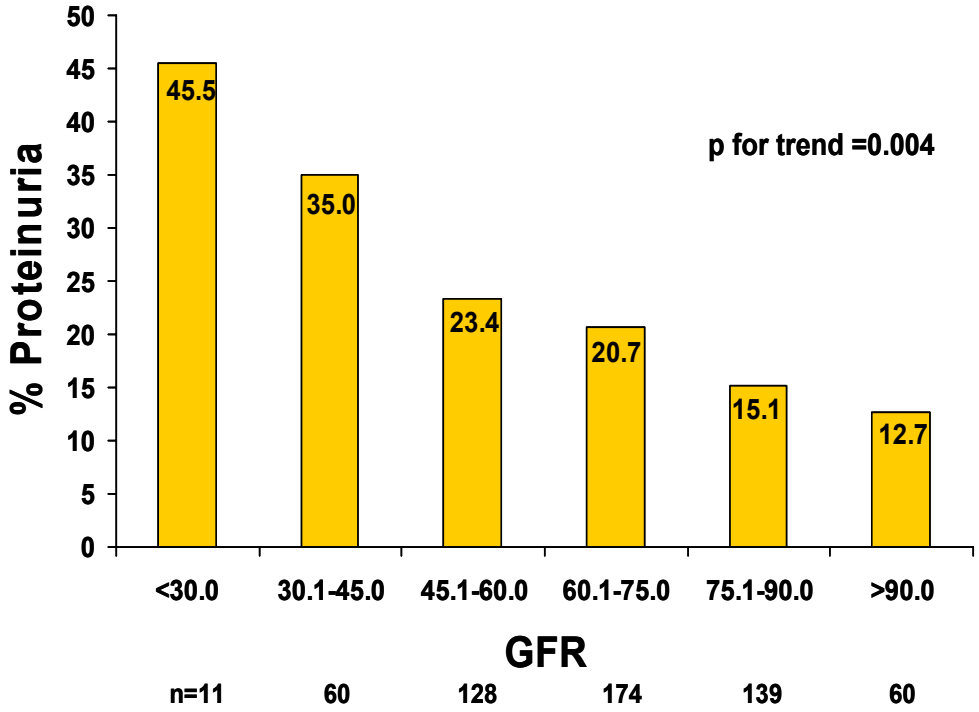

Figure 1. Prevalence of Proteinuria by GFR (ml/min/1.73m^2) (n=583)

Proteinuria was associated with a higher risk of death, and was an independent predictor of all-cause (hazard ratio [HR] 1.84, 95%CI 1.20-2.82) and cardiovascular mortality (HR 1.87, 95%CI 1.18-2.98), after adjusting for known covariates, including baseline GFR (Figure 2, Table 2).

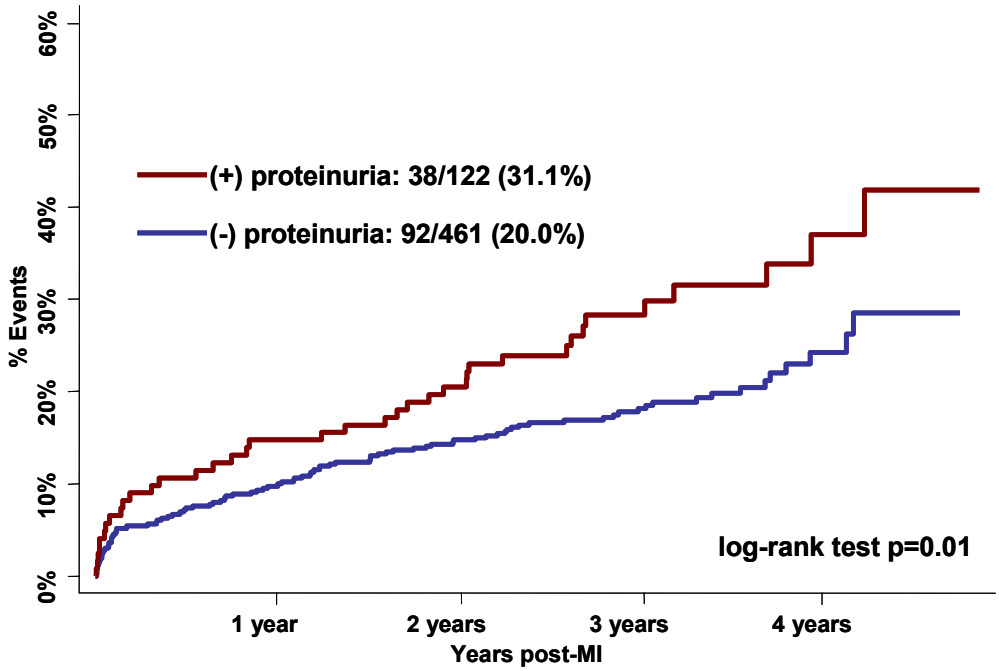

Figure 2. Death according to the Presence of Proteinuria

The combination of a GFR<60 ml/min/1.73m^2 and proteinuria conferred nearly a three-fold increased risk of death (HR 2.74, 95%CI 1.68-4.45) compared to having neither risk factor (Figure 3). There was also a stepwise progression of increased risk for cardiovascular events according to the degree of proteinuria; patients with a urine dipstick result greater-than-trace had a higher incidence of mortality (20.0%, 25.3%, and 45.7% for no proteinuria, trace, and greater-than-trace, respectively, p for trend=0.002) (Figure 4, Table 3). We found a dose effect for both proteinuria and renal dysfunction, with risk increasing in association with heavier proteinuria and lower estimated GFR. There was a higher rate of cardiovascular morbidities including stroke, recurrent MI, and hospitalization for congestive heart failure in subjects with baseline proteinuria.

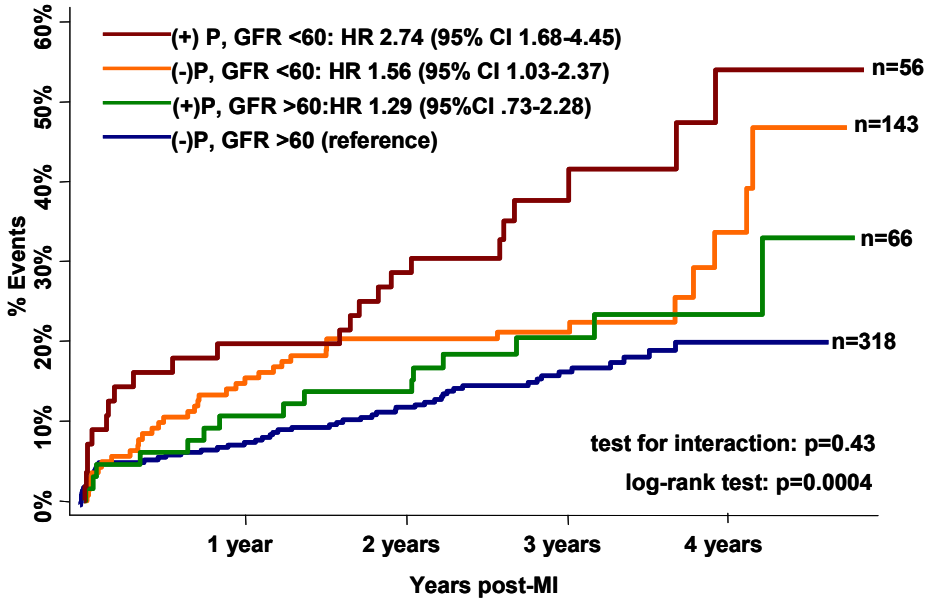

Figure 3. Death according to Proteinuria (P) and GFR

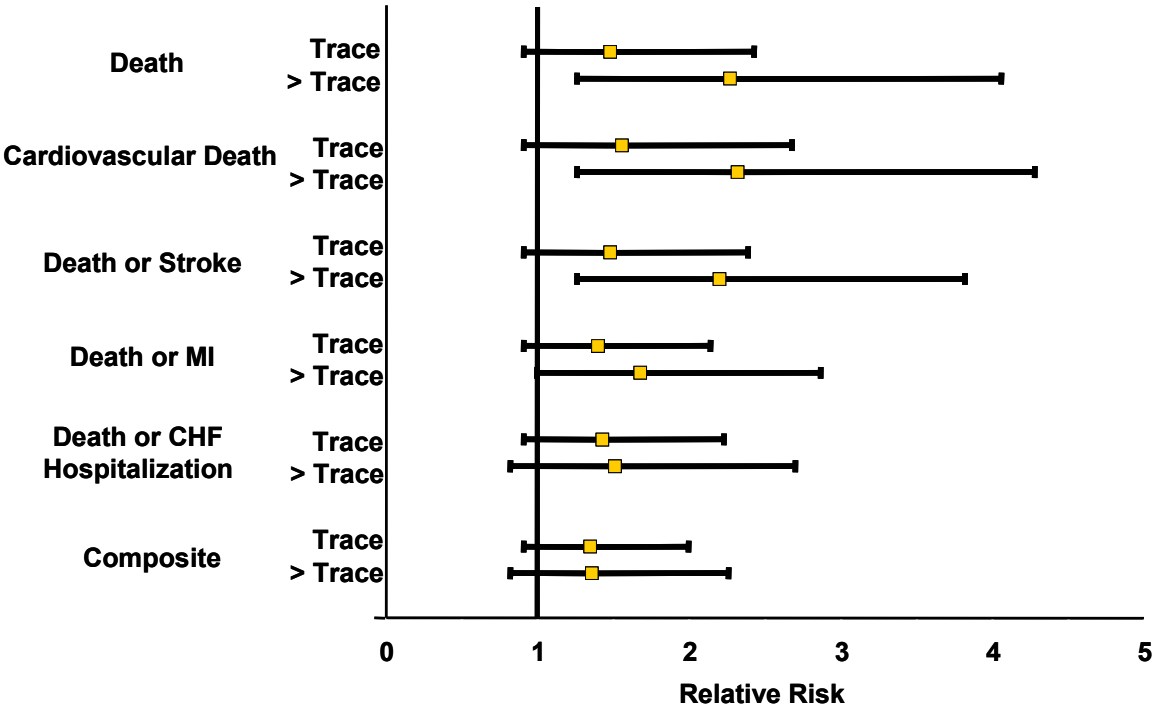

Figure 4. Relative Risk for Endpoints by Degree of Proteinuria (Referent group is no proteinuria; n=461)

Subjects with proteinuria appeared to have the greatest reduction in all-cause and cardiovascular mortality due to ACE inhibitor therapy. Assignment to captopril provided a greater benefit in lowering risk of death in patients with proteinuria (HR 0.46, 95%CI 0.24-0.89) versus patients without proteinuria (HR 0.83, 95%CI 0.55-1.25). The composite endpoint also showed an increase in benefit with captopril for subjects with proteinuria (0.41, 95%CI 0.21-0.73) compared to those without (0.87, 95%CI 0.63-1.19) (Table 4, Figure 5). In addition, there was a significant test for interaction (p=0.02) for the composite endpoint, suggesting that the presence of proteinuria may modify the efficacy of captopril and define a subset of patients who obtain additional benefit from receiving captopril.

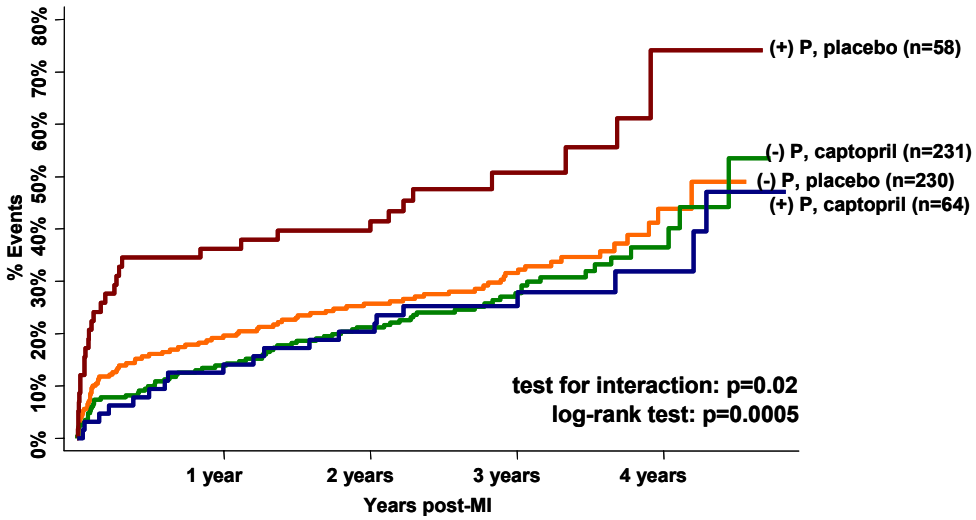

Figure 5. Composite endpoint according to Proteinuria (P) and Treatment

Worsening Renal Function

Subjects who were excluded from this analysis because they were missing serum creatinine measurements (n=356), had cardiovascular events (n=21), or were not taking medication at two weeks (n=41) were older, more likely to be female, had more hypertension, and were more frequent users of diuretics compared with those included in the analysis. Although there was a higher cardiovascular event rate in excluded subjects, there was no significant difference in baseline creatinine, change in creatinine, or treatment assignment compared with the study cohort.

The change in creatinine from baseline to two weeks for the 1854 subjects who comprised the study cohort was normally distributed, ranging from -1.2 to 2.8 mg/dl with a mean change in creatinine by treatment assignment of 0.05 ± 0.3 in both the placebo and captopril groups (p=0.9). There were 223 subjects (12.0%) who had WRF with no significant difference in timing of enrollment into SAVE between subjects with and without WRF (average 11 days post-MI). Subjects with WRF were older, more likely female, and had a higher prevalence of diabetes, smoking, and use of diuretics, but had fewer previous myocardial infarctions (Table 5). In the multivariate logistic regression model, age (odds ratio[OR] 1.02, 95%CI 1.01-1.04) and a history of diabetes (OR 1.45, 95%CI 1.02-2.05) remained significant predictors of WRF, while use of diuretics (OR 0.71, 95%CI 0.51-0.97) appeared to protect against WRF in this population of post-MI subjects with systolic dysfunction.

Worsening renal function as early as two weeks after acute MI was associated with a higher incidence of death, and was an independent predictor of death (HR 1.55, 95%CI 1.15-2.11), cardiovascular death (HR 1.71, 95%CI 1.24-2.37), and the composite

endpoint (HR 1.36, 95%CI 1.07-1.72)**.** The prognostic value of WRF not only remained significant after adjusting for covariates, but was a stronger predictor of cardiovascular outcomes than baseline creatinine (HR 1.47, 95%CI 1.05-2.05; HR 1.55, 95%CI 1.07-2.24; HR 1.38, 95%CI 1.01-1.88 for death, cardiovascular death, and composite endpoint, respectively). There were 104 subjects (5.7%) in the placebo group and 116 subjects (6.4%) in the captopril group who had WRF with no difference in the rates of WRF between treatment groups (p=0.38). When stratified by treatment, the risk of death in WRF subjects was higher in the placebo group (HR 1.78, 95%CI 1.18-2.68) than in patients who were taking captopril at two weeks (HR 1.35, 95%CI 0.85-2.16), as was the risk for cardiovascular death and the composite endpoints. Tests for interaction, however, were not significant **(**p for interaction=0.40, 0.64, and 0.37 for death, cardiovascular death, and composite endpoint, respectively) (Figures 6 and 7, Table 6).

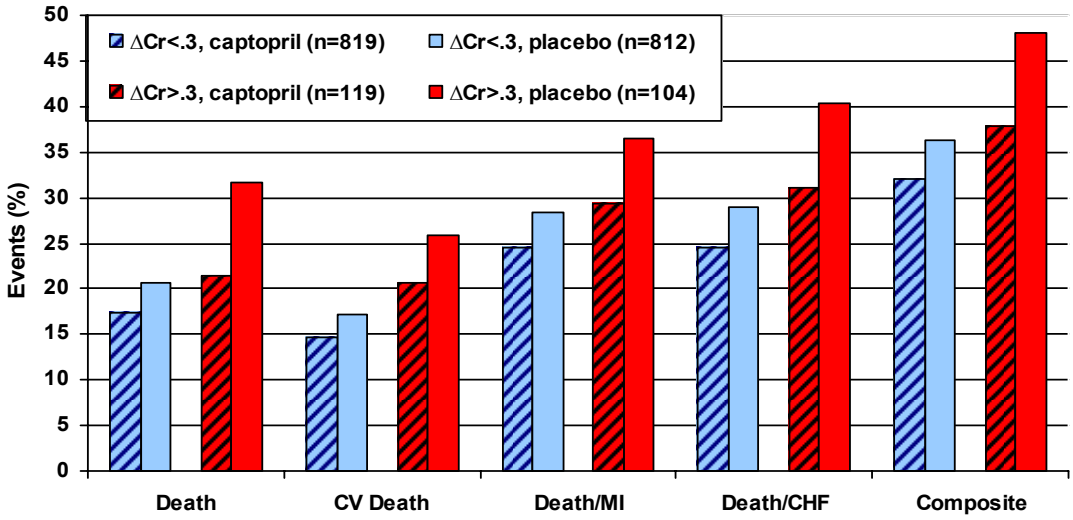

Figure 6: Event Rate according to WRF and Treatment Assignment

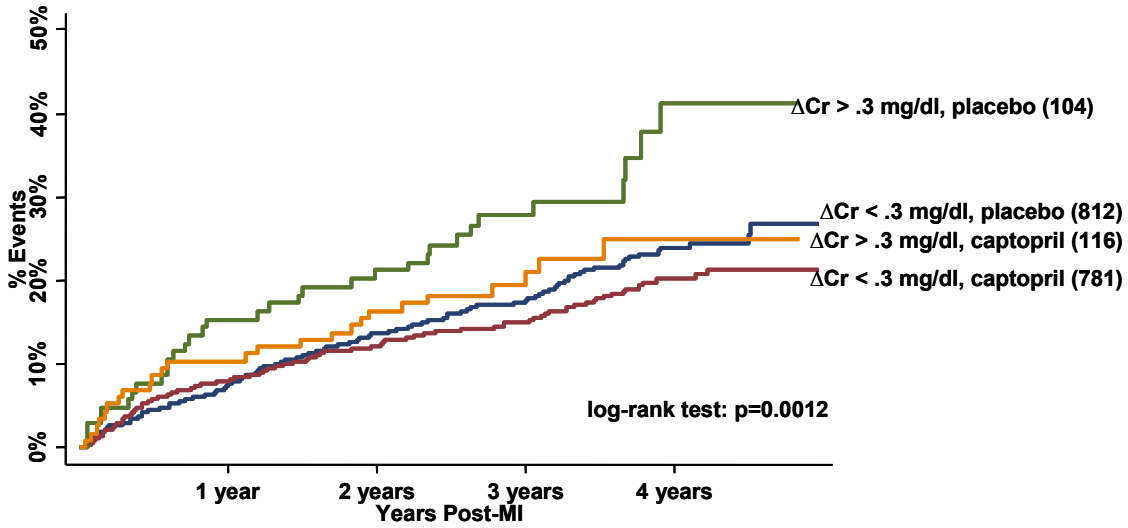

Figure 7. Death according to Worsening Renal Function and Treatment

DISCUSSION

The pathophysiology behind the cardiorenal syndrome appears to involve a complex interaction of positive feedback loops involving the renin-angiotensin system, the sympathetic nervous system, oxidative stress, and inflammation. The combination of myocardial injury and renal hypoperfusion leads to a vicious cycle involving these feedback loops resulting in further organ damage. Consequences of the cardiorenal syndrome include accelerated atherosclerosis, left ventricular hypertrophy, myocardial micro-angiopathy, and decreased capillary density (3). Because renal dysfunction is a common complication of heart failure, the cardiorenal syndrome has been primarily studied in this population. In patients after myocardial infarction, whether the cardiorenal syndrome has the same underlying pathophysiology is not as well characterized.

Furthermore, the management strategy of patients presenting with renal dysfunction in the setting of cardiovascular disease is even less defined.

This thesis aimed to investigate markers of renal dysfunction and the effect of early pharmacological intervention with ACE inhibition on cardiovascular outcomes. Proteinuria, as measured by standard urine dipstick, and worsening renal function, defined as a rise in creatinine greater-than 0.3mg/dl after two weeks, are two distinct markers of renal dysfunction. We observed that in patients with acute MI and systolic dysfunction, proteinuria and WRF were common and associated with an increased risk for all-cause and cardiovascular mortality after adjustment for known confounders. Proteinuria and WRF were independently associated with poorer outcomes even after adjustment for baseline creatinine, treatment assignment, and other known covariates. The benefit of captopril on cardiovascular mortality was found to be significantly greater in patients with proteinuria, but not in patients with WRF.

Proteinuria

Pathophysiology behind Proteinuria as a Cardiovascular Risk Factor

The relation between proteinuria and progression to renal failure has been extensively studied, and is considered an important predictor of impaired renal function (47-49). One Japanese screening trial of the general population demonstrated that a positive urine dipstick had a strong predictive value for developing end-stage renal disesase (OR 2.71, 95%CI 2.51-2.92) (50). Proteinuria has also been described as a risk factor for mortality in subjects with chronic diseases and high cardiovascular risk, particularly diabetic and hypertensive populations. Low-grade proteinuria indicates a

state of increased glomerular permeability that may not be due to glomerular disease specifically, but rather to a systemic increase in transcapillary escape of albumin. Numerous factors that affect glomerular permeability by acting on podocyte tight junctions and arterial permeability by affecting endothelial tight junctions may explain the power of albuminuria as a marker and predictor for the presence of vascular disease (45). Proteinuria reflects systemic vascular permeability and endothelial dysfunction that may have potential for lipoprotein infiltration into arterial walls and lead to symptomatic atherosclerosis (46).

Albuminuria comprises of microalbuminuria and macroalbuminuria, which are defined as urinary albumin excretions between 30-300 and >300 mg/24 hours, respectively. Albumin:creatinine ratios (2.5-25 mg/mmol or >25mg/mmol), which are more conveniently measured using spot urine specimens, are also used to quantify albuminuria (51). Microalbuminuria has traditionally been used as a screening measure for diabetic nephropathy with an estimated incidence of about 30% in diabetic patients and 10-15% in nondiabetics (52). Recent data have confirmed microalbuminuria as a legitimate risk factor for cardiovascular outcomes and a strong predictor of mortality. The Heart Outcomes Prevention Evaluation found that the presence of microalbuminuria (defined as an albumin/creatinine ratio ≥ 2mg/mmol) predicted adverse outcomes in both diabetics (RR 1.97, 95%CI 1.68-2.31) and nondiabetics (RR 1.61, 95%CI 1.36-1.90) (3).

Clinical proteinuria appears to have prognostic value even in the general population. The Framingham Heart Study evaluated a cohort of older subjects by standard urine dipstick, and discovered that baseline trace proteinuria augmented risk of death for both men (HR 1.3, 95%CI 1.0-1.7) and women (HR 1.4, 95%CI 1.1-1.7).

There was an increment in risk of all-cause mortality associated with greater-than-trace (HR 1.4, 95%CI 1.1-1.8) compared to trace (HR 1.3, 95%CI 1.1-1.6) proteinuria for the Framingham cohort as a whole (p for trend = 0.001) (12). This analysis from SAVE displayed a similar stepwise increase in risk according to the degree of proteinuria. The strength of association between proteinuria and mortality, as detected by a less sensitive test such as dipstick urinalysis, reinforces the importance of proteinuria as a risk factor for cardiovascular disease.

The prognostic significance of proteinuria in patients after an acute myocardial infarction is less understood. In 1991, Gosling et al. first noted in 44 patients an increase in the albumin excretion rate during MI with a direct correlation between the initial urinary albumin:creatinine ratio and size of the infarct (53). Studies by Berton et al. have confirmed this finding, and have shown albuminuria measured during the first week of hospitalization post-MI to be predictive of in-hospital, one-year, and three-year mortality (54-56). The albumin:creatinine ratio demonstrated a transient rise and fall during the first week post-MI in these studies, and was associated with neurohormonal markers of heart failure, including increased renin and aldosterone. One possible explanation may be due to hypoperfusion and prerenal failure producing transient proteinuria in some patients (57). Alternatively, proteinuria, and more specifically albuminuria, may serve as an additional marker of early inflammation accompanying infarction or due to coronary artery disease. An association between inflammation and albuminuria has been seen in the presence or absence of diabetes or hypertension; recent data has demonstrated increased C-reactive protein and white blood cell counts in patients with albuminuria, suggesting that inflammatory mediators may play a role in glomerular and renal damage

(58, 59). The association between albumin excretion and markers of heart failure and inflammation indicates that proteinuria is a comprehensive marker of the pathophysiological changes that occur after myocardial infarction (56).

Relationship between Proteinuria and Glomerular Filtration Rate

The relation between reduced GFR and proteinuria is complex. There is a lack of information on how proteinuria and kidney function may be used together for risk stratification. None of the major clinical trials that have proven the prognostic value of either reduced GFR or proteinuria on cardiovascular outcomes tested for potential confounding between the two risk factors themselves. Proteinuria, or more specifically albuminuria, and reduced GFR are individual predictors of cardiovascular outcomes, but only a handful of studies have explored whether these risk factors act independently from each other. Whether a combination of both risk factors exacerbates or simply reflects the same amount of kidney disease warrants further study.

The cross-sectional Third National Health and Nutrition Examination Survey (NHANES III) examined 14,622 subjects from the general population (age 20 or over) and determined the epidemiology of reduced GFR and albuminuria (60). Abnormalities in renal function were found in 11% of the study population, which would correspond to approximately 19.2 million U.S. adults. The prevalence for reduced GFR (<60 ml/min/1.73m^2) and albuminuria were 6.3% and 9.3%, respectively. In each risk stratum, which included all participants, diabetics, non-diabetic hypertensive participants, and non-diabetic non-hypertensive participants, the prevalence of albuminuria increased in a step-wise fashion with a declining GFR. A GFR >60, 30-60, and <30 ml/min/1.73m^2

corresponded to a presence of albuminuria in 8.1%, 23.3%, and 63.4% of the whole population, respectively. Having both albuminuria and reduced GFR was more common in older, diabetic, and hypertensive patients. However, persistent albuminuria with preserved GFR may be present in as many as 11.2 million people, suggesting that the correlation between renal dysfunction and albuminuria is complex and dependent on the population being studied. The number of persons needed to screen to identify one with both reduced GFR and albuminuria was 59 (95%CI 49-74) in the whole population compared to 11 (95%CI 9-14) and 28 (95%CI 23-35) in the diabetic and non-diabetic hypertensive populations, respectively.

The African American Study on Kidney Disease and Hypertension trial found an inverse relationship between baseline GFR and proteinuria (61). This relationship was evident in our cohort as well, but a substantial proportion (17.2%) of patients in our analysis who had a GFR above 60 ml/min/1.73 m^2 still had evidence of proteinuria. The HOPE trial demonstrated an additive relationship between microalbuminuria and renal dysfunction; patients with both risk factors had a 28.6% incidence of primary outcome (cardiovascular death, MI, stroke) versus 13.6% for patients with neither (HR 2.08 95%CI 1.65-2.62) (52). However, the HOPE analysis excluded participants with proteinuria on dipstick urinalysis, and did not report findings for all-cause mortality. In this analysis from SAVE, we confirmed that proteinuria was associated with death irrespective of GFR, and that the combination of both proteinuria and reduced GFR additively increased the risk of death by nearly three-fold.

NHANES III and other studies have demonstrated an increasing prevalence of albuminuria with decreasing GFR, particularly when below 60 ml/min/1.73 m^2; however,

albuminuria is also seen in patients who present with renal hyperfiltration. In early diabetic nephropathy, GFR typically follows a biphasic pattern with albuminuria and hyperfiltration in the initial phase followed by progression to proteinuria and loss of renal function as nephropathy develops (62). Similar results have been found in nondiabetic renal disease. A large cross-sectional analysis of the PREVEND study (n=7728) found an elevated creatinine clearance in subjects with high-normal levels of urinary albumin excretion (15-30mg/24hr) and microalbuminuria compared to patients with lower excretion (<15mg/24hr). GFR followed a parabolic pattern in association with increasing urinary albumin excretion which then decreased once macroalbuminuria and overt proteinuria developed. High-normal and microalbuminuria were independently associated with an elevated filtration rate (RR 1.8, 95%CI 1.3-2.5 and 1.7, 95%CI 1.2-2.4), and macroalbuminuria with a diminished filtration (RR 4.3, 95%CI 1.9-9.4). This relation persisted even after adjustment for potential confounders. Limitations of the PREVEND analysis, however, may have included selection bias with enrichment for albuminuria and more subjects with prediabetes or insulin resistance syndrome (63). Having both reduced GFR and albuminuria appears to have an independent but additive effect on cardiovascular risk.

Whether proteinuria and reduced GFR influence cardiovascular outcomes by the same or separate pathophysiological mechanisms requires further study. Several theories have been proposed, but to date no consensus has been reached due to lack of sufficient power in clinical trials. Elevated serum creatinine points to a reduced rate of glomerular filtration, while an increased rate of albumin or protein excretion points to a derangement in the glomerular filtration barrier. Proteinuria generally indicates the existence of

established renal parenchymatous damage**.** Animal experiments suggest that increased intraglomerular pressure due to hyperfiltration induces proteinuria and progressive renal decline. Insulin resistance has also been reported to regulate GFR and alter permeability of the glomerular membrane for albumin (64). Data from clinical trials support the idea that reduced GFR is a distinct entity, whose pathogenesis may be different than albuminuria, which typically results from diabetic glomerulosclerosis (65). Whether one direct mechanism of association exists, or if the effects of proteinuria and reduced GFR are part of a larger cardiovascular risk profile, is still unclear.

Influence of Proteinuria and Reduced GFR-Analysis from CARE

In order to better characterize the relative contributions of the combination of proteinuria and reduced GFR on cardiovascular risk, we conducted an analysis using data from the Cholesterol and Recurrent Events study (CARE) (66). CARE was a randomized trial of pravastatin versus placebo in 4159 individuals with hyperlipidemia and a history of myocardial infarction, and has been described in detail elsewhere (67). Briefly, CARE demonstrated that the reduction in LDL concentrations achieved during treatment with pravastatin was associated with a reduction in coronary events (68). We used data from 4098 CARE participants who had serum creatinine and proteinuria measured at baseline. Reduced GFR was defined by a GFR<60 ml/min/1.73m^2 and proteinuria by 1+ or greater protein on dipstick urinalysis. We examined four mutually exclusive strata defined by the presence and absence of reduced GFR and proteinuria. Cox proportional hazards models were used to examine the risk of death and cardiovascular events over approximately 60 months of follow-up.

The findings in CARE were similar to those seen in SAVE. Subjects who had both reduced GFR and proteinuria were at the highest risk of death (HR 2.39, 95%CI 1.72-3.30) compared to participants with neither proteinuria nor impaired kidney function. There was an intermediate risk for death in subjects with only proteinuria (HR 1.69, 95%CI 1.32-2.16) or reduced GFR (HR 1.41, 95%CI 1.12-1.79). There was also evidence of a graded increase in the risk of death for both severity of renal impairment (estimated GFR $\geq$60, 45-59.9, and <45 ml/min/1.73m^2) and degree of proteinuria by dipstick (none, trace, 1+ or greater). Other cardiovascular outcomes, including new heart failure, stroke, and the composite of coronary death or non-fatal myocardial infarction, exhibited similar increases in risk. Limitations included unknown etiologies of renal dysfunction in study participants, single baseline dipstick urinalysis and serum creatinine measurements, and potential misclassification of subjects with respect to reduced GFR.

These analyses from both SAVE and CARE demonstrate that in patients with either acute or prior myocardial infarction, the risk of death associated with reduced GFR is higher with concomitant proteinuria than without. These results have important clinical implications in the management of post-MI patients who have renal dysfunction. Using a simple measure such as urine dipstick to assess for proteinuria may help to refine estimates of cardiovascular risk which would otherwise be based on kidney function alone.

Impact of ACE Inhibition on Proteinuria and Cardiovascular Outcomes

Interventions known to delay or prevent progression of renal disease and reduce cardiovascular risk include tight control of blood pressure and glucose, and inhibition of the renin-angiotensin system. Lipid-lowering therapy has also been associated with protective effects. Previous analyses from CARE have shown that treatment with pravastatin significantly reduced rates of renal decline in individuals with moderate renal insufficiency. The beneficial effects of pravastatin on preventing loss of renal function were greater in patients not only with lower levels of GFR at baseline, but also in subjects with proteinuria (69). In the Pravastatin Pooling Project, the absolute benefit in reduction of adverse outcomes from using pravastatin was greater in patients with chronic kidney disease (70). Results from CARE and additional studies have justified the use of statin therapy in patients with chronic kidney disease to slow progression of renal failure and to prevent cardiovascular events.

ACE inhibitors and angiotensin-receptor blockers have been proven to be nephroprotective in patients with reduced GFR and proteinuria, but whether improved renal function leads to a reduction in cardiovascular risk independent of blood pressure effects has not been specifically addressed. We observed in SAVE that treatment with captopril showed the greatest absolute benefit in reducing cardiovascular events in post-MI subjects with trace or higher proteinuria. Kaplan-Meier survival curves (Figure 5) demonstrated a dramatic attenuation of risk (59%, $p<.002$) for subjects with proteinuria taking captopril compared to placebo and a significant interaction between captopril and proteinuria ($p=0.02$). In contrast, the risk reduction of captopril in patients without proteinuria was not significant (13%, $p=0.37$).

The explanation for this novel finding remains unclear. Clinical benefits in patients with albuminuria taking ACE inhibitors or angiotensin-receptor blockers, which can lower urinary albumin excretion by an average of 40% irrespective of its effect on blood pressure, have been reported (46). A meta-analysis of antihypertensive medications indicated that the mean antiproteinuric effect of ACE inhibitors was greater than of other antihypertensive drugs despite similar blood pressure lowering between both groups (71). Studies have suggested that the benefits of ACE inhibitors in reducing progression of renal disease are greater for patients with proteinuria at onset of treatment or during follow-up (49). The HOPE trial examined the use of ACE inhibition in improving GFR and microalbuminuria and its potential influence on cardiovascular outcomes. Low-dose ramipril reduced incidence of outcomes in patients with and without renal dysfunction and albuminuria. The cardiovascular benefits of ramipril were greater in patients with both risk factors (HR 0.48 95%CI 0.24-0.98) compared to those with neither (HR 0.78 95%CI 0.70-0.87) (62). A recent study by Asselbergs et al. randomized 864 subjects with microalbuminuria to fosinopril or placebo, and found that treatment with fosinopril lowered urinary albumin excretion by 26% ($p<.001$). Although not significant, the incidence of cardiovascular morbidity or mortality was also lowered by 40% (HR .60, 95%CI 0.33 to 1.10) (72).

The added benefit seen in proteinuric patients most likely reflects the increased risk observed in this population. Although this finding is hypothesis-generating and must be validated with larger clinical trials designed to examine the cardiovascular benefits in proteinuric patients, it appears that proteinuria may define a subgroup of post-MI patients who are more sensitive to the protective effects of captopril.

Worsening Renal Function

Changes in Creatinine and Cardiovascular Risk

Although baseline renal dysfunction is considered a potent cardiovascular risk factor in post-MI patients, the predictive value of worsening renal function has not yet been adequately addressed in this population. The majority of studies that have examined the prognostic value of reduced renal function have focused on serum creatinine values or GFR at one point in time. The predictive value of an increase in creatinine over time, however, has been less clear, and has primarily been determined in patients hospitalized for heart failure, in which the incidence of WRF (27% and 28%) was consistently greater than that seen in this analysis (12.0%) (23, 24). More risk factors have proven predictive of WRF in the heart failure population (baseline creatinine, systolic blood pressure, history of diabetes or congestive heart failure) than were seen in this population of post-MI subjects with systolic dysfunction (age, history of diabetes).

Few trials have assessed the prognostic value of WRF in the setting of coronary artery disease. Shilpak et al. examined the influence of a change in creatinine greater-than 0.3mg/dl, in postmenopausal women with coronary artery disease in the Heart and Estrogen/Progestin Replacement Study (73), and observed no association between subjects with WRF (9% of cohort) and cardiovascular risk. In this healthier population with stable coronary disease, changes in creatinine were measured longitudinally over four years, however, and thus may have been relatively small.

Most clinical studies have defined WRF as an increase in creatinine greater-than 0.3mg/dl, a threshold that has been found in prior studies to have the highest sensitivity (81%) and specificity (62%) for predicting mortality (43). Initial analyses in our cohort

demonstrated a similar threshold effect with a higher event rate occurring in subjects with a change in creatinine greater-than 0.3 mg/dl. Lower magnitude changes may be less clinically relevant and represent transient changes or inherent variability in creatinine measurement. However, a more linear or J-shaped association between small changes in creatinine and risk for adverse cardiovascular outcomes has also been suggested (74, 75). An acute rise in creatinine of at least 25-30% has also been recommended as a threshold for WRF (76). Although the various thresholds may vary according to patient population, there is definitive evidence that small changes in creatinine confer adverse prognostic value.

ACE Inhibition and Reduced Renal Function-Analysis from PEACE

Physicians are hesitant to use ACE inhibitor therapy in patients with renal dysfunction. This remains the norm in clinical practice despite recent data that has demonstrated the efficacy and safety of ACE inhibition in patients without diabetes who have advanced renal insufficiency, irrespective of baseline GFR or blood pressure (77). Results from the clinical trial by Hou et al. indicated that end-stage renal disease would take almost twice as long to develop in the patients given benazepril (7 years) compared to the control cohort (3.5 years). While this evidence suggests the safety of ACE inhibition in nondiabetic patients with renal insufficiency, the use of ACE inhibitors in patients with coronary artery disease and renal dysfunction requires further investigation.

We explored the influence of renal function, using estimated GFR, on cardiovascular outcomes and the response to ACE inhibition in the recently published Prevention of Events with ACE Inhibition (PEACE) trial (78). PEACE did not

demonstrate a benefit of the ACE inhibitor trandolapril in reducing cardiovascular morbidity or mortality in patients with stable coronary disease and preserved left ventricular systolic function (79). Unlike the results that were observed in the HOPE and EUROPA trials demonstrating the cardiovascular benefit of ACE inhibition in patients with chronic coronary artery disease, the lack of benefit observed in PEACE was attributed to an overall lower risk patient population. The majority of patients enrolled in PEACE had received effective concomitant therapy, such as coronary revascularization and statins more frequently than patients in the previous trials.

The PEACE trial included patients at least 50 years old, with stable coronary artery disease and preserved systolic function who were randomly assigned to treatment with the ACE inhibitor trandolapril or to placebo and followed for a median of 4.8 years (80). A total of 8290 patients were enrolled in PEACE. Of these, 10 patients had missing data on baseline serum creatinine and/or race, variables required to estimate glomerular filtration rate, and were therefore excluded, leaving 8280 patients for this analysis. Cox proportional hazards models were used to conduct a post-hoc analysis examining the association between GFR and cardiovascular endpoints. Potential confounding variables that were considered in the models included age, sex, history of diabetes, history of myocardial infarction, hypertension, and left ventricular ejection fraction (<0.50; ≥ 0.50). We also examined GFR as a categorical variable to aid in the interpretation of potential interaction between GFR (<60.0; ≥ 60.0 ml/min/1.73m^2) and treatment group.

The mean GFR was 77.6 ± 19.4 ml/min/1.73m^2; 1355 (16.3%) patients had reduced renal function (GFR<60 ml/min/1.73m^2). In patients with reduced renal

function, trandolapril was associated with a reduction in total mortality (HR 0.73, 95%CI 0.54-1.00). This benefit was not demonstrated in patients with preserved renal function (HR 0.94, 95%CI 0.78-1.13). We observed a significant interaction between GFR and treatment group with respect to cardiovascular and all-cause mortality ($p = 0.02$), suggesting that ACE inhibition modifies the relationship between GFR and outcome. Not only did trandolapril attenuate the relationship between decreasing GFR and mortality, but the effectiveness of trandolapril appeared to increase as GFR decreased.

A previous SAVE analysis demonstrated a trend similar to that found in PEACE where patients with reduced GFR taking captopril had a nominally greater reduction in cardiovascular risk than those taking placebo (19). However, there was not a statistically significant interaction between reduced GFR and captopril ($p=0.29$) as was seen in PEACE. In contrast to the findings in SAVE, in which ACE inhibitors were as effective in patients with reduced GFR as in those with preserved renal function, this analysis from PEACE suggests that ACE inhibitors were only effective for reducing all-cause and cardiovascular mortality in patients with reduced renal function. These results may be related to the relatively low-risk patient population, and could help explain the lack of overall benefit in PEACE. While hypothesis generating, these data indicate that ACE inhibition may be most effective at lowering cardiovascular risk in patients with reduced GFR. Patients with stable coronary artery disease and reduced GFR may more likely benefit from the cardiovascular protective effects of ACE inhibition.

Clinical Implications of ACE Inhibition in Patients with WRF

The decision to withdraw ACE inhibition in patients who experience small elevations in serum creatinine has been controversial (81). Physicians are reluctant to continue treatment with ACE inhibitors when creatinine begins to rise for concerns of precipitating acute renal failure (76). However, minor increases in serum creatinine that occur with initiation of ACE inhibitor may paradoxically indicate improved renal hemodynamics, at least in the setting of proteinuric renal disease, and have been associated with long-term preservation of renal function (36, 37, 82). More rapid increases would suggest conditions such as bilateral renal artery stenosis or severe hypoperfusion, and would warrant discontinuation of ACE inhibition. Butler et al. did not find an association between WRF and ACE inhibitors in heart failure patients (83). Similarly, we did not observe a greater incidence of WRF in patients receiving ACE inhibition in SAVE.

Our data may suggest that the relationship between WRF and increased cardiovascular risk could be altered by ACE inhibitor therapy in patients after myocardial infarction. While a formal test for interaction was not significant, most likely due to inadequate sample size and statistical power given the relatively small number of subjects with WRF for each endpoint, the increased risk associated with WRF still appeared to be attenuated in the captopril group. We thus cannot exclude the possibility that ACE inhibition may alter the relationship between elevation in creatinine and cardiovascular outcomes given the consistently lower risk for each primary endpoint. Recommendations for starting ACE inhibitor therapy in patients with renal dysfunction include beginning with a conservative initial dose, increasing the dose only when well-tolerated, and having

once-daily morning dosing to permit nocturnal excretion of potassium to avoid hyperkalemia (84). Although there is no convincing evidence based on pharmakinetics that one ACE inhibitor is superior to another in providing renal and cardiovascular benefits, captopril would not be recommended over ACE inhibitors that are once-daily dosing because its shorter half-life would likely increase noncompliance and undertreatment. Blood pressure, renal function, and serum potassium levels should be closely monitored in patients with renal dysfunction and changes in serum creatinine, particularly during the first few months after initiation of ACE inhibitor therapy.

Limitations

This assessment of the impact of renal dysfunction and response of ACE inhibition in post-MI patients with left ventricular dysfunction is not without limitations. In the case of proteinuria, because only a subset of patients enrolled in SAVE underwent dipstick analysis, our statistical power is limited. Nevertheless, even in this small sample, we are able to demonstrate an independent increase in cardiovascular risk associated with proteinuria and a clear differential benefit to ACE inhibitor therapy in this population. Dipstick urinalysis gives only a crude estimate of protein excretion, which may vary depending on the hydration status of the patient. Tests with a higher sensitivity and specificity for quantifying microalbuminuria may be more accurate indicators of cardiovascular risk (85). However, the ability of a qualitative measure such as dipstick urinalysis to demonstrate significant risk according to the degree of proteinuria emphasizes the importance of proteinuria as a cardiovascular risk factor. Sodium intake, which was not quantified, is known to blunt the antiproteinuric effects of

ACE inhibitors in spite of blood pressure reduction, and may have influenced the response to treatment with captopril (86, 87).

In the analysis of WRF, serum creatinine was measured two weeks after randomization, which occurred on average eleven days post-infarction. The variation in time may have affected the results through either deterioration or improvement of renal function. However, this variation in time underscores not only the prognostic value of WRF, but also emphasizes the value of measuring serum creatinines anywhere from one to three weeks after the acute event and during outpatient follow-up for accurate risk stratification. Subjects who were excluded from the analysis due to missing serum creatinine measurements or cardiovascular events prior to two weeks demonstrated a higher rate of events during follow-up. Although this introduces possible selection bias, there was no difference in baseline creatinine, change in creatinine, or treatment assignment compared with the study cohort and thus should not have altered the influence of WRF on cardiovascular risk.

The dose of study medication (placebo or captopril) was also variable; titration regimens were left to the discretion of each subject's physician. Subjects who tolerated the initial test dose were included regardless if the study medication was not fully titrated to the target dose of 25mg TID by the end of two weeks. The majority of subjects were started at 12.5mg and titrated upwards, but there were subjects who started at lower doses or were down-titrated due to adverse drug reactions or cardiovascular events prior to two weeks, which might influence the predictive value of increased creatinine. Our findings in the placebo group, however, would not have been influenced by dose titration.

Finally, SAVE was conducted between 1988-1991, and thus we cannot exclude the possibility that changes in the management of post-MI patients may have altered the current relation between proteinuria, worsening renal function, and cardiovascular risk. However, SAVE was conducted in a randomized, placebo-controlled setting, and therefore allowed us to assess the true effect of ACE inhibition on cardiovascular outcomes in the setting of renal dysfunction.

CONCLUSIONS

In summary, we observed that two markers of renal disease, proteinuria and worsening renal function, are associated with significantly increased risk for cardiovascular outcomes and mortality in patients with systolic dysfunction after myocardial infarction. This association is independent of baseline renal function, as assessed by estimated glomerular filtration rate. The benefit of captopril in reducing cardiovascular morbidity and mortality was greatest in patients with proteinuria, suggesting that this measure may help identify a group of patients who are at higher risk. Although a significant interaction between worsening renal function and ACE inhibition was not demonstrated, the risk was most prominent in patients receiving placebo, and appears to be attenuated in patients receiving captopril.

Given the rising incidence of chronic kidney disease in the United States, understanding the cardiovascular risk associated with having one or both of these markers of kidney disease is of profound clinical importance. The cardiorenal syndrome, which has primarily been studied in the heart failure population, needs to be better characterized

in patients after myocardial infarction as it may help in elucidating the complex pathophysiology surrounding this growing problem. These findings suggest the importance of using relatively simple and inexpensive measures, such as urine dipstick analysis and serum creatinine, to follow renal function during the first few weeks after acute myocardial infarction. Even during outpatient follow-up, close monitoring for renal dysfunction may aid in long-term risk stratification for cardiovascular events. These results not only appear to identify the additional benefit post-MI patients who have proteinuria receive from ACE inhibitor therapy, but may argue against discontinuation of ACE inhibitor therapy after small, nonprogressive increases in creatinine. However, more data from clinical trials are needed to better understand the interaction between kidney and cardiovascular disease, and to improve utilization of aggressive therapeutic strategies, such as ACE inhibition.

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TABLES

Table 1. Comparison of Baseline Characteristics of Patients by Proteinuria

Characteristics[A]	(-) Proteinuria (n=461)	(+) Proteinuria (n=122)	P-value
Age (yr)	59.7 ±10.5	62.3 ± 9.7	.003
Baseline Creatinine (mg/dl)	1.16 ± 0.3	1.35 ± 0.5	<.001
Baseline eGFR (ml/min/1.73m^2)	69.9 ± 19.6	60.9 ± 19.2	<.001
Systolic BP	112.7 ±14.5	115.7 ± 18.7	.08
Diastolic BP	70.5 ±10.4	70.3 ±11.5	.83
Body Mass Index	26.4 ± 4.2	26.5 ± 4.5	.75
Female gender (%)	91 (19.7)	22 (18.0)	.67
LVEF (%)	31.2 ± 6.5	29.8 ± 7.7	.05
Killip class ≥2 (%)	165 (35.8)	65 (53.3)	<.001
Hypertension (%)	155 (33.6)	54 (44.3)	.03
Diabetes (%)	81 (17.6)	28 (22.9)	.18
Previous MI (%)	163 (36.2)	35 (29.2)	.15
History of CHF (%)	20 (4.3)	5 (4.1)	.91
Ever smoked (%)	102 (22.1)	29 (23.8)	.70
Alcohol use (%)	269 (58.3)	66 (54.1)	.40
Medications[B]:			
Diuretics (%)	169 (39.5)	54 (50.0)	.05
B-blockers (%)	140 (32.1)	35 (31.8)	.95
Captopril Assignment (%)	231 (50.1)	64 (52.5)	NS[C]

[A] Plus-minus values are mean ± SD; Student's t-test for continuous variables, chi2 for categorical
[B] Medications-sustained drug treatment within 24 hours prior to randomization
[C] by design

Table 2. Outcomes by Proteinuria in Cox Proportional Hazard Models

Outcomes	(-) Proteinuria (n=461) Events (%)	(+) Proteinuria (n=122) Events (%)	Univariate Analyses HR (95%CI)	Multivariate Analyses[A] HR (95%CI)
Death	92 (20.0)	38 (31.1)	1.63 (1.12-2.38)	1.84 (1.20-2.82)
Cardiovascular Death	79 (17.1)	33 (27.1)	1.64 (1.09-2.46)	1.87 (1.18-2.98)
Death or Stroke	100 (21.7)	41 (33.6)	1.65 (1.15-2.38)	1.83 (1.21-2.98)
Death or MI	123 (26.7)	45 (36.9)	1.47 (1.05-2.07)	1.52 (1.03-2.24)
Death or CHF Hospitalization	123 (26.7)	43 (35.2)	1.40 (.99-1.99)	1.57 (1.06-2.32)
Composite[B]	152 (33.0)	51 (41.8)	1.35 (0.98-1.86)	1.41 (0.99-2.02)

[A] Multivariate model adjusted for age, gender, previous MI, history of hypertension, history of diabetes, history of CHF, body mass index, systolic/diastolic blood pressure, left ventricular ejection fraction , glomerular filtration rate, use of diuretics, and study medication (captopril vs placebo).
[B] Composite Endpoint includes death, recurrent MI, CHF hospitalization, and stroke
HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; CHF = congestive heart failure

Table 3. Association of Degree of Proteinuria with Outcomes[A]

Outcomes	Events (%)	Univariate Analysis HR (95% CI)	Multivariate Analysis HR (95% CI)
Death			
Trace (n=87)	22 (25.3)	1.33 (.84-2.12)	1.46 (.89-2.41)
> Trace (n=35)	16 (45.7)	2.37 (1.39-4.03)	2.30 (1.29-4.09)
P for trend		.002	.003
Cardiovascular Death			
Trace (n=87)	19 (21.8)	1.33 (.81-1.20)	1.55 (.90-2.67)
> Trace (n=35)	14 (40.0)	2.39 (1.35-4.22)	2.30 (1.24-4.26)
P for trend		.003	.004
Death or Stroke			
Trace (n=87)	24 (27.6)	1.38 (.88-2.16)	1.51 (.94-2.42)
> Trace (n=35)	17 (48.6)	2.30 (1.37-3.84)	2.20 (1.26-3.82)
P for trend		.001	.002
Death or MI			
Trace (n=87)	28 (32.2)	1.31 (.87-1.98)	1.38 (.89-2.12)
> Trace (n=35)	17 (48.6)	1.86 (1.12-3.08)	1.66 (.97-2.85)
P for trend		.011	.03
Death or CHF Hospitalization			
Trace (n=87)	27 (31.0)	1.26 (.83-1.92)	1.44 (.92-2.24)
> Trace (n=35)	16 (45.7)	1.72 (1.02-2.90)	1.46 (.84-2.55)
P for trend		.03	.067
Composite Endpoint			
Trace (n=87)	33 (37.9)	1.25 (.86-1.83)	1.34 (.90-1.99)
> Trace (n=35)	18 (51.4)	1.57 (.96-2.57)	1.33 (.79-2.23)
P for trend		.042	.122

[A] Patients with no proteinuria (n=461) as the referent Group

Table 4. Efficacy of Captopril by Proteinuria

Variable	Placebo Events/Pts (%)	Captopril Events/Pts (%)	HR[A] (95% CI)	Test for Interaction
Death				
(-)Proteinuria	50/230 (21.7)	42/231 (18.2)	.83 (.55, 1.25)	
(+)Proteinuria	23/58 (39.7)	15/64 (23.4)	.46 (.24, .89)	P=.14
SAVE	275/1116 (24.6)	228/1115 (20.4)	.81 (.68, .97)	
Cardiovascular Death				
(-)Proteinuria	48/230 (20.9)	31/231 (13.4)	.64 (.40, 1.00)	
(+)Proteinuria	21/58 (36.2)	12/64 (18.7)	.40 (.20, .81)	P=.29
SAVE	234/1116 (20.9)	188/1115 (16.9)	.79 (.65, .95)	
Composite Endpoint[B]				
(-)Proteinuria	80/230 (34.8)	72/231 (31.2)	.87 (.63, 1.19)	
(+)Proteinuria	31/58 (53.4)	20/64 (31.2)	.41 (.23, .73)	P=.02
SAVE	450/1116 (40.3)	395/1115 (35.4)	.84 (.73, .96)	

[A] Hazard Ratio was calculated using unadjusted Cox proportional hazards model
[B] Composite Endpoint includes death, recurrent MI, CHF hospitalization, and stroke

Table 5. Baseline Characteristics according to Worsening Renal Function (WRF)			
Characteristics[A]	**ΔCr ≤ .3 (n=1631), 88.0%**	**ΔCr > .3 (n=223), 12.0%**	**P-value**
Age (yr)	58.8 ± 10.6	60.7 ± 10.8	.01
Creatinine (mg/dl)	1.20 ± .32	1.09 ± .35	<.001
LVEF (%)	31.3 ± 6.6	30.7 ± 6.4	.20
Systolic BP	112 ± 15	114 ± 16	.06
Diastolic BP	70 ± 10	70 ± 10	.99
Female gender (%)	257 (15.7%)	53 (23.8%)	.003
GFR < 60 ml/min/1.73m^2	549 (33.7%)	61 (27.3%)	.06
Hypertension (%)	677 (41.5%)	103 (46.2%)	.18
Diabetes (%)	333 (20.4%)	62 (27.8%)	.012
Previous MI (%)	584 (37.6%)	63 (29.4%)	.020
History of CHF (%)	99 (6.1%)	9 (4.0%)	.22
Smoking (%)	328 (20.1%)	60 (26.9%)	.019
Medications[B]: Diuretics (%)	538 (34.5%)	89 (41.9%)	.034
Captopril Therapy	819 (50.2%)	119 (53.4%)	.38[C]

[A] Plus-minus values are mean ± SD; Student's t-test for continuous variables, chi2 for categorical
[B] Medications-sustained drug treatment within 24 hours prior to randomization
[C] By design

Table 6. Events and Risk in Patients according to presence of WRF and Treatment

Events (%)	ΔCr≤.3 (n=1631)	ΔCr>.3 (n=223)	Unadjusted HR (95%CI)	Adjusted HR[A] (95%CI)	Adjusted HR by Treatment (n=1813) (95%CI)[C]	
					Placebo (n=916)	Captopril (n=897)[D]
Death	316 (19.4%)	58 (26.0%)	1.46 (1.10-1.93)	1.55 (1.15-2.11)	1.78 (1.18-2.68)	1.35 (.85-2.16)
CV Death	260 (15.9%)	51 (22.9%)	1.55 (1.15-2.09)	1.71 (1.24-2.37)	1.89 (1.20-2.97)	1.57 (.97-2.55)
Death and MI	438 (26.8%)	72 (32.3%)	1.33 (1.03-1.70)	1.28 (.97-1.68)	1.45 (1.00-2.11)	1.14 (.75-1.73)
Death and CHF	443 (27.2%)	78 (34.9%)	1.51 (1.19-1.93)	1.48 (1.13-1.92)	1.70 (1.19-2.43)	1.33 (.89-1.97)
Composite Endpoint[B]	564 (34.6%)	94 (42.1%)	1.41 (1.14-1.76)	1.36 (1.07-1.72)	1.57 (1.13-2.17)	1.22 (.86-1.75)

[A] Adjusted for age, sex, baseline creatinine, GFR <60ml/min/1.73m^2, history of hypertension, history of diabetes, history of CHF, left ventricular ejection fraction, previous myocardial infarction, use of diuretics, treatment assignment

[B] Composite endpoint: Death, MI, CHF Hospitalization, Stroke;

[C] From the original cohort of 1854 subjects, 41 were excluded who were not taking captopril at two weeks due to adverse drug reactions (hypotension, dizziness) in order to stratify risk associated with WRF by treatment

[D] Test for interaction: p >.15

HR: Hazard Ratio; CI: Confidence Interval