

Growth curve analysis in outcomes
research: development of chronic kidney
disease and decline of renal function in
patients with hypertension

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Also starring...

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- ...with financial support provided by NHLBI (1 U01 HL079208 and 1U01 HL079160)

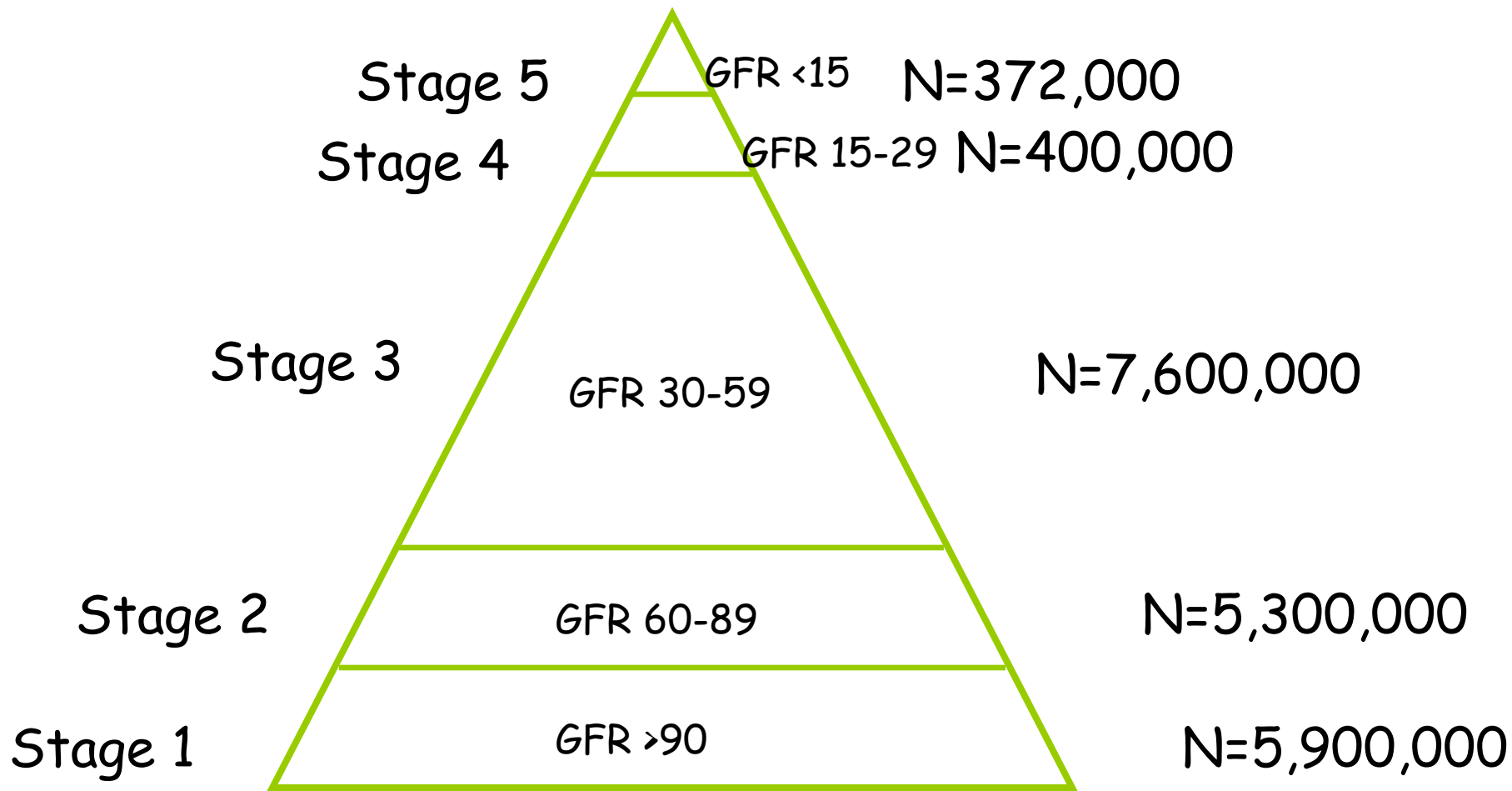
Clinical problem

- Chronic kidney disease (CKD) is common, and may progress to end-stage renal disease (ESRD) requiring dialysis
- Even at earlier stages, CKD disease is a risk factor for adverse health outcomes; more patients with CKD die of CVD than of CKD
- Some interventions have proven effective at slowing the progression of CKD

The tip and the iceberg

- Prior research has focused on the tip of the iceberg – progression and interventions for advanced CKD at risk of dialysis. Risk factors include age, African-American race, hypertension, and diabetes
- Most studies include participants in cohort studies (e.g. Framingham), or the control groups of RCTs – selected populations!
- Little is known about... the iceberg, i.e. risk factors for declining renal function or progression to CKD in the broader population of individuals who do not enroll in NIH-funded studies
- Little is known about... the trajectory of renal function in Latinos

Stages and Prevalence of CKD

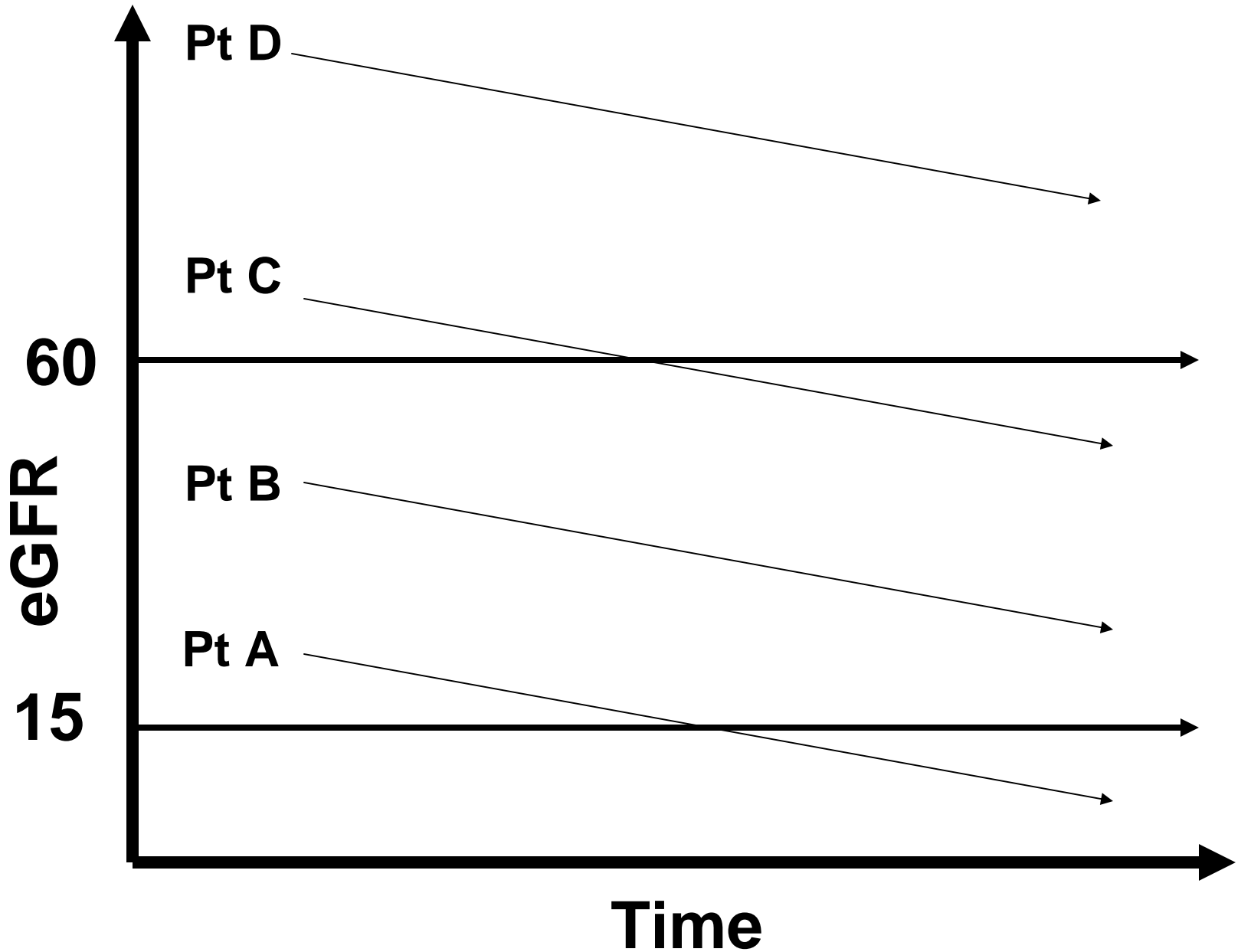


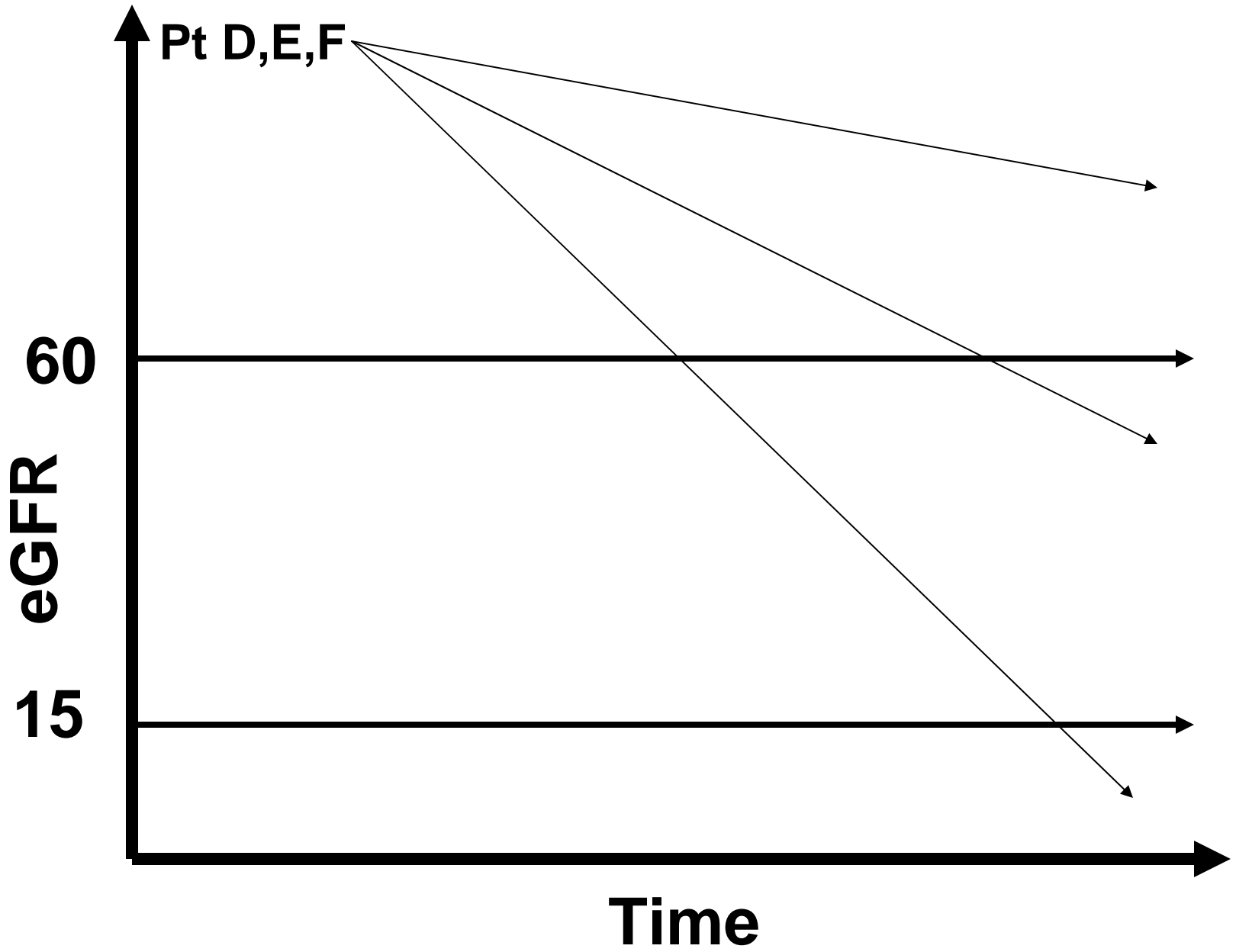
Measuring renal function

- Best measure of renal function is glomerular filtration rate (GFR); higher is better
- Variable of interest is decline in GFR over time
- Accurate measures of GFR not available in routine clinical practice
- GFR can be approximated (eGFR) by measurement of serum creatinine, using a formula (MDRD) that takes into account age, gender, and race
- Even this formula was developed in patients with existing CKD, and may be inaccurate in those with higher GFR

Progression of kidney disease

- Progression” usually defined dichotomously, by development of either ESRD or CKD (eGFR < 60)
- Slope of decline in eGFR assessed only in individuals with established CKD





LUCHAR Study

- NHLBI-funded cooperative agreement (2004-9) between Denver Health and UCD
- Goals are to develop and test CVD prevention strategies and reduce health care disparities for Latinos
- Developed a hypertension registry of 35573 individuals seen at DH for one or more visits for hypertension, 2000-2007

Cohort for today's study

- Individuals in hypertension registry
- Exclusions:
 - Single visit with DH system
 - < 21 years old
 - Any pregnancy care
 - < 3 serum creatinines (first 2 less than one month apart to establish baseline, last at least 1 year after first)
 - Individuals with ESRD
 - Individuals with CKD (eGFR < 60) at baseline

Research Objective

- Among individuals with hypertension, to determine baseline sociodemographic and clinical predictors of incident CKD or decline in renal function (by looking at associations with slope GFR/time) in patients without CKD at baseline (eGFR \geq 60)
- Hypothesis: Black race, male gender, and diabetes will be associated with incident CKD or more rapid decline of GFR

Data and Definitions

- **LUCHAR HTN registry -**
 - Inpatient and outpatient
 - billing data, ICD-9 codes, labs, pharmacy
- **Time zero –**
 - date of first creatinine after 1st ICD-9 code for hypertension
- **Baseline (for co-morbidities) –**
 - extend back to include all diagnoses in the registry prior to time zero and in 180 days after time zero
- **Baseline GFR –**
 - we initially planned to use the average of the 1st two measures

Analytic Approaches and Measures

- **Analyses**

- Logistic regression
- Mixed effects longitudinal modeling

- **Outcome**

- incident GFR (logistic) or GFR over time (longitudinal)
- estimated by MDRD study equation

$eGFR(\text{ml}/\text{min}/1.73\text{m}^2 = 186 \times (\text{sCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$

- **Independent variables**

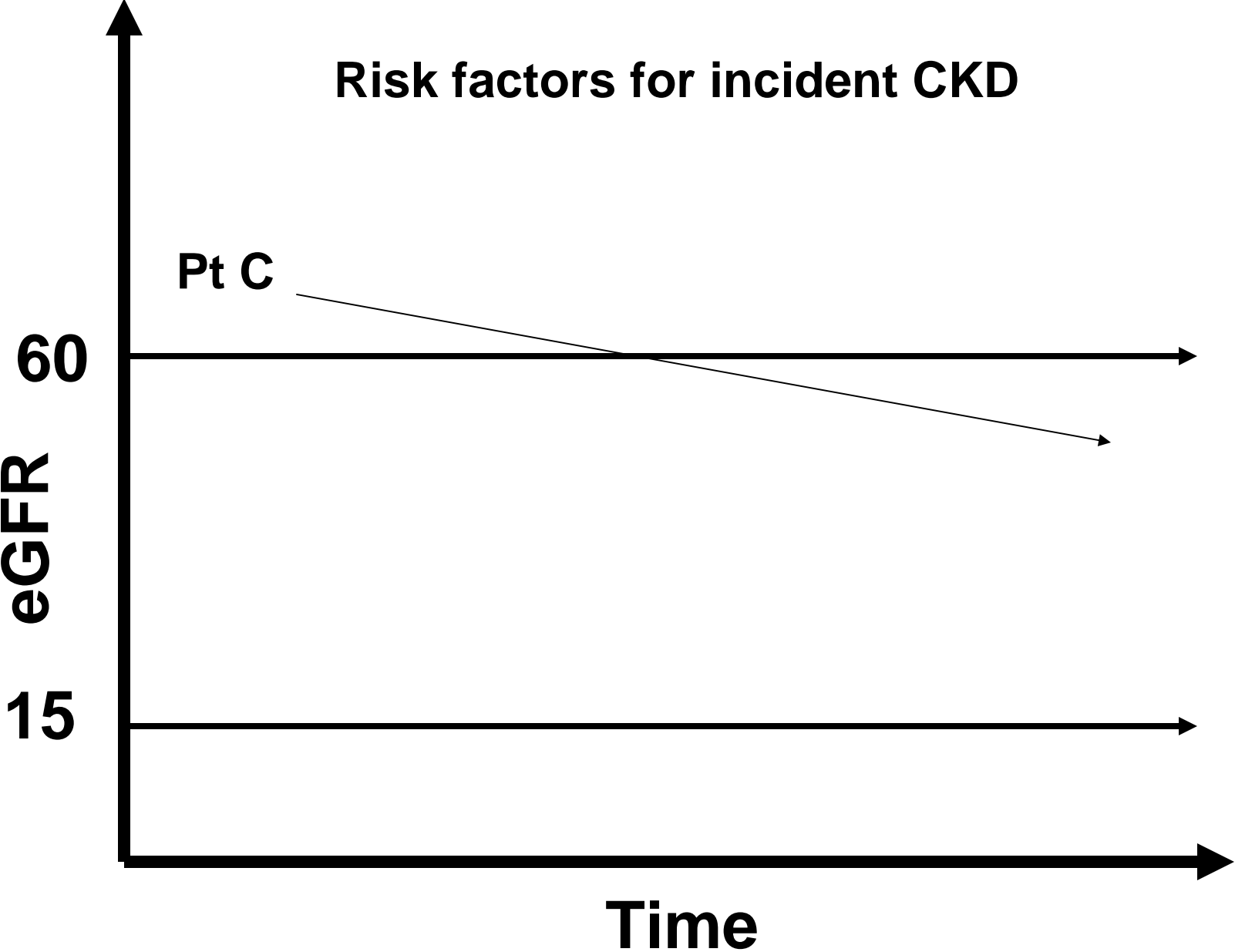
- Age (centered), gender, race/ethnicity, dominant payer, language, marital status
- Comorbidities
 - diabetes, vascular disease (cerebrovascular, peripheral vascular or coronary artery disease), heart failure, dyslipidemia, mental health, substance use

Baseline patient characteristics	N=10420 N (%)
Age at Time Zero - Mean (sd)	55.0 (11.9)
% Male	4672 (44.8%)
Race/ethnicity	
African American	2805 (26.9%)
Hispanic	4556 (43.7%)
White	2722 (26.1%)
Other	209 (2.0%)
Missing	128 (1.2%)
Marital status	
Married	3224 (30.9%)
Other	6467 (62.1%)
Unknown	729 (7.0%)

Baseline patient characteristics	N=10420 N (%) or mean (sd)
Language	
English	7157 (68.7%)
Spanish	1785 (17.1%)
Other	384 (3.7%)
Missing	1094 (10.5%)
Duration of Hypertension, years	
Mean (sd)	5.2 (1.6)
Period of observation, months	
Mean (sd)	44.7 (20.1)
Baseline eGFR	
Mean (sd)	98.7 (23.6)
Median	94.0
Min / Max	60.0/ 199.6

Baseline Comorbidities	Total N=10420 N (%)
Medical Comorbidities	
Diabetes	3822 (36.7%)
Vascular	1721 (16.5%)
Congestive Heart Failure	37 (0.4%)
Dyslipidemia	1766 (17.0%)
Mental Health Comorbidities	
Depression, Bipolar or Psychotic Disorder	2614 (25.1%)
Substance Abuse Comorbidities	
Substance or Alcohol Abuse	1666 (16.0%)

Risk factors for incident CKD

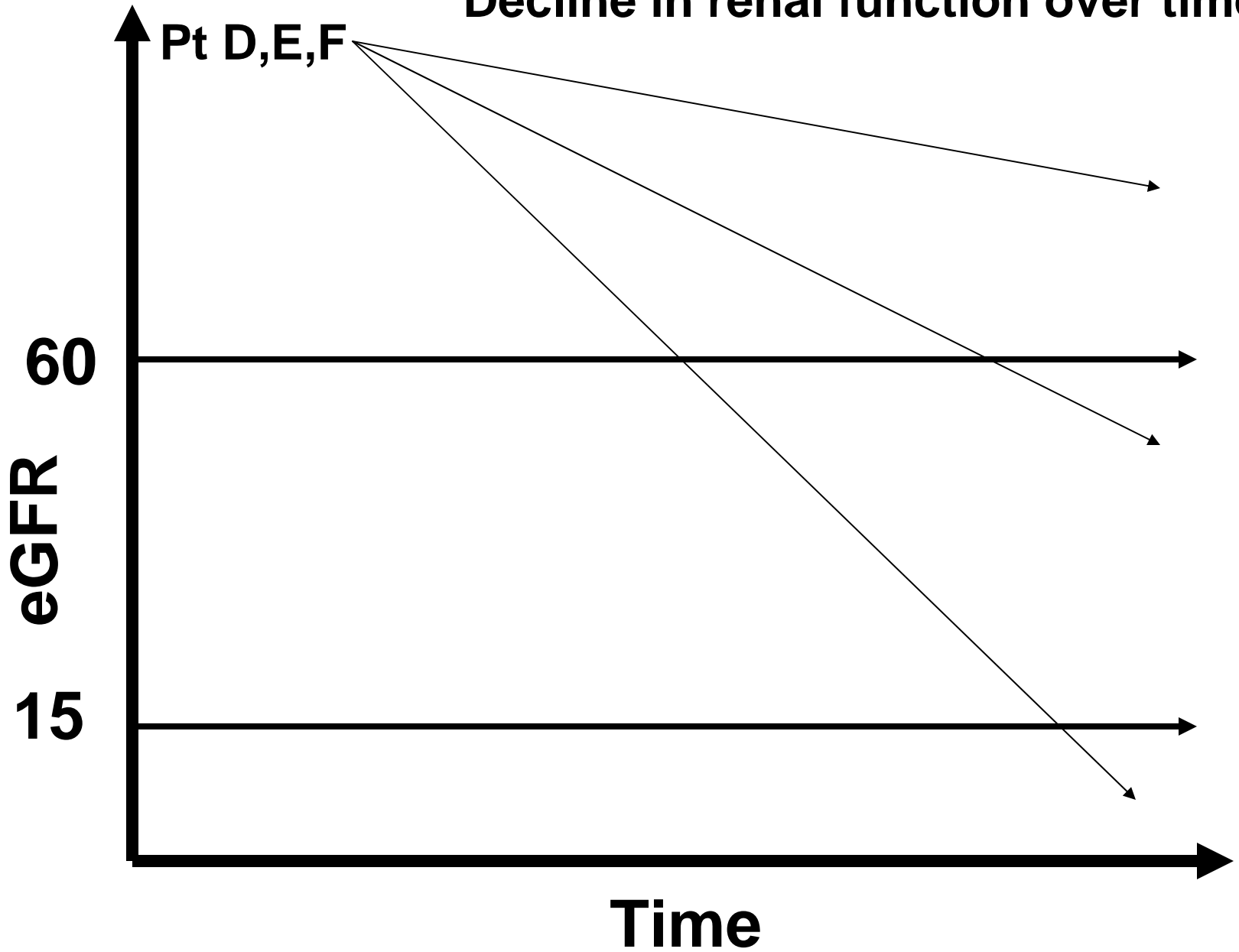


Predictors of Incident CKD: Final Logistic Regression Model

	Adjusted OR (95% CI)	Adjusted p value
Age (per 10 years)	1.13 (1.03 – 1.24)	0.008
Period of observation, per 6 months	1.21 (1.17 – 1.25)	<.0001
Baseline eGFR**, per 10 units	0.69 (0.65 – 0.73)	<.0001
Comorbidities		
Diabetes	3.66 (2.97 – 4.51)	<.0001
Vascular	1.67 (1.32 – 2.10)	<.0001

** Baseline eGFR is first measurement after HTN diagnosis
C statistic: 0.81

Decline in renal function over time



Mixed effects longitudinal model with random intercept and slope

- **Level 1 model**. Repeated measures within patients will be modeled as a *linear time trend* (growth curve) model. Time coded as actual time since baseline. The outcome (GFR) for patient i measured at time t is Y_{ti}

$$Y_{ti} = \pi_{0i} + \pi_{1i} (\text{time})_{ti} + \varepsilon_{ti}$$

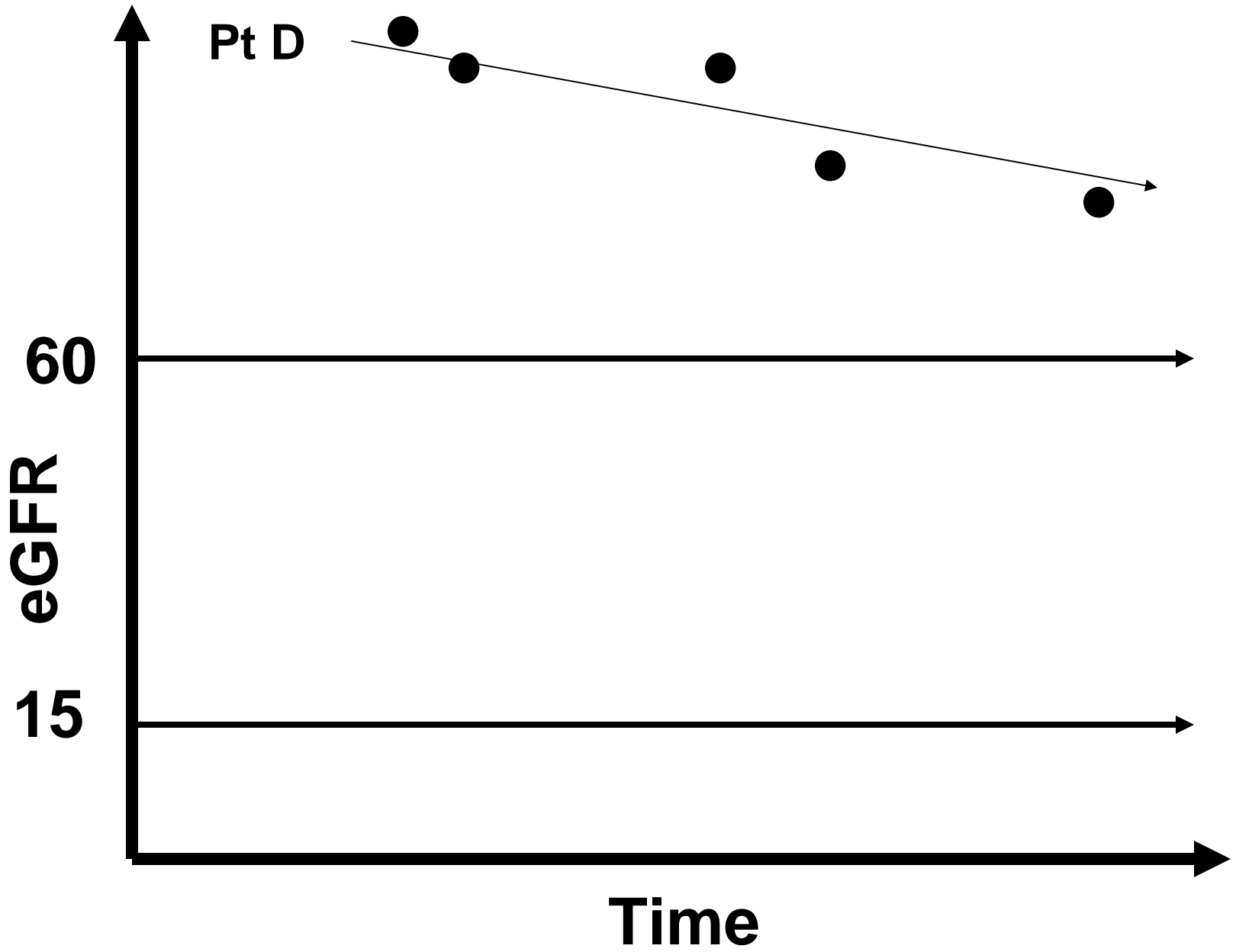
- **Level 2 model**. The patient level models specify the relationship between the patient-level coefficients and the coefficients in the Level 1 model. Fixed patient-level covariates (X_j) included at this level.

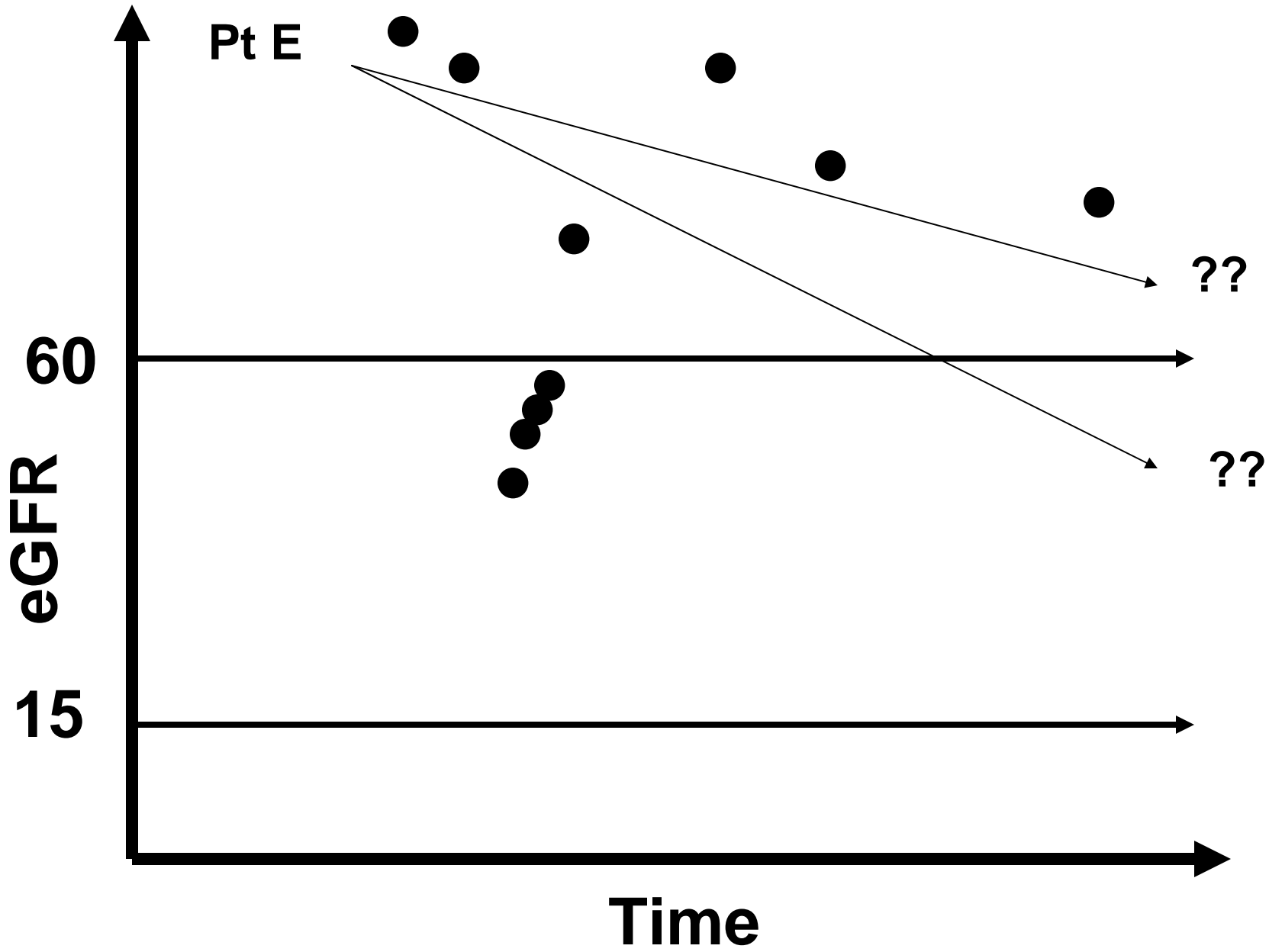
Random intercept: $\pi_{0i} = \beta_{00} + \Sigma \beta_{0p} (X_i) + r_{0i}$

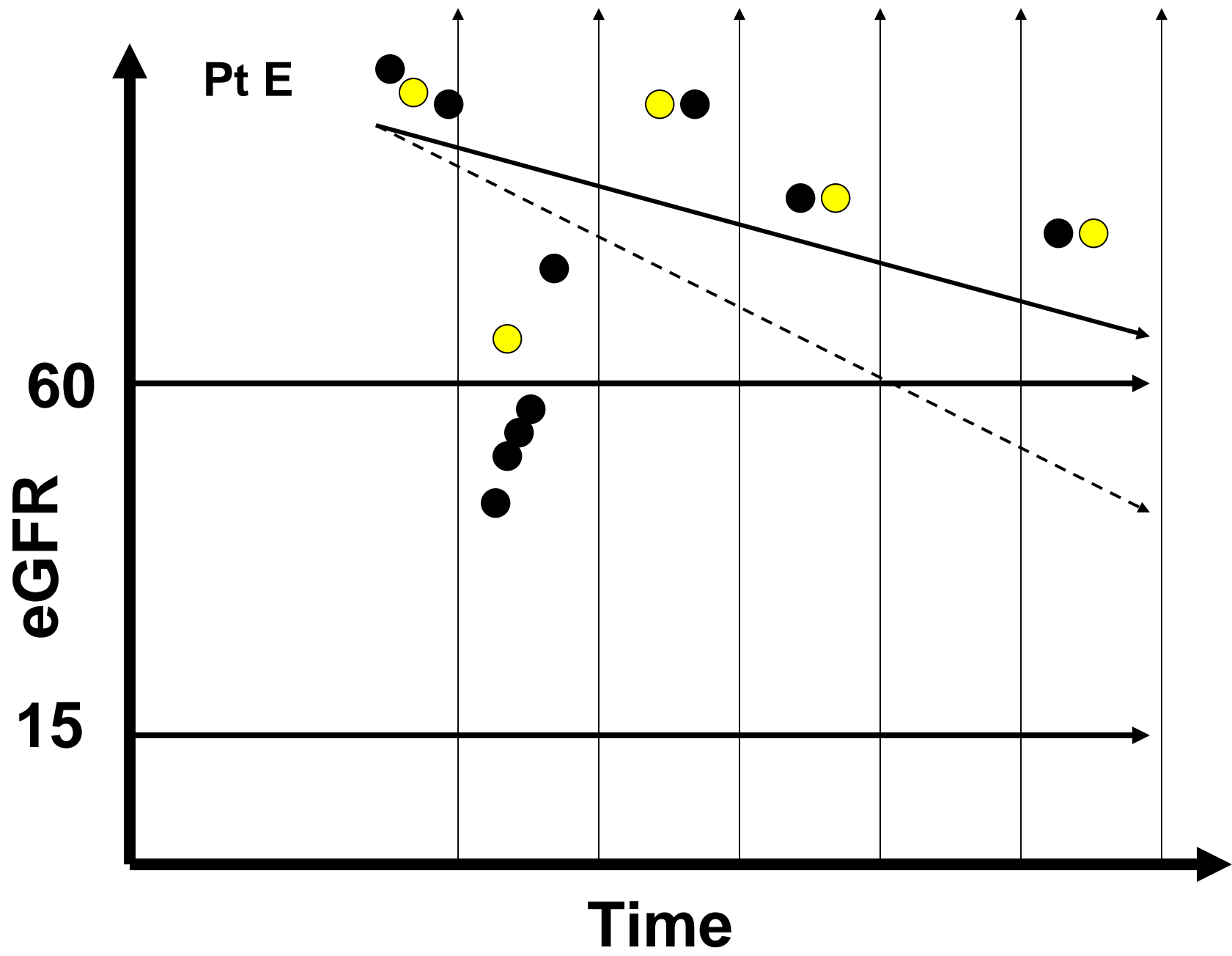
Random slope: $\pi_{1i} = \beta_{10} + \Sigma \beta_{1p} (X_i) + r_{1i}$

Analytic Challenges and Solutions

- GFR highly variable within individuals
- Random slope models failed to converge
- Potential solutions
 - Use average creatinine for 6-month blocks and compute GFR to stabilize GFR measures
 - Set any GFR > 200 to 200
 - Set any GFR < 15 to 15
 - Time coded ordinally as 6-month block, starting with baseline = 0







SAS code: Random intercept model with covariates

```
proc mixed data=newall2 covtest;  
  class study_no race gender cmdm cmvasc;  
  model egfr=race gender cmdm cageatt0 cmvasc  
    time/solution ddfm=kr;  
  random intercept / subject=study_no;  
run;
```

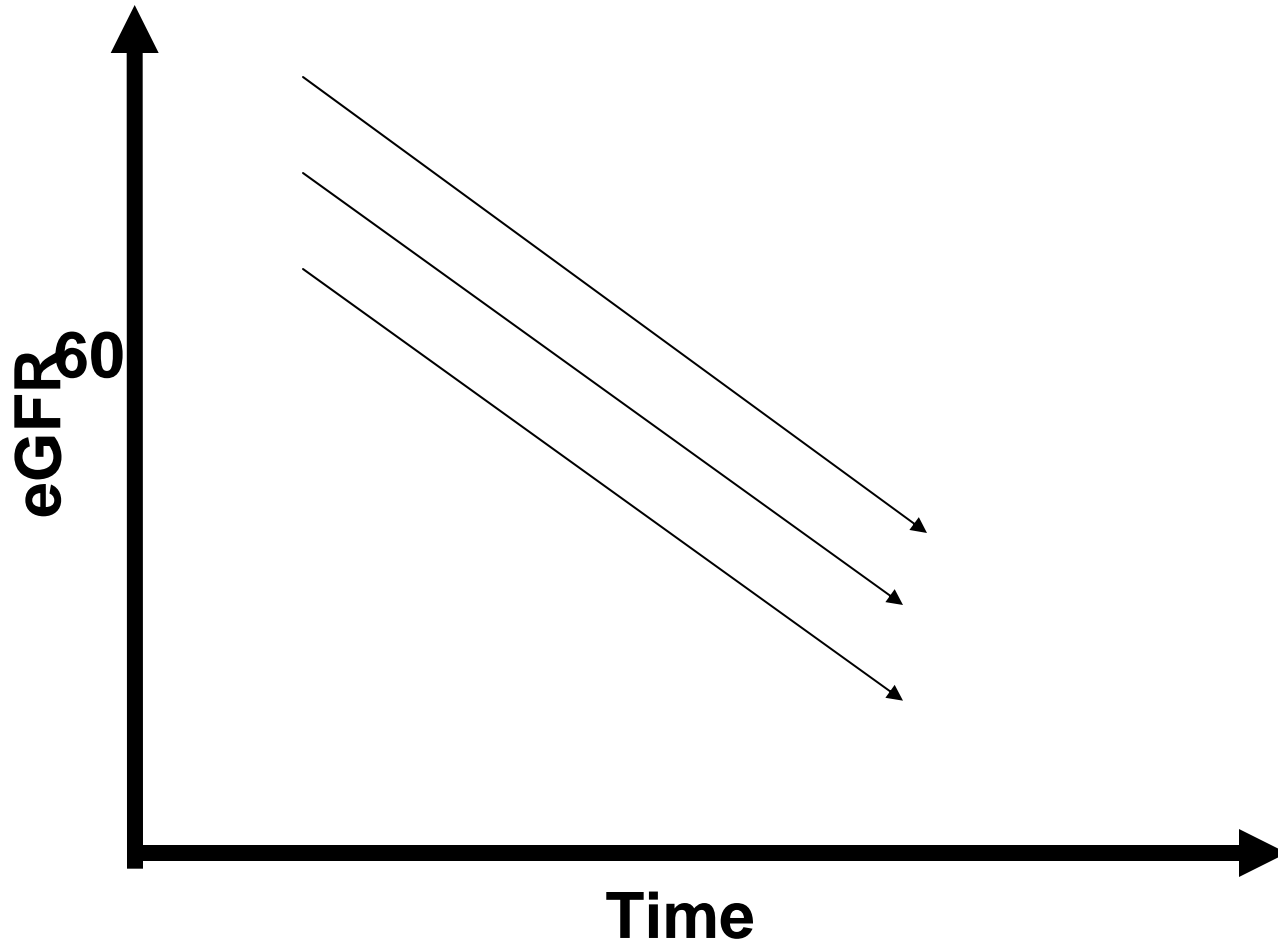
Covariance Parameter Estimates					
Cov Parm	Subject	Estimate	Standard Error	Z Value	Pr > Z
Intercept	study_no	354.52	5.6088	63.21	<.0001
Residual		217.07	1.4620	148.47	<.0001

Results: Random intercept model with baseline covariates

Solution for Fixed Effects					
Effect	Estimate	Standard Error	DF	t Value	Pr > t
Intercept	97.5464	0.4653	11E3	209.64	<.0001
*African American	3.9352	0.5458	1E4	7.21	<.0001
*Latino	2.9177	0.4986	1E4	5.85	<.0001
*Other race	-1.5006	1.1736	11E3	-1.28	0.2010
Female	-2.8812	0.4041	1E4	-7.13	<.0001
Diabetes	-1.2814	0.4162	1E4	-3.08	0.0021
Age	-0.5728	0.01708	1E4	-33.53	<.0001
Vascular	-1.2442	0.5421	1E4	-2.30	0.0217
time	-1.0472	0.02028	47E3	-51.63	<.0001

*reference white

Random Intercept Model



Random coefficients with covariates

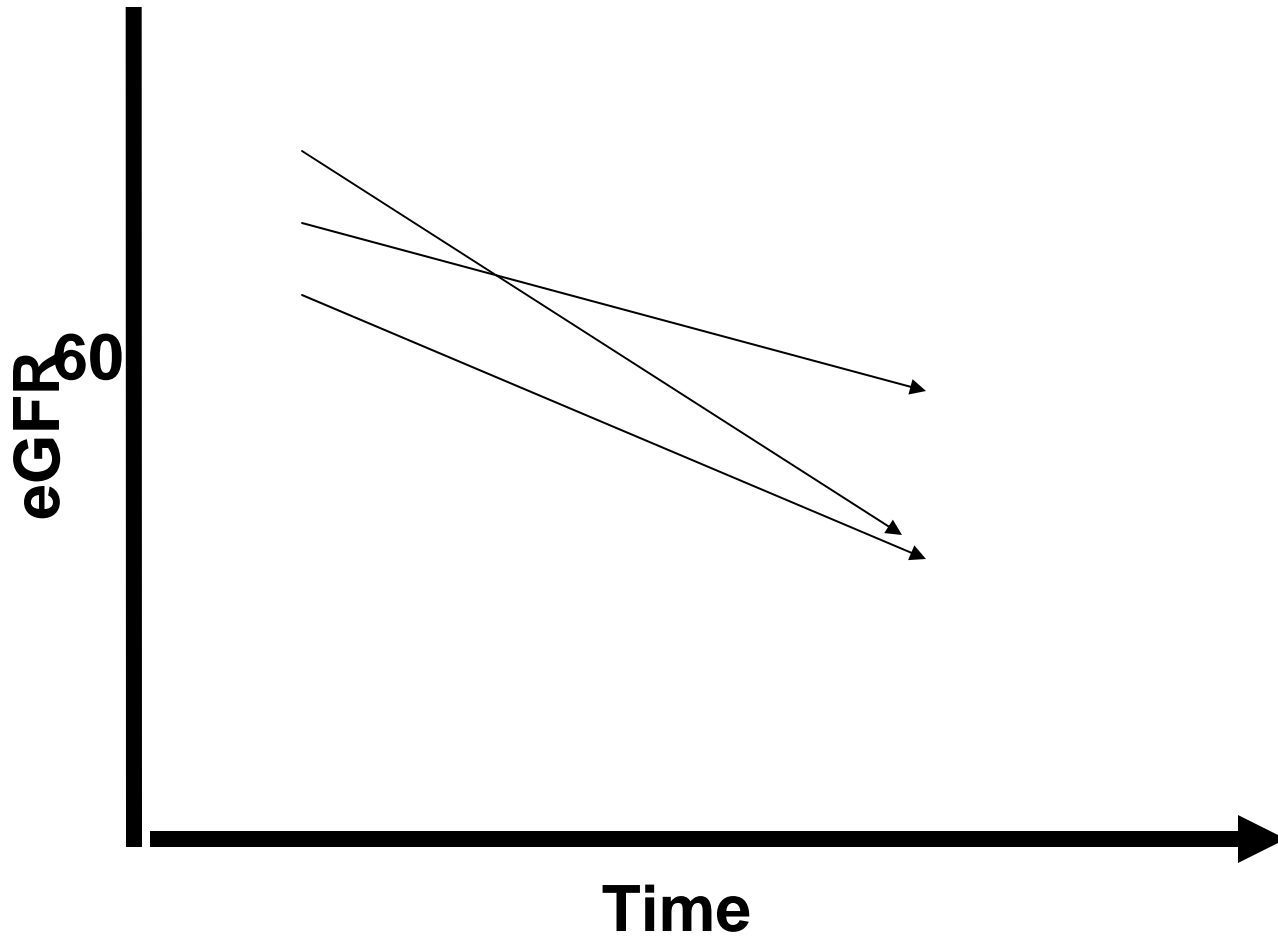
- **proc mixed** data=newall2 covtest;
class study_no race gender cmdm cmvasc;
model egfr=race gender cmdm cageatt0 cmvasc
time/solution ddfm=kr;
random intercept time/ subject=study_no;
run;

Covariance Parameter Estimates					
Cov Parm	Subject	Estimate	Standard Error	Z Value	Pr > Z
Intercept	study_no	327.75	5.4535	60.10	<.0001
time	study_no	2.9952	0.1055	28.38	<.0001
Residual		183.65	1.3663	134.41	<.0001

Results: random coefficients model with baseline covariates

Effect	Estimate	Standard Error	DF	t Value	Pr > t
Intercept	96.8881	0.4563	11E3	212.33	<.0001
African American	4.0507	0.5375	1E4	7.54	<.0001
Latino	2.9881	0.4909	1E4	6.09	<.0001
Other race	-1.6777	1.1535	11E3	-1.45	0.1458
Female	-2.7219	0.3980	1E4	-6.84	<.0001
Diabetes	-0.02099	0.4101	1E4	-0.05	0.9592
Age	-0.5767	0.01681	1E4	-34.30	<.0001
Vascular	-0.9858	0.5338	1E4	-1.85	0.0648
time	-1.0593	0.02875	6785	-36.84	<.0001

Random Coefficients Model



Results: random coefficients model with selected interactions

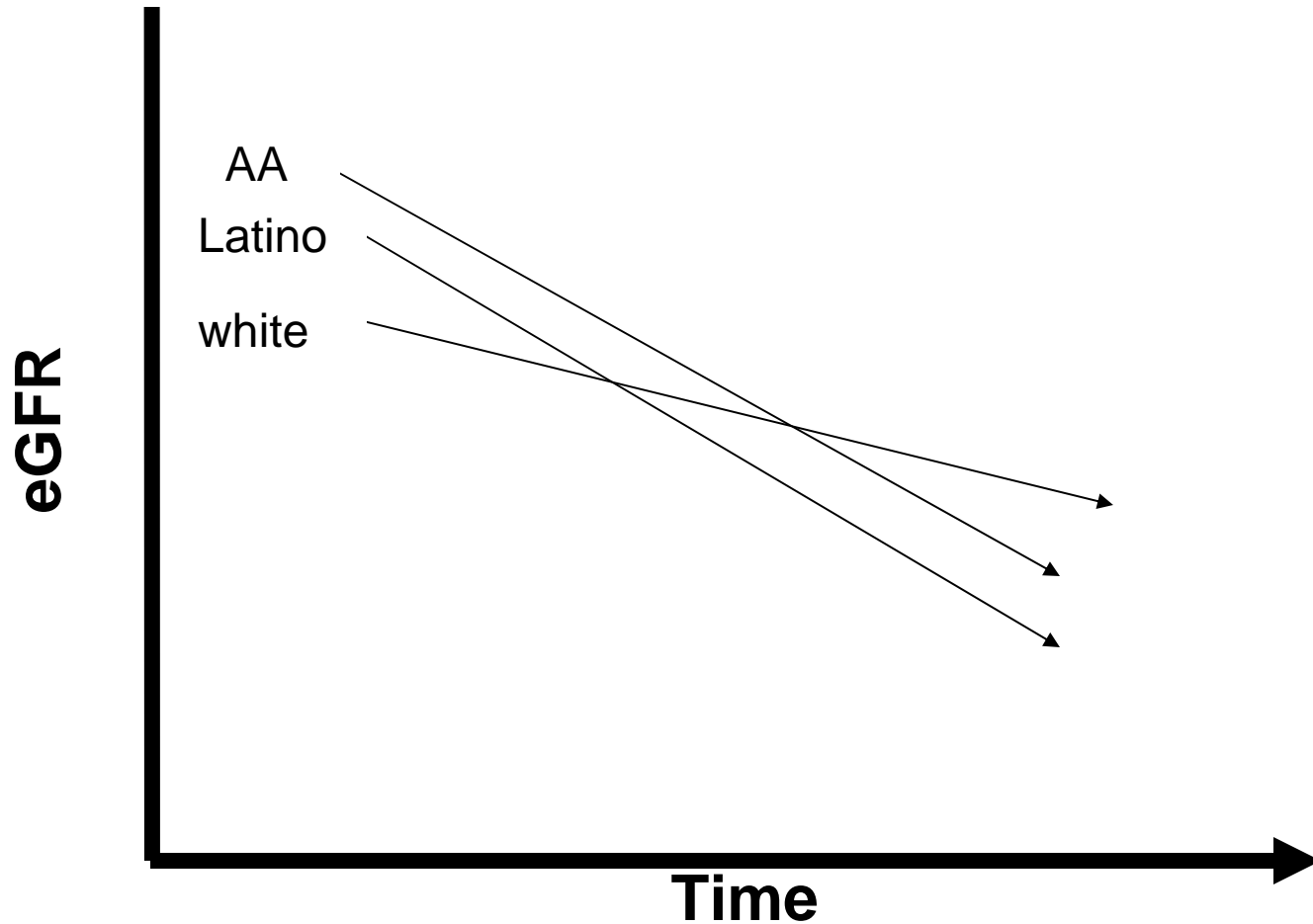
- Tested interactions of race, gender, diabetes, and vascular disease with time in separate models
- Final model - interactions that were significant ($p < .05$) in individual models
- model egfr=race race*time gender cmdm cmdm*time cageatt0 cmvasc cmvasc*time time/solution ddfm=kr;
- random intercept time/ subject=study_no;

Covariance Parameter Estimates					
Cov Parm	Subject	Estimate	Standard Error	Z Value	Pr > Z
Intercept	study_no	328.17	5.4524	60.19	<.0001
time	study_no	2.8695	0.1030	27.86	<.0001
Residual		183.61	1.3648	134.53	<.0001

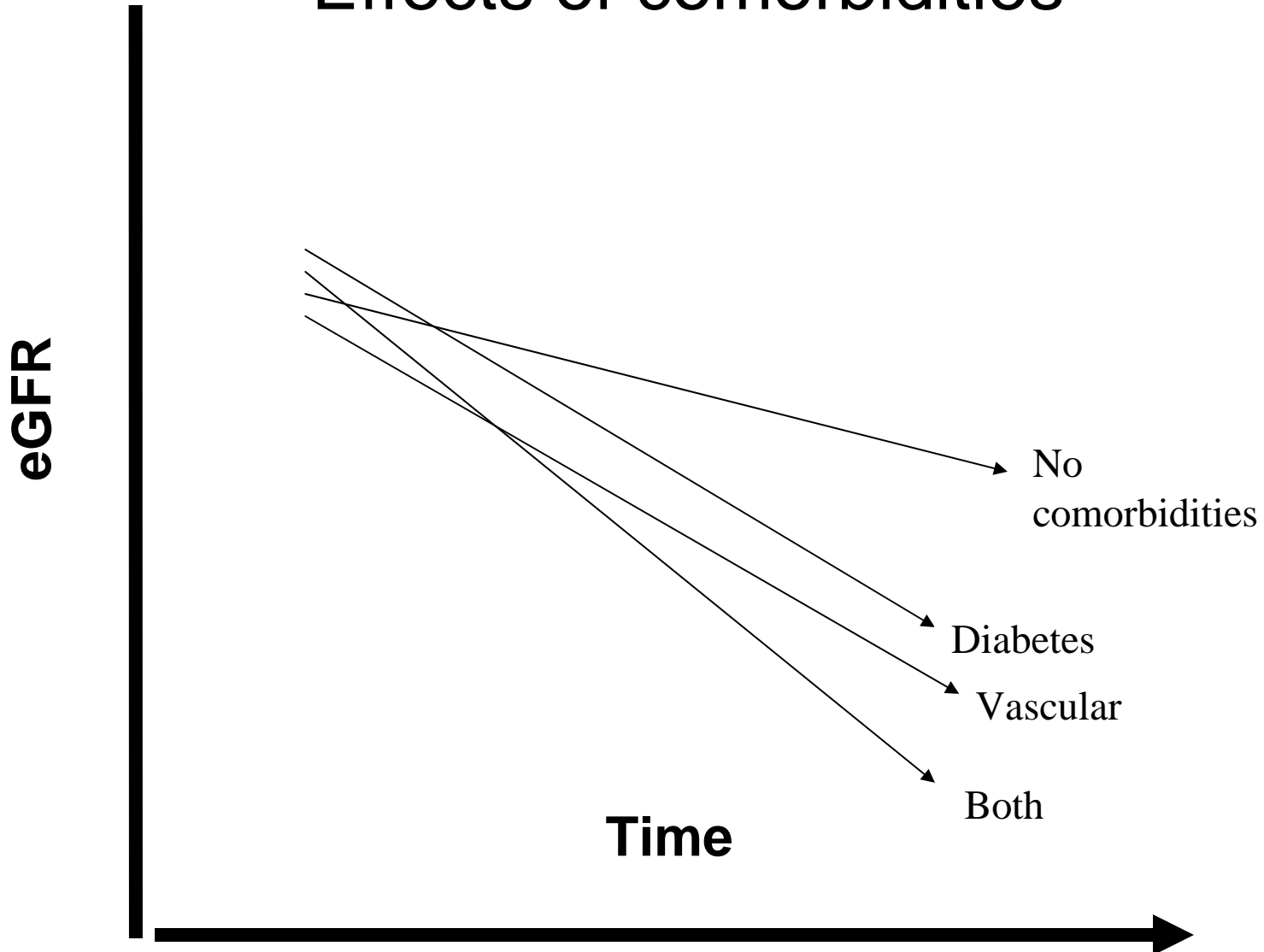
Final model: Intercepts and slopes as outcomes

Effect	Estimate	Standard Error	DF	t Value	p Value
Intercept	96.2002	0.4684	12E3	205.39	<.0001
African American	4.1404	0.5592	12E3	7.40	<.0001
Latino	3.0830	0.5109	12E3	6.03	<.0001
Other race	-1.8694	1.2049	13E3	-1.55	.1208
time*RACE AA	-0.7576	0.05805	6696	-13.05	<.0001
time*RACE Latino	-0.7585	0.05278	7014	-14.37	<.0001
time*RACE Other	-0.6118	0.1707	8074	-3.58	.0003
Time (white)	-0.7057	0.06163	7182	-11.45	<.0001
Female	-2.7283	0.3980	1E4	-6.86	<.0001
Diabetes	1.3698	0.4261	12E3	3.21	.0013
time*diabetes	-0.7280	0.05970	6523	-12.19	<.0001
Age	-0.5768	0.01681	1E4	-34.31	<.0001
Vascular	-0.5608	0.5538	12E3	-1.01	.3112
time*vascular	-0.2232	0.07694	6504	-2.90	.0037

Intercepts and Slopes as Outcomes Model: effects of race/ethnicity



Intercepts and Slopes as Outcomes Model: Effects of comorbidities



Summary of Results

- There is significant decline in GFR over time
- Patients who are African American, Latino, or other race have significantly greater decline in GFR than whites
- Patients with diabetes have significantly greater decline in GFR than patients without diabetes
- Patients with vascular disease have significantly greater decline in GFR than patients without vascular disease

Comparison of modeling approaches

- Risk factors for incident CKD
 - Age
 - Duration of observation
 - Diabetes
 - Vascular disease
 - Baseline eGFR
- Risk factors for decline in eGFR
 - Age
 - Duration of observation
 - Diabetes
 - Vascular disease
 - Race/ethnicity
 - Gender

Growth Curve Models in Outcomes Research

- With expansion of electronic databases, increasing amount of patient-level, time series data (BP, creatinine, depression scores...)
- Time horizons are longer than in clinical trials, but highly variable between patients
- Trajectories of change are important, even if patients don't reach an arbitrary threshold of disease (e.g. eGFR < 60)
- Large sample sizes allow detection of trends that are not apparent even in traditional cohort studies

Beyond logistic regression

- Because the data are improving, we need more sophisticated analytic approaches that take time into account!
- These approaches can complement simpler analytic models (e.g. logistic regression model for incident CKD)