

Getting started: The 1-page protocol synopsis

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Idea

**Research
Methods**

Results

Components of a Clinical Research protocol

Introduction

Research objectives

Primary and secondary endpoints

Background and rationale

Methods

- Study design
- Selection of subjects. Case definition. Inclusion/exclusion criteria
- Detailed procedures for patient entry. Randomization.
- Detailed study evaluations and procedures visit by visit
- Flow chart of study events
- Stopping criteria and safety
- Statistical Methods
 - Sample size calculation
 - Statistical analysis

Administrative aspects. Humans subjects research. HIPPA

1- Page Protocol Synopsis

Introduction/Background: 5-10 sentences.

Research objectives

- The objective(s) of this study is/are... (List 1-3)
- Primary and secondary endpoints (1-3)

Methods

- Study design and overview (4-5 sentences)
- Study participants and entry (4-5 sentences)
 - Inclusion criteria (5-10)
 - Exclusion criteria (5-10)
- Participant safety/risks (4-5 sentences)
- Statistical Methods (3-4 sentences)
 - Sample size calculation
 - Statistical analysis

1- Page Protocol Synopsis

1. Concise overview to share with potential collaborators, research unit directors, clinic faculty
2. Detailed enough to allow determination of merit and feasibility
3. Less time consuming than attempting an entire protocol from scratch
4. Promotes moving ahead with an idea
5. Flexible: Can be modified easily
6. Key elements are there: Can be expanded to full protocol when ready

Case Example

Mechanisms of impaired potassium handling with dual RAAS blockade in patients with CKD

1- Page Protocol Synopsis

Introduction/Background: 5-10 sentences.

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Chronic kidney disease (CKD) in US

20 million in US with stage III chronic kidney disease (GFR<60 ml/min)

10-fold increase in risk for CVD.

Leading cause of CKD is **Diabetes Mellitus**

Highest prevalence of CKD is among the **elderly**

292,000 patients with ESRD requiring renal replacement

5-year survival is 32%. Estimated 2.2 million with ESRD by 2030

Effective treatment options to delay progression to ESRD are limited

1. BP control <130/80 (125/75 if proteinuria > 1 gram)
2. **Single agent** RAAS blockade with either ACE inhibitor or AII blocker
3. **Dual agent** RAAS blockade with ACE inhibitor or ARB plus Aldosterone antagonist

The main adverse effect that limits the use of RAAS blockade is hyperkalemia

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- **Participant safety/risks**
- Statistical Methods
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Participant safety/risks

The study participants will be monitored closely in the Division of Clinical Pharmacology inpatient research center. The study coordinators and the study PI will assess all adverse events (AE) immediately. In the event of an AE, the PI and the study team will carefully assess the nature, severity, and possibility of study medication relatedness. If, in the opinion of the PI, there is a likely possibility of a clinically important drug-related AE, the study medication will be discontinued. This will be handled under the care of the PI on a case by case basis.

Increase in serum potassium

1. Study participants will be required to have a serum potassium of less than 5.0 mmol/L prior to entry into the study.
2. Serum potassium will be determined at each outpatient visit and on admission to the research unit.
3. Calcium Chloride for IV injection as well as 50% glucose and insulin injection will be readily available during the entire potassium handling study.
4. Participants will be discontinued from the study for $K > 5.5$ at any point in the study except during acute K-loading study.
5. ECG changes suggestive of changes of hyperkalemia from baseline ECG (peaked T waves, shortened PR interval) will be followed immediately with a STAT sample for potassium and appropriate intervention as determined by the study PI.

Statistical Methods

1. Sample size is calculated to be 15 to allow detection of 1 mmol/hour reduction of U_{kV} at hour 2-3 with alpha 0.05 and power 0.80. 20 subjects is conservative enrollment.
2. Paired t-tests used to detect differences in hour 2-3 U_{kV} and K during K-handling study between drug and placebo
3. Mixed models to investigate the predictive relationship between dynamic K-handling variables (K , U_{kV}) and ambulatory K

$$\text{Ambulatory } K = F(U_{kV}, K, \text{eGFR}, \text{drug}, \text{demographic})$$

Sample size N required to demonstrate a Difference in UKV (mmol/hr) between Group A and Group B (t-test)

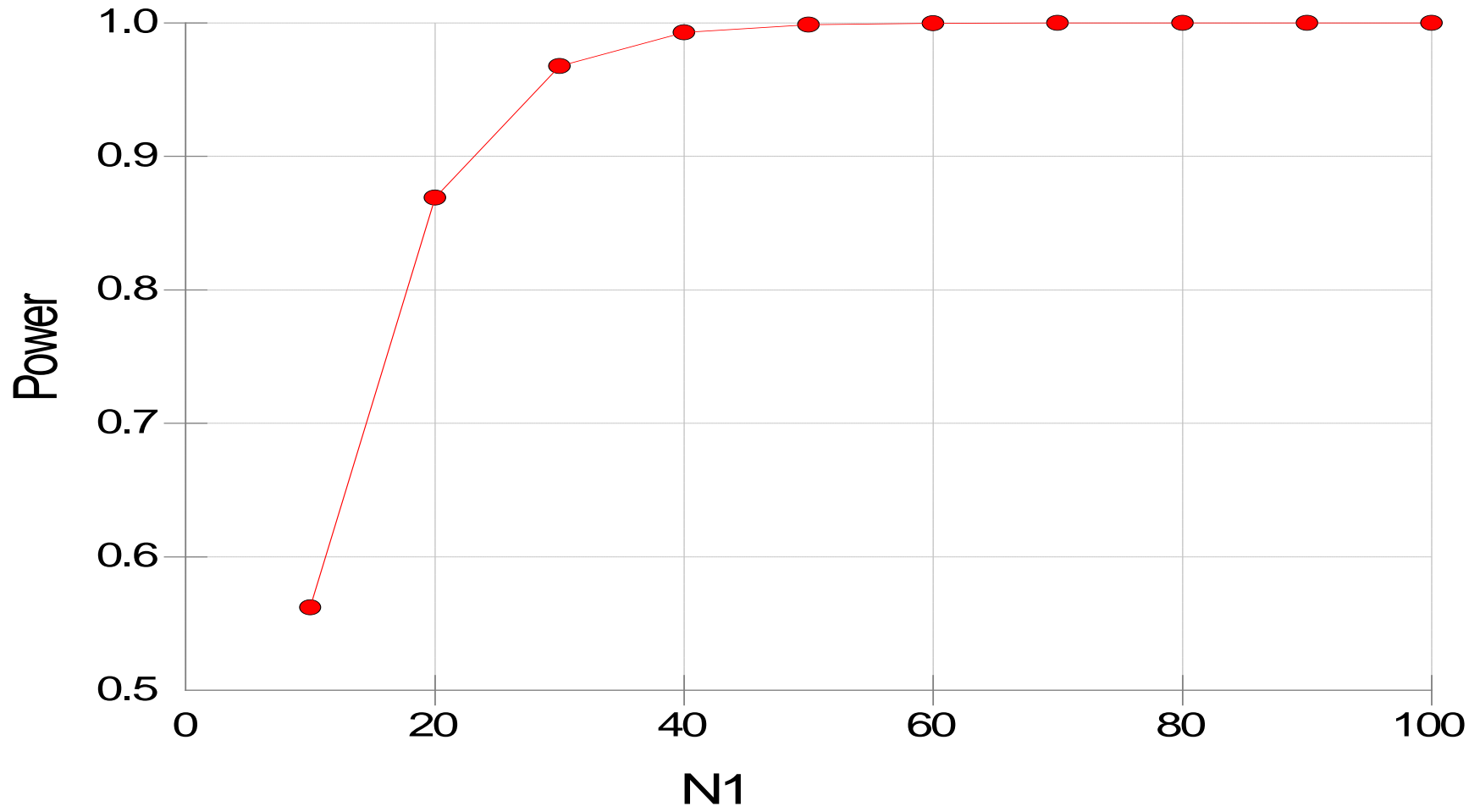
$$N \propto \frac{\text{Power, Alpha, SD}^2}{\text{Difference}^2}$$

Greater SD	Larger N
Greater Power	Larger N
Smaller alpha	Larger N
Smaller Difference	Larger N

Find Sample Size N for K-handling study: Endpoint UkV (mmol/hr) with the following assumptions

- Set the difference we want to detect to 1 mmol/hr
- Set the SD of the variable to 1 mmol/hr
- Set the desired power to 0.8
- Set alpha to 0.05

Statistical test: t-test
Difference = 1 mmol/hr
Standard deviation = 1 mmol/hr
Power = 0.80
Alpha = 0.05



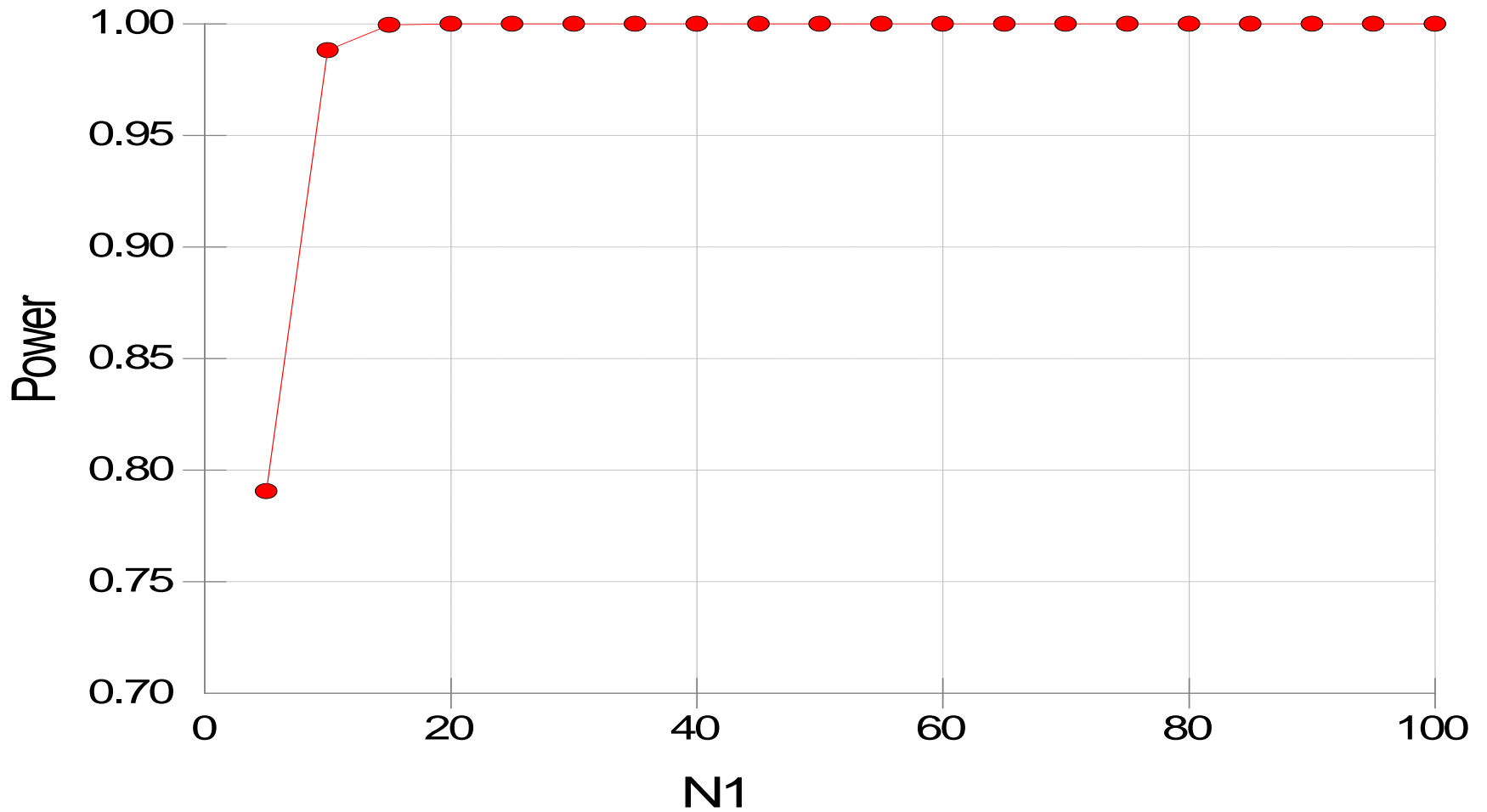
Statistical test: t-test

Difference = 1 mmol/hr

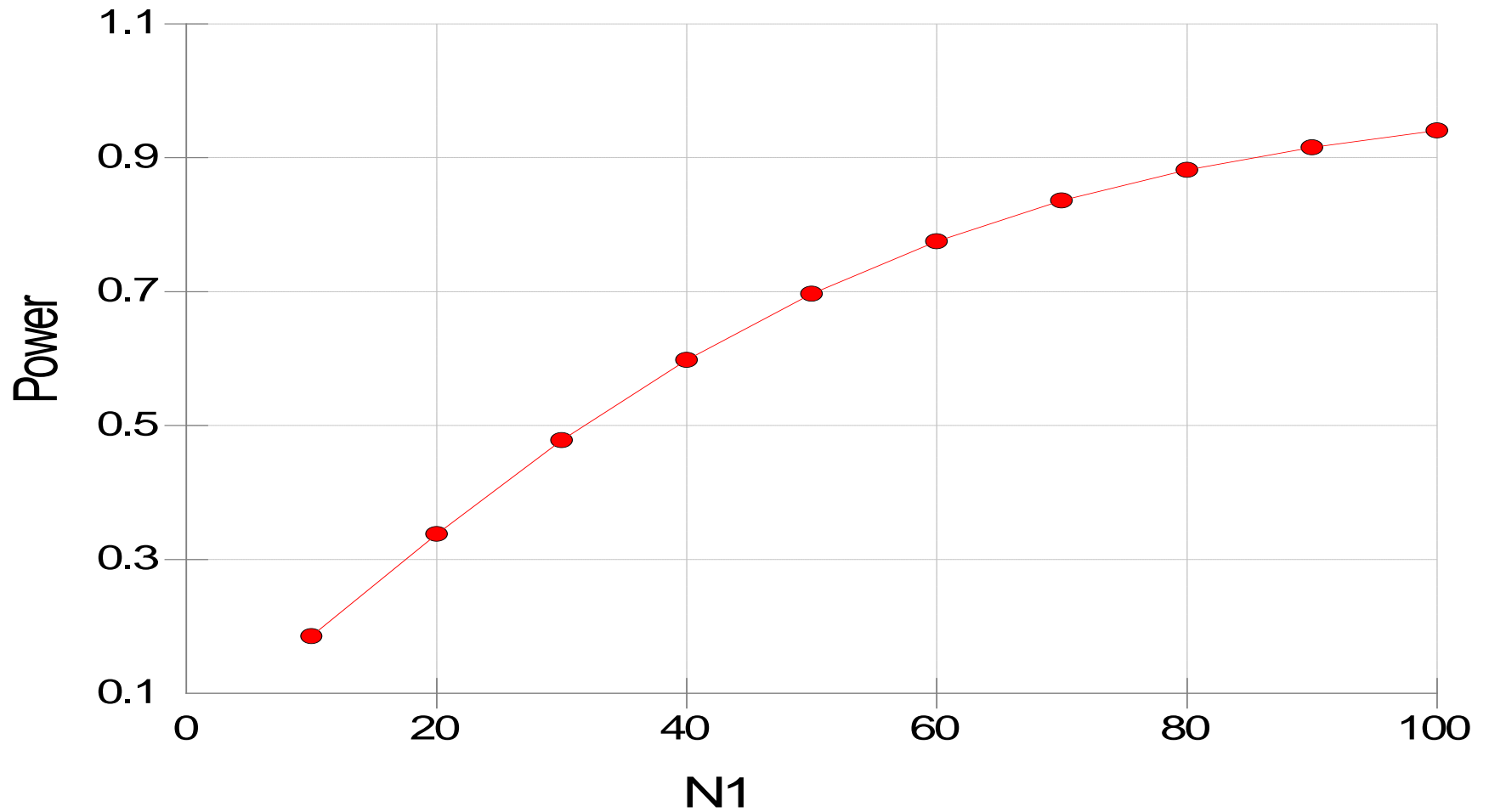
Standard deviation = 0.5 mmol/hr

Power = 0.80

Alpha = 0.05



Statistical test: t-test
Difference = 1 mmol/hr
Standard deviation = 2 mmol/hr
Power = 0.80
Alpha = 0.05



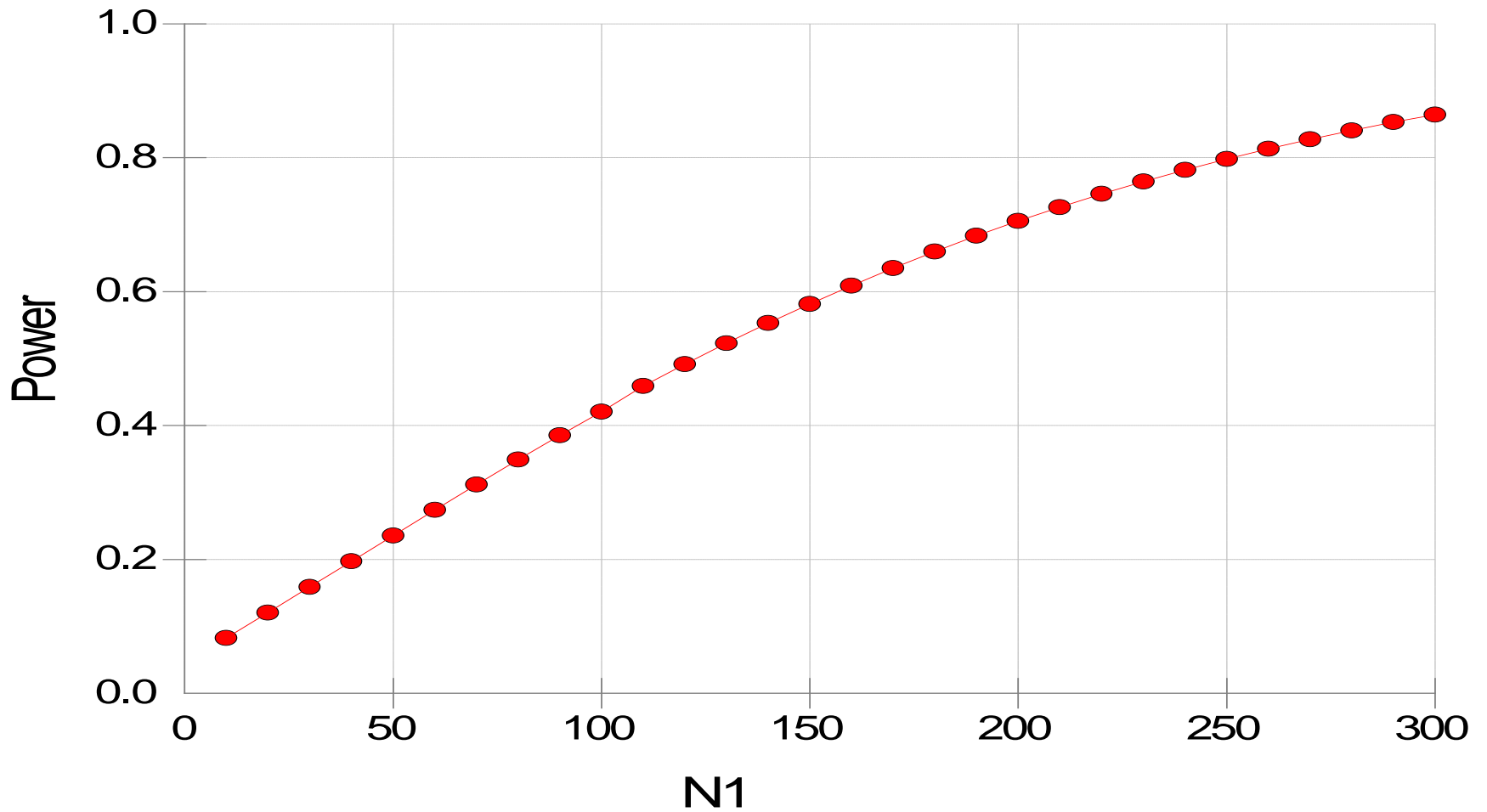
Statistical test: t-test

Difference = 0.5 mmol/hr

Standard deviation = 2 mmol/hr

Power = 0.80

Alpha = 0.05



Summary: 1- Page Protocol Synopsis

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Results

Results: Baseline and Demographic Characteristics

Characteristic	CKD (N=18)	Control (N=18)	P-value
Age	66.5(6.84)	39.05(7.68)	< .001
Gender (M/F)	14/4	14/4	1.0
Race/ethnicity			
Hispanic Caucasian	13	16	.40
Hispanic Black	1	0	
African American	3	1	
American Caucasian	1	1	
BMI (kg/m ²)	29.83 (4.26)	28.95 (2.56)	.46
Systolic BP (mm Hg)	141.44 (16.20)	117.22 (9.17)	< .001
Diastolic BP (mm Hg)	81.55 (10.17)	74.16 (7.13)	.017
GFR (MDRD, ml/min)	45.15 (14.44)	112.10 (13.04)	< .001
Serum K (mmol/L)	4.48 (.47)	4.39 (.42)	0.55
Hypertensive renal disease	10/18		
Diabetes Mellitus	8/18		
DM nephropathy	5/8		
Insulin-requiring	3/8		

Phase 1. UkV in CKD versus control

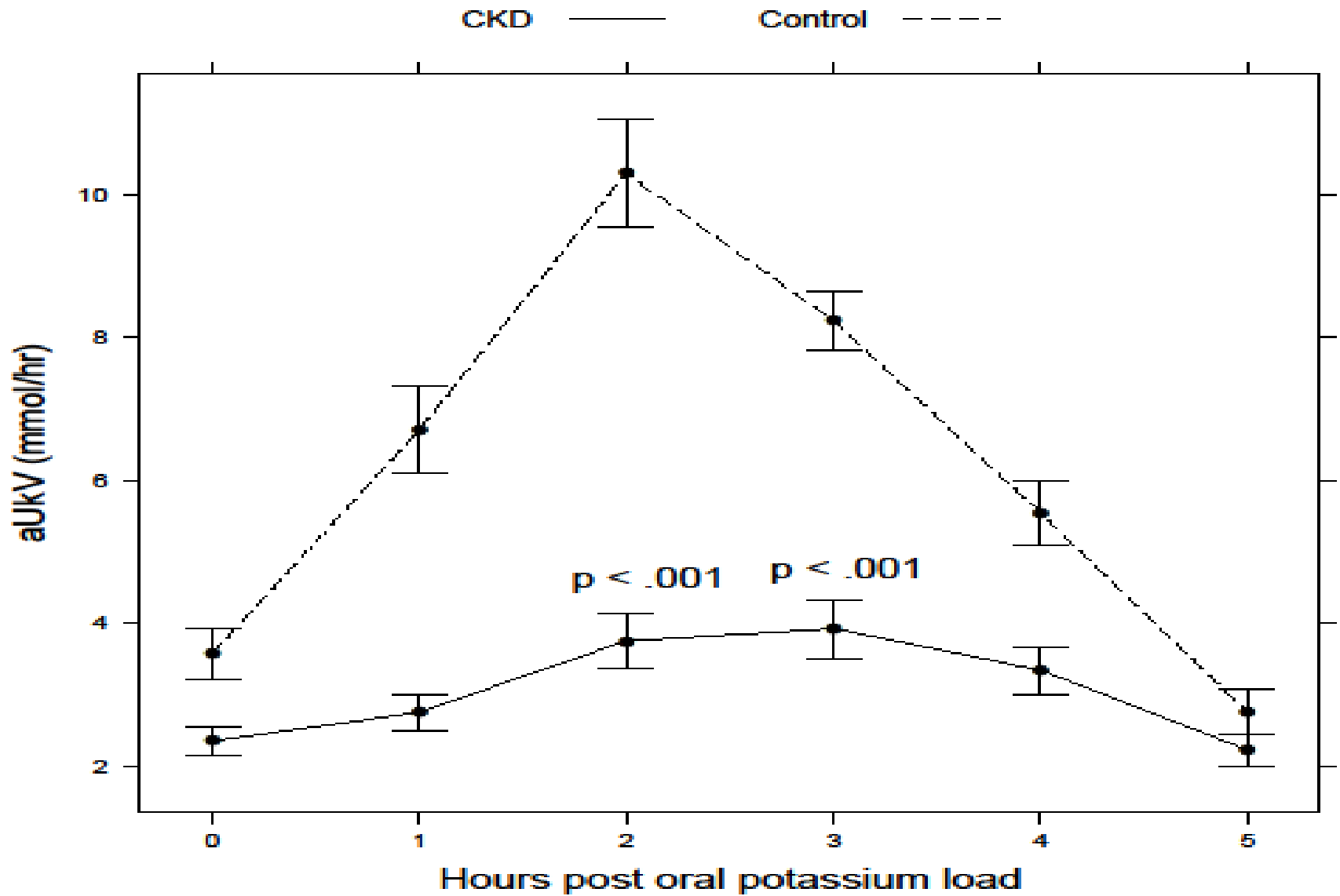


Figure 1a

Hourly SEK in control versus CKD

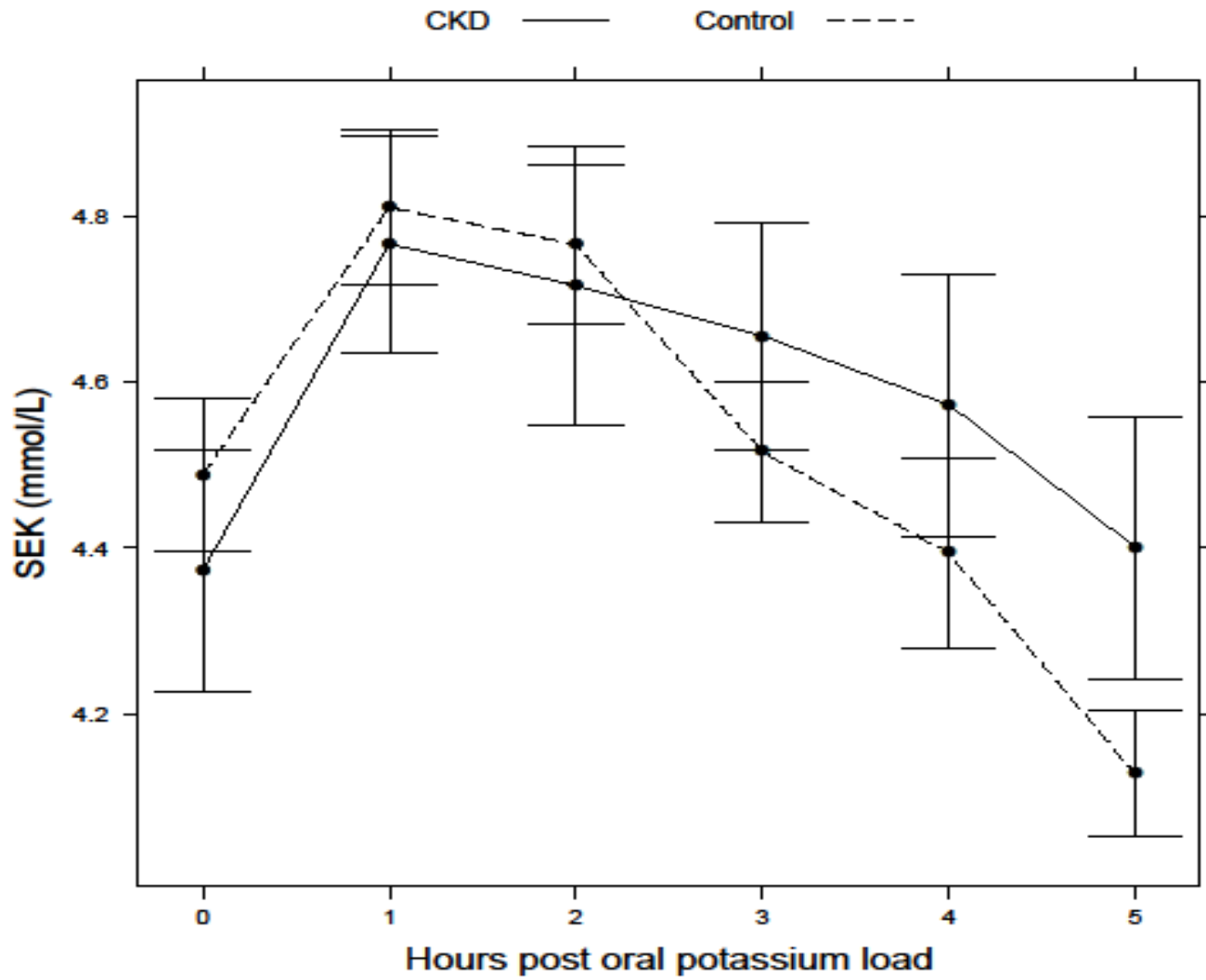


Figure 1c

Ambulatory serum K Lisinopril/spironolactone versus placebo in CKD patients (N=18)

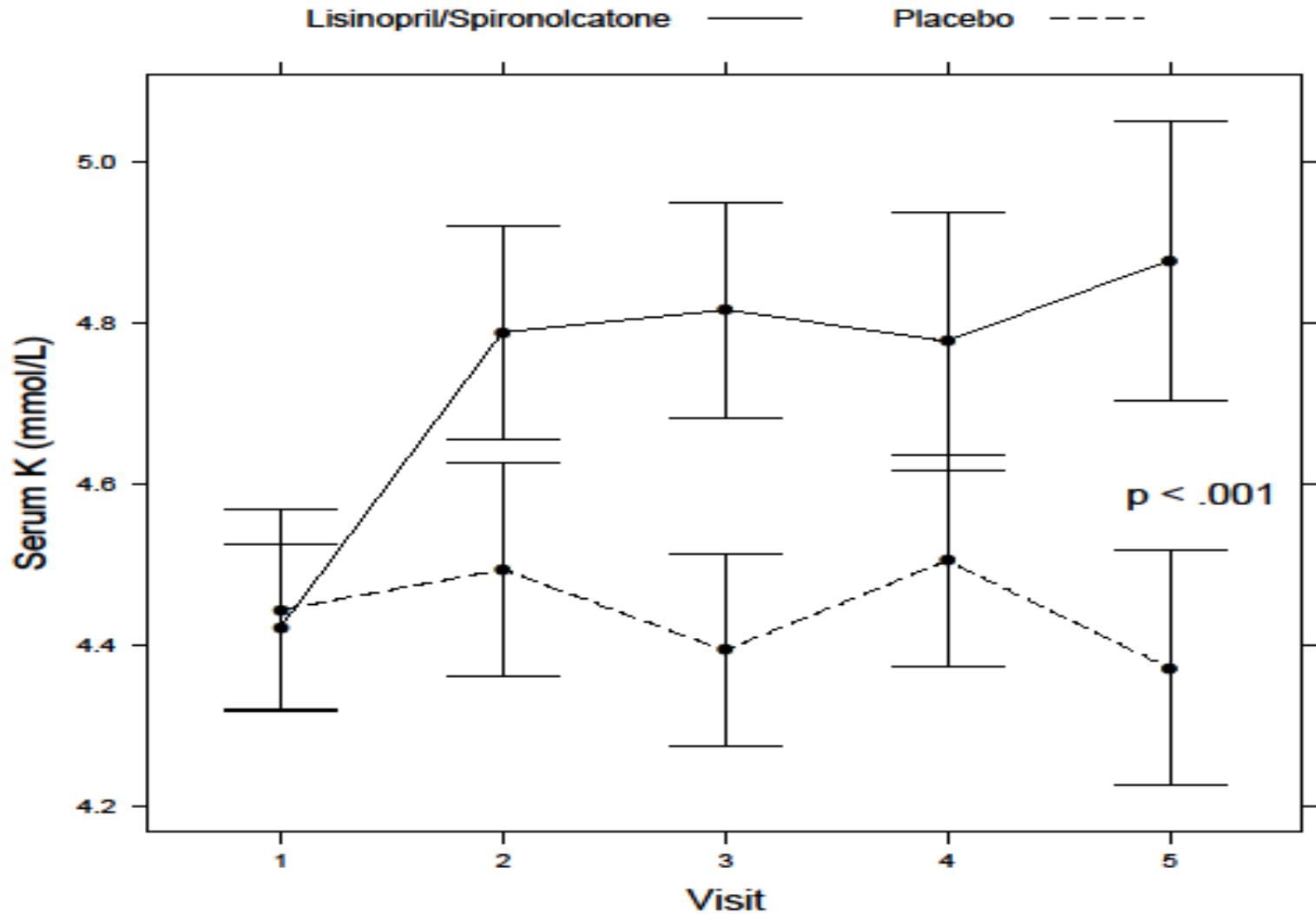


Figure 2c

UkV Lisinopril/spironolactone versus placebo

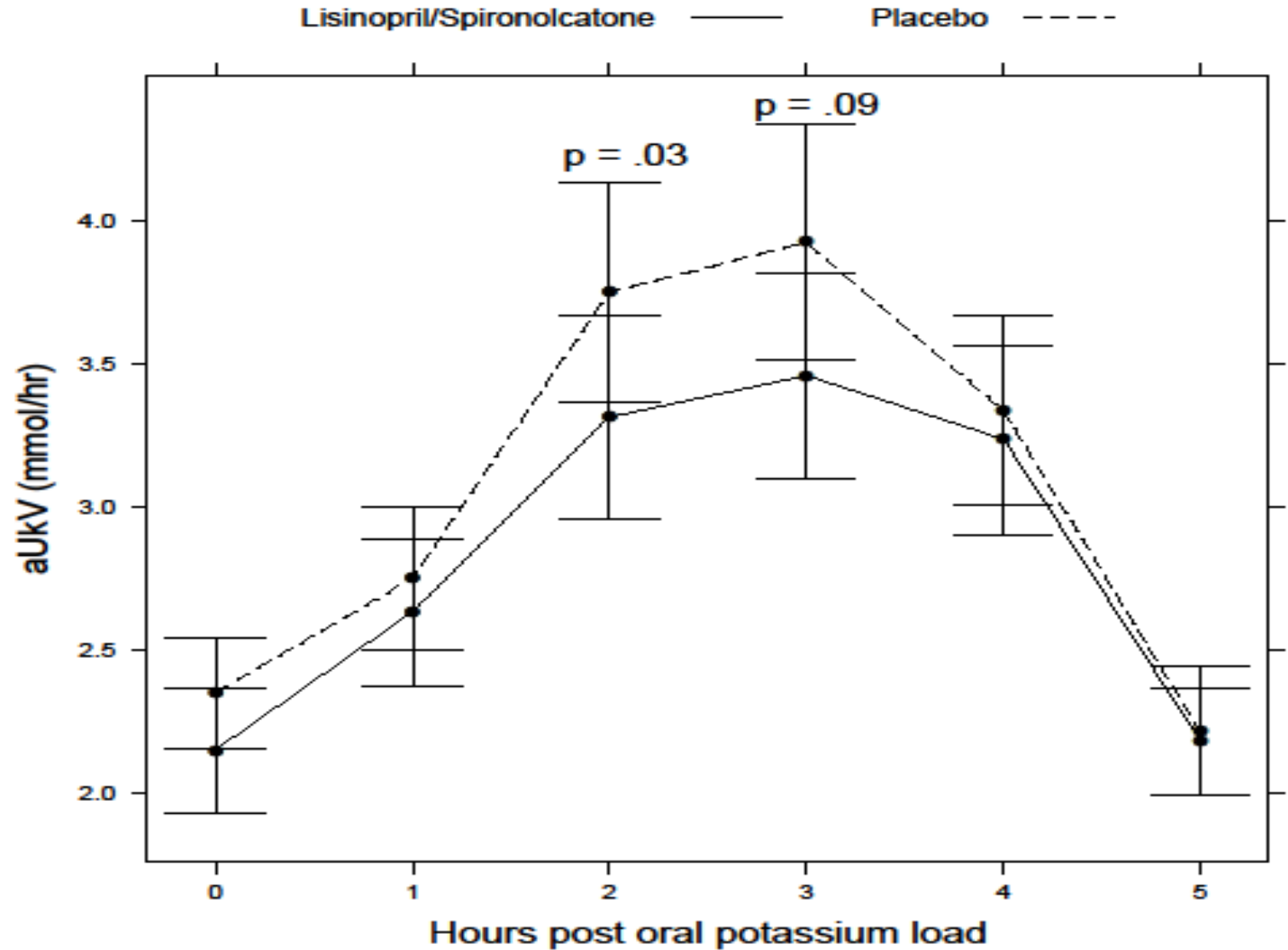


Figure 3a

Serum K

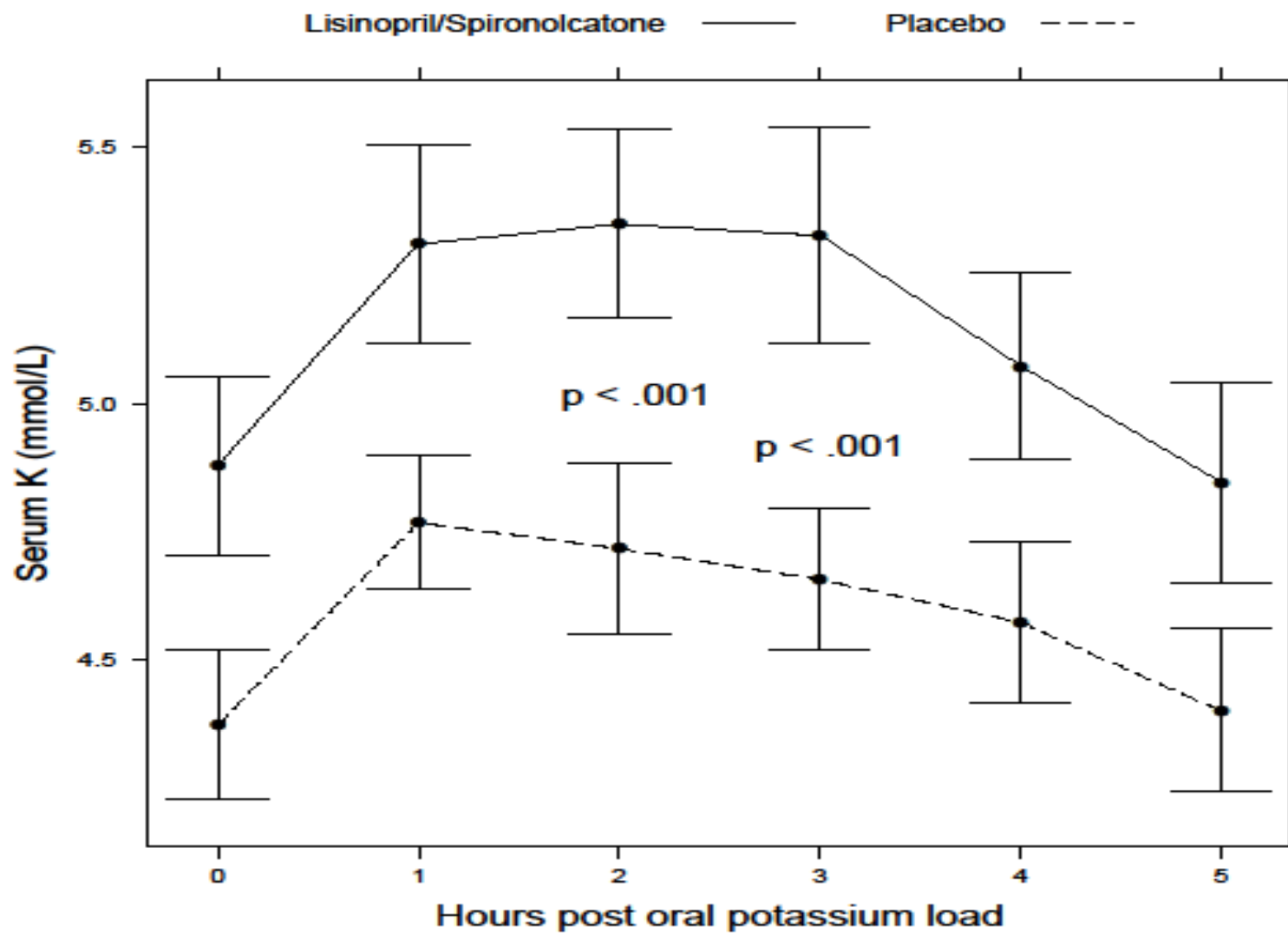


Figure 3e

Dynamic delta serum K predicts ambulatory serum K

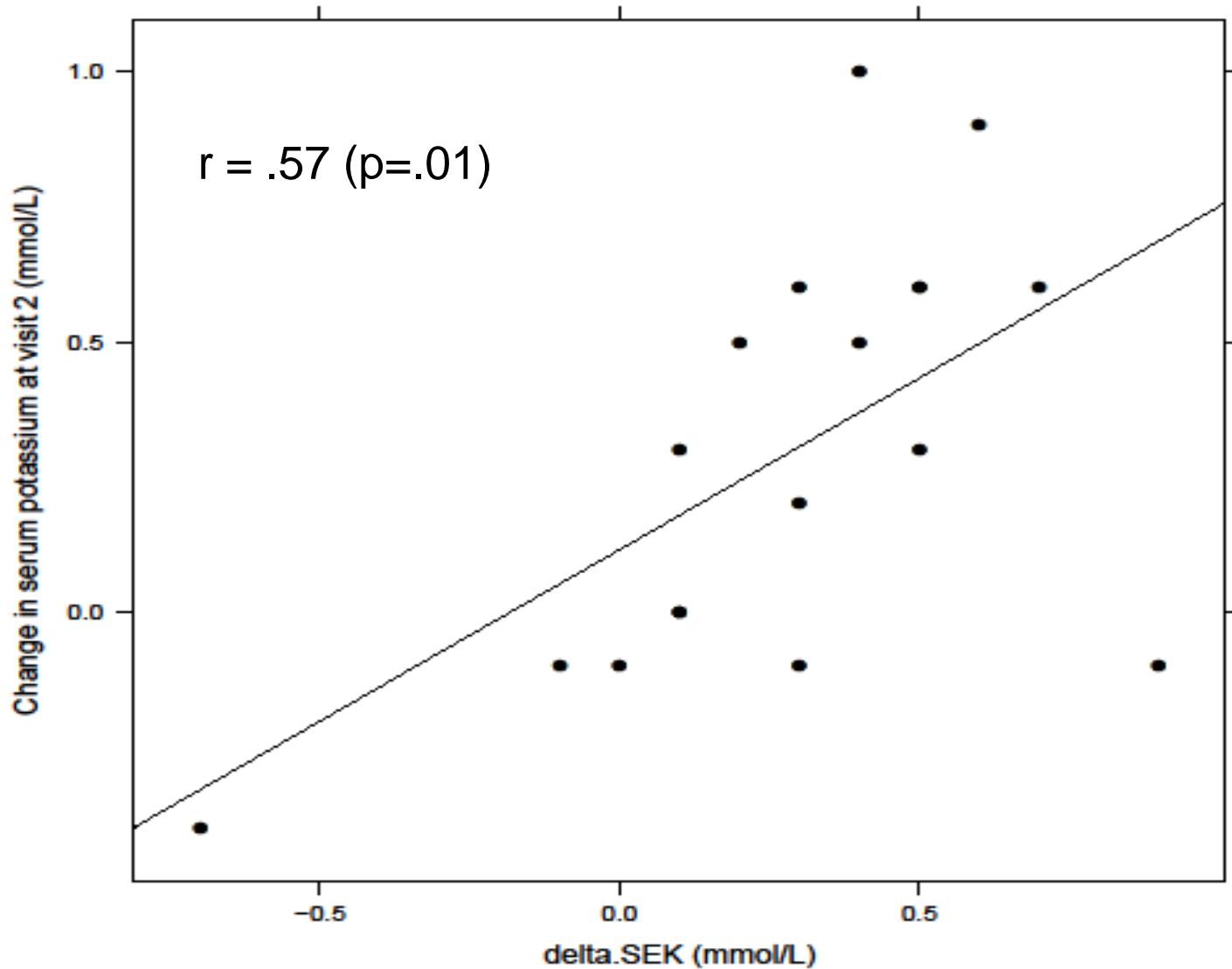


Figure 4c

Mixed effect model for ambulatory K as a function of baseline and K-handling variables

$$\begin{aligned} Y_{ijk} = & (\gamma_{10} + \gamma_{11}\text{Drug}_k + \gamma_{12}\text{Drug}_k \times \text{delta.SEK} + \gamma_{13}\text{Drug}_k \times \text{d.UKV} + \gamma_{14}\text{Drug}_k \times \text{MDRD} + u_{1ik}) \\ & + (\gamma_{20} + \gamma_{21}\text{Drug}_k + \gamma_{22}\text{delta.UKV} + \gamma_{23}\text{Drug}_k \times \text{delta.UKV} + u_{2ik})t_{ij} \\ & + \gamma_{30}\text{delta.SEK} + \gamma_{40}\text{delta.UKV} + \gamma_{50}\text{MDRD} + \varepsilon_{ij}, \end{aligned} \quad (1)$$

Prediction model for increase in K with dual blockade

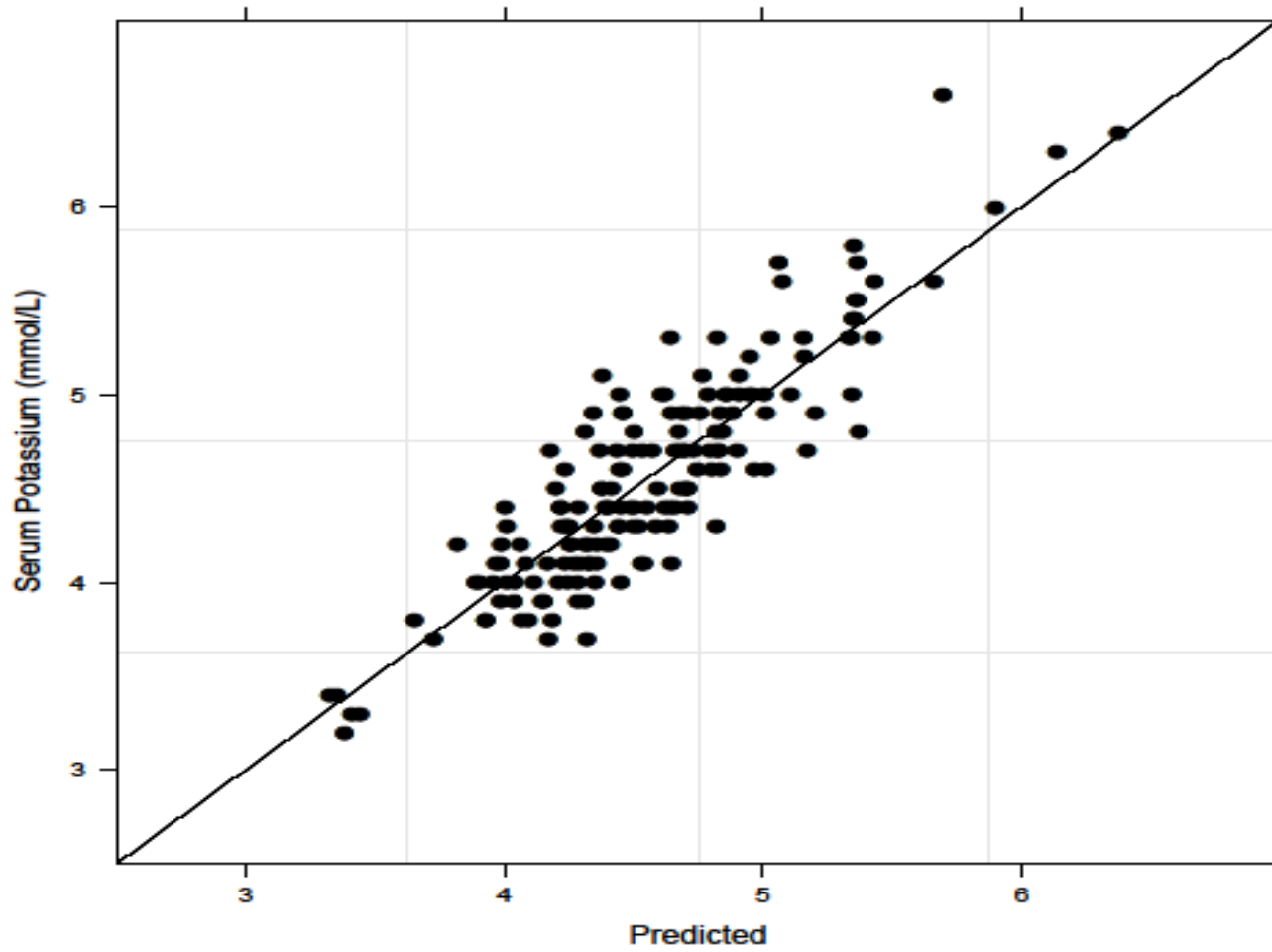


Figure 4a

Summary

- 1. Hypothesis:** CKD patients have a markedly reduced ability to excrete an acute K load but can maintain serum K in an acceptable range by increased cellular translocation
- 2. Hypothesis:** Dual RAAS blockade reduces K excretion **and** the ability to translocate K. Role of aldosterone in translocation of K
- 3. Hypothesis:** Steady-state ambulatory K is achieved in most patients within one week of starting dual RAAS blockade. Best time to check K is 1-2 weeks after starting dual RAAS blockade
- 4. Hypothesis:** In principle K-handling data ($U_{K/V}$, K) following an oral K load can predict the rise in ambulatory K with dual RAAS blockade. This suggests a simple and inexpensive office test to predict the K response to dual RAAS blockade

