A Pilot Study of Dual Anti-Hypertensive Medication Management with Novel Lab Monitoring in Rural Western Uganda: An Initiative of the Bugoye Hypertension Improvement Project (B-HIP)

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Overview

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- Objectives
- Background
- Methods
- Preliminary Results
- Discussion

Objectives

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- Define and discuss hypertension (HTN), its risks, and its global and regional burden
- Consider sub-Saharan Africa (SSA) and projected changes in population, demographics, and burden of disease
- Discuss HTN treatment
- Present the Bugoye Hypertension Improvement Project (B-HIP)
- Describe HTN treatment and the addition of novel lab monitoring in Bugoye, Uganda
- Reflect on this process and its ramifications for HTN and non-communicable disease (NCD) management in similar settings

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Background

The Story of Joseph

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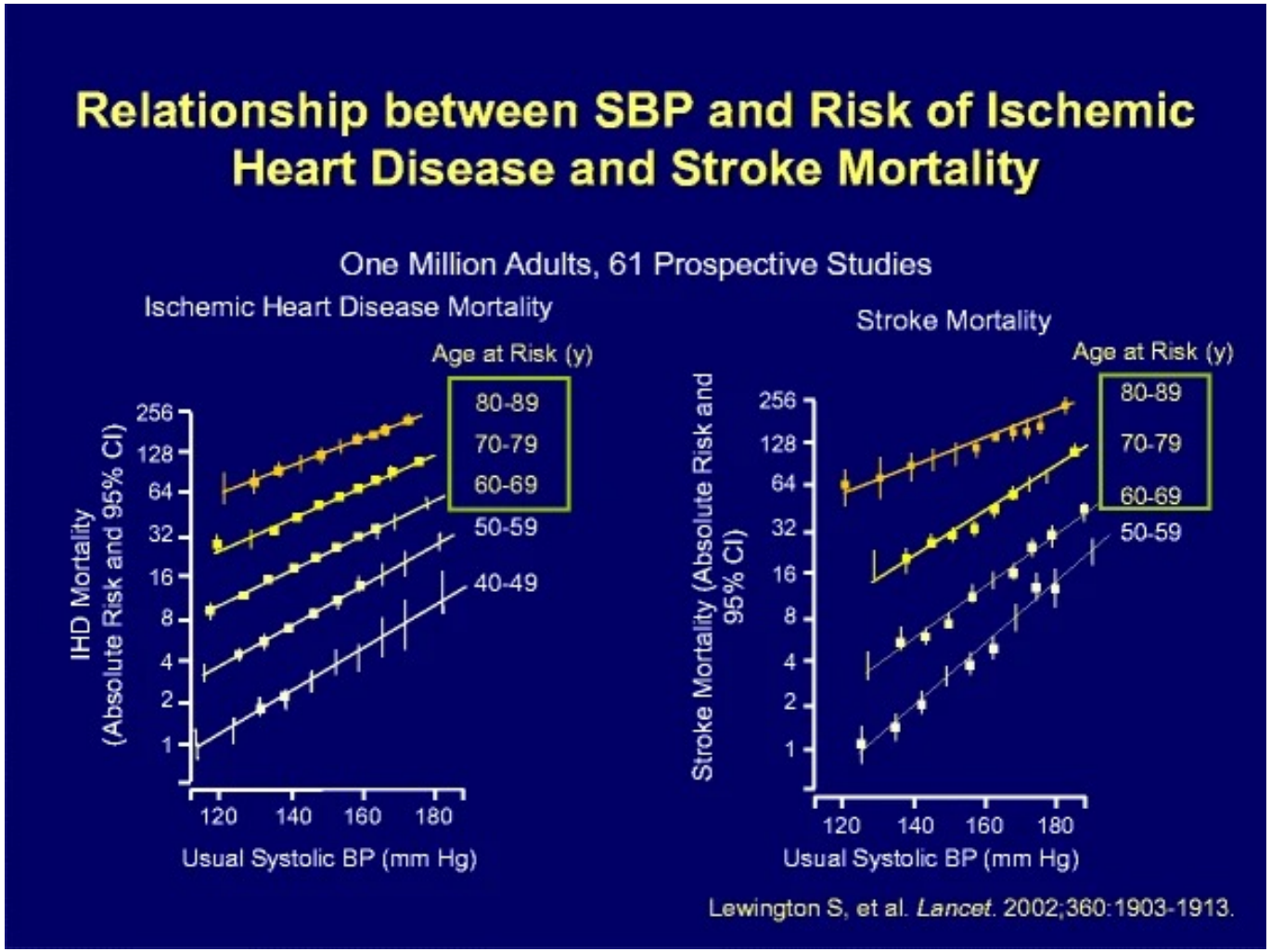
HTN and Cardiovascular Disease (CVD)



As SBP/DBP increases 20/10, 2x risk of CVD and stroke death

Hypertension (HTN)

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- Previously: JNC8 guidelines (2014):
  - SBP > 140 or DBP > 90*
  - Treatment guidelines:
    - If age < 60, start meds for goal BP < 140/90
    - If age > 60, start meds for goal BP < 150/90

- Latest update: ISH guidelines (2020):

Blood Pressure Categories

American Heart Association | American Stroke Association

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

*SBP = systolic blood pressure; DBP = diastolic blood pressure

Burden of HTN: Globally & in Sub-Saharan Africa (SSA)

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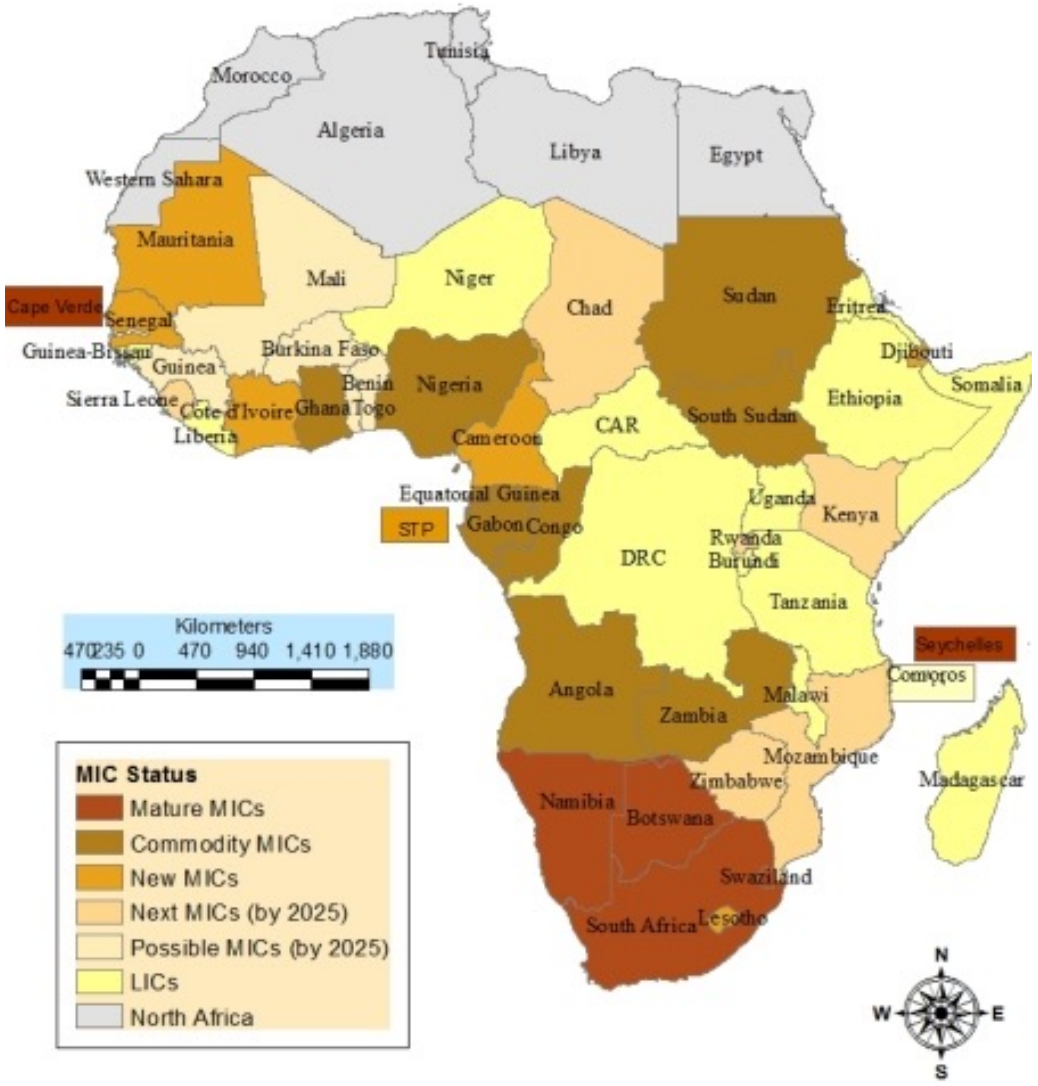
- Leading cause of preventable deaths globally
- Affects 1.39 billion people
  - >80% of this global burden is in LMICs
- SSA: 10-20 million out of 650 million
  - As high as 38% among some communities
  - Data limitations
- 2015 cross-sectional study sampling Uganda, South Africa, Tanzania, and Nigeria
  - Increased with age, BMI
  - Increased with urban (vs rural)
  - Pre-HTN rates: 21% - still at risk



SSA: Population Projections

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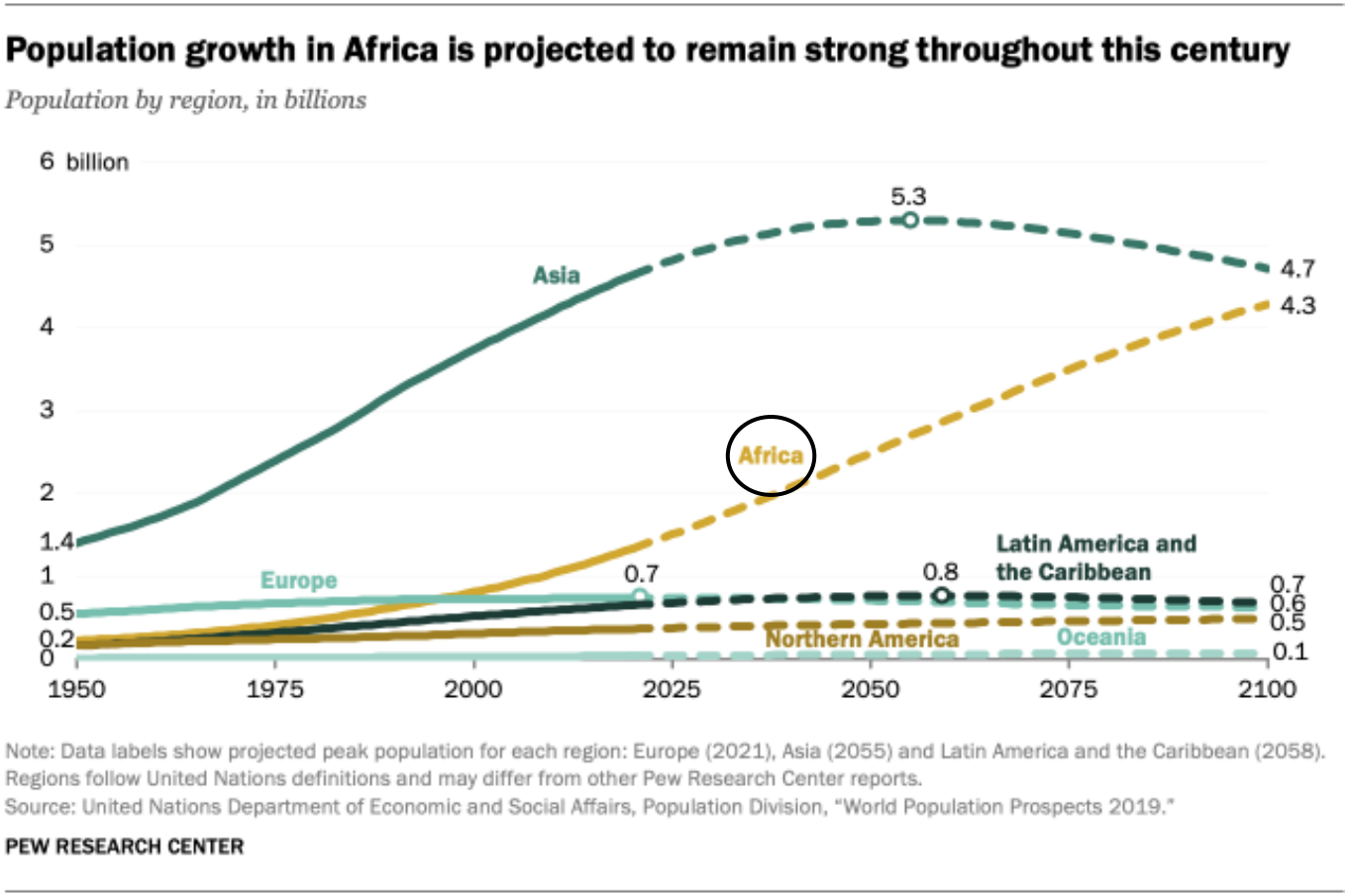
- Expansive population growth projected in SSA:
  - 2000-2050: 800 million to 2.4 billion
  - 2050-2100: 2.4 billion to 4.2 billion
- By 2100:
  - Population of SSA ≈ Asia
  - Nearly 2 out of every 5 people will be African



Treatment of HTN

- 1st line: lifestyle interventions
  - Weight loss
  - Dietary modifications (Dietary Approaches to Stop HTN [DASH], Mediterranean)
  - Sodium reduction
  - Increased potassium
  - Physical activity

Anti-HTN Medications

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- 1st line medications:
  - Dihydropyridine (DHP) calcium channel blockers (e.g. **amlodipine**, **-pine**, etc.)
  - Renin-angiotensin II-aldosterone system (RAAS) inhibitors:
    - Angiotensin-converting enzyme (ACE) inhibitor: **lisinopril**, **-pril**, etc.
    - Angiotensin II receptor blocker (ARB): **valsartan**, **-sartan**, etc.
  - Thiazide diuretics: **chlorthalidone**, **hydrochlorothiazide** (HCTZ), **-thiazide**, etc.
- 2nd line medications: many
  - Beta-blockers (**carvedilol**, **metoprolol**, **-lol**, etc.)
  - Mineralocorticoid receptor antagonists (MRAs) – aka **spironolactone**, **-one**, etc.
  - Alpha-blockers (doxazosin, prazosin, **-osin**, etc.)
- Notes:
  - Best evidence: combo therapy with first-line medications
  - Multiple mechanisms

Treatment Strategies in Rural Contexts

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- "Cascade of care" in rural Uganda (Kotwani et al.)
  1. Community or health center screening → HTN diagnosis
  2. Establishing care
  3. Management, starting medications
  4. Patient retention
  5. HTN control
- Leverages successful HIV care delivery systems

The Bugoye Hypertension Improvement Program (B-HIP)

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- Established 2014 within the Bugoye Health Center due to local HTN morbidity & mortality
- Bugoye Health Center (BHC):
  - Kasese District of western Uganda
  - Referral center for the Bugoye sub-county
  - Serves rural population, ~50K
    - Most transit by foot; ~45 minutes one-way
  - Level III health center:
    - Has outpatient clinic, maternity ward, and lab testing
    - No guaranteed federal support

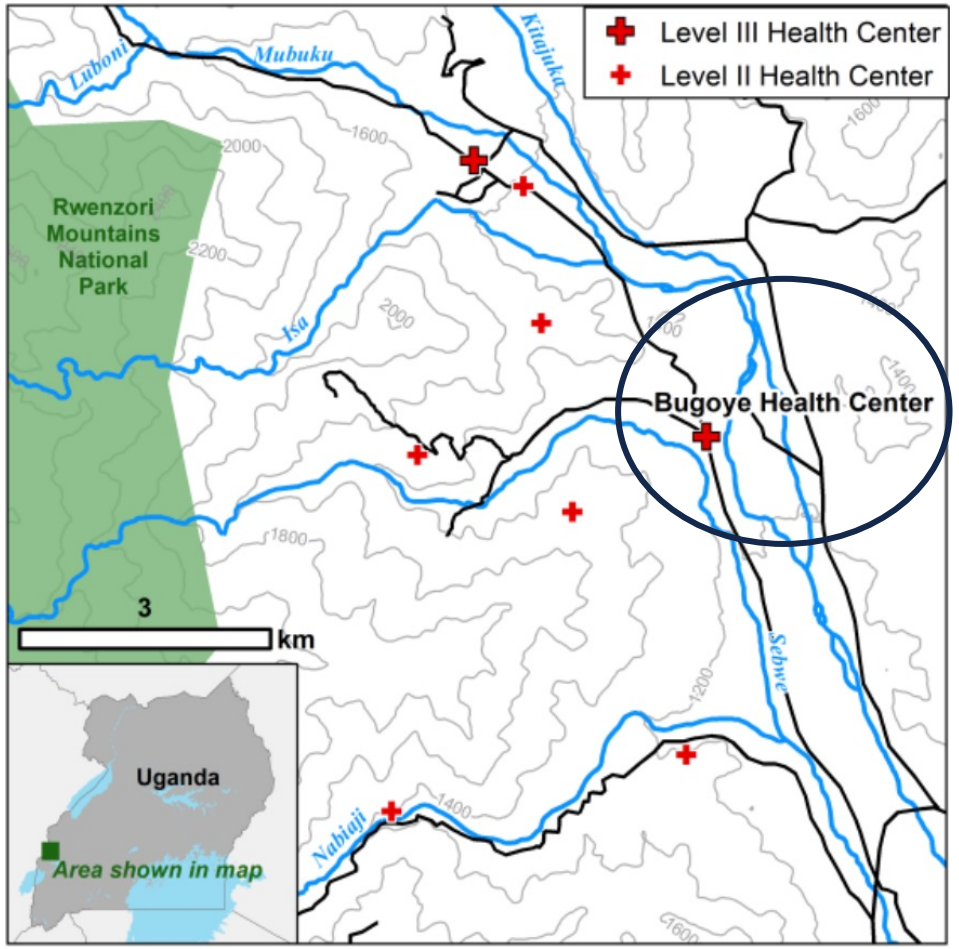

Figure 1: Map of the Bugoye sub-county showing the location of health facilities.

Establishing BHIP

- Weekly HTN clinic with community health workers (CHW) and research assistants
- Before opening, trained clinic workers on emphasizing lifestyle modifications with teaching on medication mgmt.
- Local thiazide diuretic (Bendroflumethiazide, aka BFT) on formulary
  - However, inconsistent availability locally
- Later, grant from Pfizer & Direct Relief procured amlodipine for many patients
- Over 600 patients currently enrolled

Our Study

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- Some research suggests specific combo of amlodipine & thiazide diuretic is optimal in SSA population (Ojji et al., CREOLE Study)
- Though thiazides (& other anti-HTN medications) can cause electrolyte abnormalities and renal changes, regular lab monitoring is not standard of care in resource-limited contexts (WHO, Ugandan Ministry of Health)
- **We present a subset of HTN patients on maximum amlodipine therapy, hypothesizing combination with thiazide diuretics are associated with better BP control with minimal adverse effects and low cost**
- **We introduce electrolyte and renal function measurement (Na, K, Cr) to optimally describe our patients and introduce novel monitoring of adverse medication effects**

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Methods

Study Protocol: Recruitment and Population

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- Clinic patients (non-pregnant adults) with SBP ≥ 140 and/or DBP ≥ 90 who are already on amlodipine 10mg daily (maximum dose) but not currently on BFT
  - Recruited over 6 months from either previously established patients with highest BP (most clinical benefit) or new patients with HTN on amlodipine 10mg
- Presented to clinic with blood pressure checked (per clinic protocol) and prescribed BFT 5mg daily
- Follow up appointment in 2 weeks for phlebotomy-drawn sodium (Na), potassium (K), and creatinine (Cr) and rechecked blood pressure
- All data recorded in shared RedCap
- Meetings between US-based team and Uganda-based team conducted approximately weekly for updates and troubleshooting

Methodological Challenges

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- A few weeks into study, lab results notable for higher-than-expected rates of hypernatremia and hyperkalemia
  - Thiazide diuretics should be associated with low Na and low K
- Team coordinated meeting with contracted lab manager to inquire about quality control mechanisms
- Due to our concerns, we tested a limited sample of study patients at a secondary lab facility
  - More plausible results at 2ndary location, and different from 1st lab's results
- Ultimate decision made to terminate old contract and start new contract with secondary lab
  - Attempted to contact patients with erroneous labs for repeat draw

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Preliminary Results

Enrollment Challenges

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- Planned for 80 study participants, but 92 patients were seen for blood pressure checks (due to lab quality setback)
  - 76 patients ultimately had accurate labs
  - About 43 patients lost-to-follow-up
    - New patients; patients who did not return as scheduled for follow-up

Baseline Characteristics

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Characteristics (N=92)	Mean
Years of follow-up (minimum, maximum)	0.5 (0,6)
Gender (Female)	64 (70%)
Age, yrs median (IQR)	60 (IQR 51-66)
HIV positive	0
Any smoking?	0
BMI	24.7 (SD 4.90)

Method of Transportation to Clinic	
Foot	40
Boda boda (motorcycle)	49
Other (car or bicycle)	1
Transit Time to Clinic (minutes, mean)	2
Occupation	
Farmer	79
Business	6
Civil Servant	5
Other	2

Blood Pressure Changes

Category (N=49)	Results
Baseline Mean SBP	154
Follow-up Mean SBP	141
Difference	**13 mmHg**

Category (N=49)	Results
Baseline Mean DBP	93
Follow-up Mean DBP	84
Difference	**9 mmHg**

Adverse Effects, Lab Studies (& Future Analysis)

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Adverse Effects	n
Hyponatremia (Na < 130)	1
Hypokalemia (K < 3)	0
Elevated creatinine	2
Dizziness	0

Labs	Mean	SD
Sodium (Na)	142	4.2
Potassium (K)	4.3	0.4
Creatinine (Cr)	0.68	0.27

- Still to come:
  - Overall proportion of BP control in cohort
  - Measures of association for various demographics in our study (e.g. gender, mode of transport, occupation, etc.)
  - Additional descriptive analysis

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Discussion

Study Results

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- Our addition of BFT 5mg to amlodipine 10mg daily was associated with a clinically significant reduction in both SBP (13mmHg) and DBP (9mmHg)
- However, results limited by loss-to-follow-up
- Very few patients in our sample had labs concerning for renal dysfunction, and only one had sodium abnormalities
  - However, notable on individual level – this person had Na of 118
  - Unable to reach after appointment to assess symptoms
  - Returned after 3 months, sodium had normalized on repeat check

NCD Management in Rural Uganda (and Beyond?)

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- Model proposed by Kotwani et al. provides helpful framework for HTN management in this context
  - Linkage to care progresses from screening all the way to management and control
  - Our study supports the utility of this model
  - Could this be expanded to other NCDs? Other LMICs?
    - Future BHIP goals: diabetes management, aspirin for primary prevention of ASCVD
- Any worthwhile global health project should be scalable
  - Hope to work on this with another new HTN clinic during upcoming trip to Uganda in March

Limitations

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- High loss-to-follow-up in the study
  - Adherence rates are high in the clinic overall
  - Good referral base
- Small sample size, so low power
  - We present a pilot study which demonstrates ability to scale
- Difficult to adjudicate adherence (self-reported)
  - However, decreased adherence would indicate under-estimating results
- Initial confounder of reliable lab monitoring
  - Requires community-based partnerships for effective patient care and research

Conclusions

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- Combination therapy with amlodipine and thiazide diuretic associated with decreased BP and improved BP control in this rural western Ugandan cohort
- Consistent follow-up remains challenging in this remote region
- Benefits of lab monitoring in this context remain debatable
- Cost-effective:
  - 1 pack (100 tablets) of BFT = 4618.28 UGX ≈ $1.22 USD
    - Therefore, one-year supply of BFT for one patient: <$4.50
- Opportunities for HTN “cascade of care” guiding other NCD management

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Consider supporting the work of P-HEALED: