

Pilot Study for a Pragmatic Trial Comparing Chlorthalidone and Hydrochlorothiazide: Results and Lessons Learned

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PCPs and patients at HP and KPNW

Rationale

- ▶ Low-dose diuretic recommended as initial therapy for hypertension in U.S. guidelines (so millions are treated with these drugs)
- ▶ Trials show chlorthalidone (CTD)-based regimens significantly reduce rates of CVD
 - ▶ Placebo, usual care, or active comparators in HDFP, SHEP, ALLHAT, SPRINT
- ▶ Few outcome studies have compared HCTZ-based regimens with other treatments
 - ▶ Generally, HCTZ less effective than comparators in preventing CVD (ANBP2, ACCOMPLISH)
- ▶ HCTZ and CTD never compared directly in a large trial with CVD outcomes, but ~20% reduction in major CV events shown in
 - ▶ Observational analysis of MRFIT (Dorsch, Hypertension 2011;57:689-94)
 - ▶ Network meta-analysis (Rousch et al, Hypertension 2012;59:1110-7.)
- ▶ Nevertheless, 95% of thiazide prescriptions are for HCTZ

Why might chlorthalidone be better than HCTZ?

- ▶ Twice as potent (Ernst, et al Hypertension 2006;47(3):352-8)
 - ▶ 12.5-25 mg of chlorthalidone = 25-50 mg of HCTZ
 - ▶ Most clinicians do not use higher, more effective doses of HCTZ
- ▶ Longer elimination half-life (50-60 hours vs. 9-10)
 - ▶ Lower night-time BP
 - ▶ Occasional non-adherence not as likely to affect BP
- ▶ “Pleiotropic effects” (eg, decreased platelet aggregation), but no evidence for clinically important effects

Design of THIAZIDES

(Treatment of Hypertension in Adults with Thiazides)

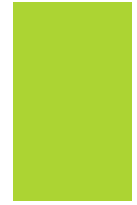
- ▶ Long-term goal: Low-cost pragmatic multicenter RCT comparing effects of HCTZ and CTD on cardiovascular events (MI, stroke, HF, mortality)
- ▶ Pilot study of feasibility using existing clinical systems and EHR (no study visits)
 - ▶ Identify and recruit eligible study patients
 - ▶ Distribute study medication using routine health system
 - ▶ Collect operational, safety, and outcomes data
- ▶ Pilot sites: HealthPartners (Minneapolis, MN) and Kaiser Permanente Northwest (Portland, OR)
- ▶ Cluster-randomized: 40 physicians and 2000 patients

Patients

- ▶ Age 18 and older
- ▶ HTN diagnosis
- ▶ On HCTZ 12.5-50 mg as a single agent (not part of a fixed-dose combination)
 - ▶ All other antihypertensive drugs permitted
- ▶ Most recent Na \geq 135 mEq/L and K \geq 3.5 mEq/L
- ▶ Can communicate in English
- ▶ No history of intolerance to chlorthalidone
- ▶ Health plan members with pharmacy benefit

Intervention

- ▶ Modeled on the common practice of within-class “therapeutic substitution” based on cost, safety, or efficacy
- ▶ Substitute chlorthalidone at about the time of an expected refill
 - ▶ KP Northwest – can fill Rx at low cost only at health system pharmacies
 - ▶ HealthPartners – can fill Rx at health system or commercial pharmacies
- ▶ Physician selected as unit of randomization based on cost and concerns about contamination if individuals randomized
- ▶ Similar method could be used to seamlessly disseminate results if chlorthalidone found to be superior to HCTZ



40 PCPs, 2000 of Their Patients

1000 Intervention (500 each site)
1000 Usual Care (500 each site)
PCPs consented, review list of eligible patients, exclude if unsuitable for trial.
PCPs randomized after lists returned.

Usual Care
Patients stay on HCTZ 12.5-50 mg/day

Intervention
HCTZ discontinued, switched next refill
12.5mg HCTZ = 12.5mg CTD
25mg HCTZ = 12.5mg CTD
50mg HCTZ = 25mg CTD

All later HTN treatment adjusted by PCP

9 months follow-up after first fill date
-Claims/fills for HCTZ and chlorthalidone
-Completeness of EHR data for safety measures
-Other characteristics for trial planning

Aims and Outcomes

- ▶ Aim 1: Intervention efficacy
 - ▶ Switch to CTD occurs as intended
 - ▶ Adherence using pharmacy claims
- ▶ Aim 2: Safety using electronic data
 - ▶ Laboratory, BP, and diagnosis codes
- ▶ Aim 3: Refine the study design
 - ▶ Mixed-methods approach - interviews with physicians, patients, pharmacists
- ▶ Aims 4 and 5: Refine estimates of sample size and per-participant costs for the full-scale trial

Funding

- ▶ Funded by NHLBI: R34 HL119790
 - ▶ Start-up July 2015, 2 years, \$450,000 in direct costs
- ▶ VA Cooperative Study (Diuretic Comparison Project) also funded at about the same time
 - ▶ Similar design except individually randomized with consent, only age \geq 65 with fee-for-service Medicare, very few women, only include patients on HCTZ 25-50 mg
 - ▶ Full-scale trial with Vanguard sites at Boston and Minneapolis VA, N=13,500

Expected Problems at Start-up

- ▶ Chlorthalidone AWP increased 500% since 2003 (120% from 2013-2015)
 - ▶ Average out-of-pocket \$25 for 90-d supply (wide variation) vs. \$3 for HCTZ
 - ▶ Debit card
- ▶ Smallest chlorthalidone pill is 25 mg unscored tablet
 - ▶ Most patients get 12.5 mg
 - ▶ Mailed pill-splitter
- ▶ Ethics approval
 - ▶ Approved following extensive consultation with HP and KPNW IRBs and NHLBI
 - ▶ DSMB approved safety monitoring plan

Unexpected Problems - 1

- ▶ Easy to order medications, no simple electronic way to discontinue them
- ▶ Discontinuing Rx in EHR not transmitted to pharmacy
- ▶ Auto-refills and reminders from pharmacy common, or patient can initiate refill

	Quantity	Refills	Start	End
chlorthalidone (HYGROTON) 25 MG tablet	45 Tab	3	9/9/2016	9/9/2017

Sig : Take 0.5 Tabs by mouth daily. **Discontinue hydrochlorothiazide (HCTZ). See notes.** Indications: High Blood Pressure

Route: Oral

Comment: Start chlorthalidone 12.5 mg now. HCTZ has been discontinued. Counsel patient to stop HCTZ and discard remaining pills. For questions call 952-967-5554.

Unexpected Problems - 2

- ▶ Many patients don't read their mail
- ▶ Pragmatic comparative effectiveness trials are unfamiliar
 - ▶ “Experimental Misconception” – neither treatment is experimental
 - ▶ No extra tests or visits are needed
 - ▶ Less active forms of obtaining consent are unacceptable to many patients
 - ▶ Cho MK, et al. Ann Intern Med 2015;162:690-696
- ▶ Opt-out method we chose is largely untested
 - ▶ Many assume that if you do nothing, you are NOT in the study
- ▶ Combined with unexpected problem 1, concern about patients taking both HCTZ and CTD

Unexpected Problems - 3

- Real-time pharmacy claims are a nightmare!

rx_written_dt	fill_dt	CLAIM_NO	CLAIM_STATUS_CD_DESC	RX_NO_2	DOB	Last Name	First Name	LABEL_NM
4/22/2016	10/3/2016	5365723948	APPROVED	7237182	8/31/xxxx	Doe	Jane	HYDROCHLOROTHIAZIDE 25 MG TAB
10/7/2016	10/7/2016	5372258654	RDA (REVERSED)	7253994	8/31/xxxx	Doe	Jane	CHLORTHALIDONE 25 MG TABLET
10/7/2016	10/7/2016	5372305252	RLA (REVERSAL)	7253994	8/31/xxxx	Doe	Jane	CHLORTHALIDONE 25 MG TABLET
10/7/2016	10/7/2016	5372332490	RDA (REVERSED)	7253994	8/31/xxxx	Doe	Jane	CHLORTHALIDONE 25 MG TABLET
10/7/2016	10/7/2016	5372333302	RLA (REVERSAL)	7253994	8/31/xxxx	Doe	Jane	CHLORTHALIDONE 25 MG TABLET
10/7/2016	10/7/2016	5372333746	APPROVED	7253994	8/31/xxxx	Doe	Jane	CHLORTHALIDONE 25 MG TABLET

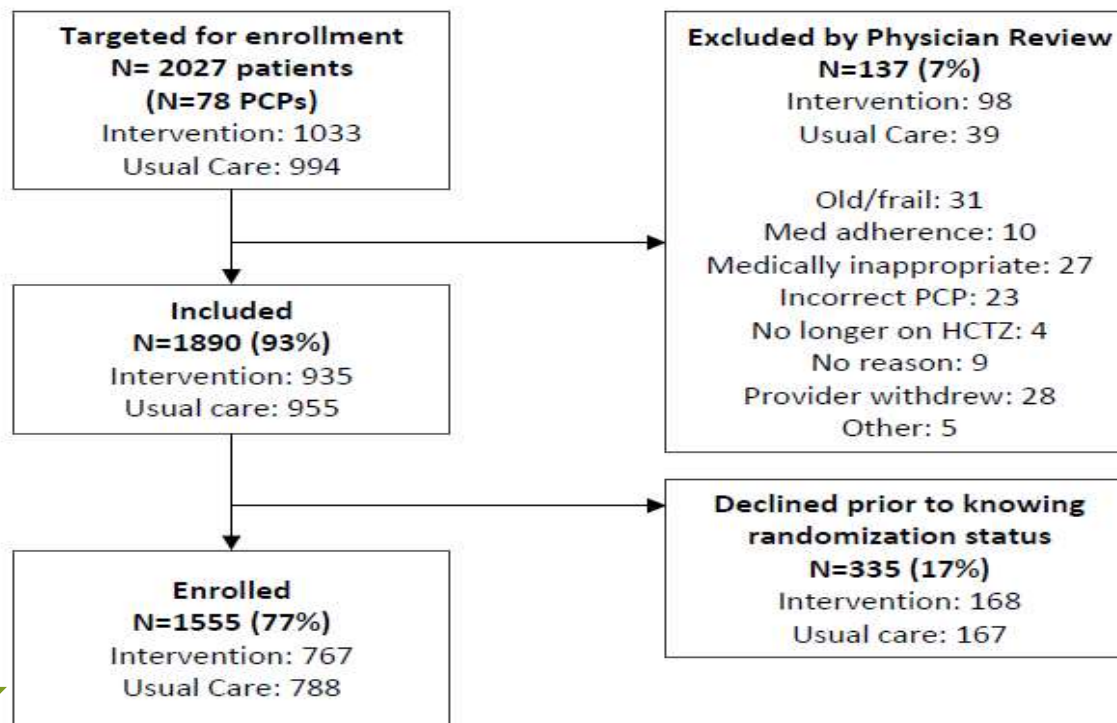
PCP Communication

- ▶ Provider Letter 1: Introduction to seek interest
 - ▶ Interested: Send Letter 2
 - ▶ Not interested: Exclude
 - ▶ No response: Recontact once, exclude if still no response
- ▶ Provider Letter 2: Complete elements of consent & patient exclusion form
 - ▶ Return of patient form assumed to imply consent
 - ▶ PCP then enrolled
 - ▶ Recruitment of patients not excluded proceeds.
- ▶ PCPs offered nominal monetary compensation for participation (\$300) at HP (not allowed at KPNW)

Patient Communication

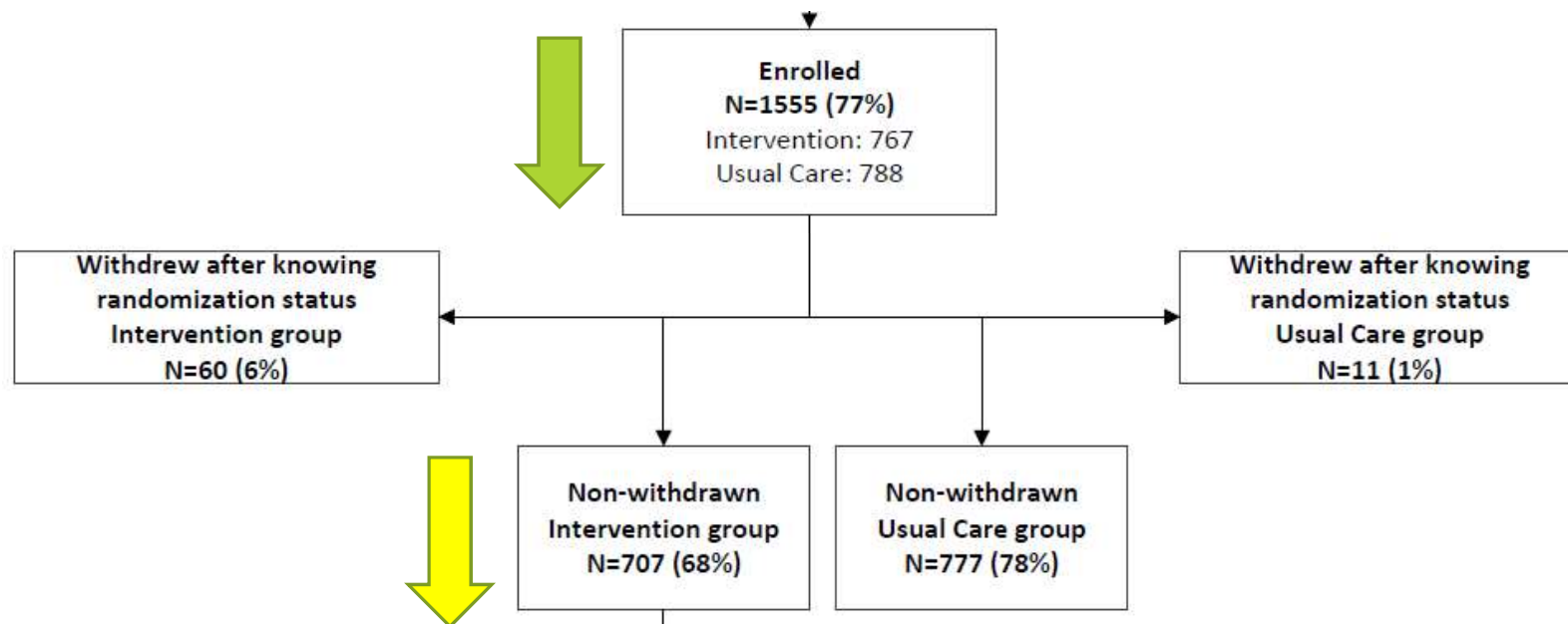
- ▶ 1st letter signed by PCP and study PI informing them of trial and possibility that their PCP may be in the group that switches patients to chlorthalidone (2 pages)
 - ▶ Letter included elements of consent, option to opt out of study by postage-paid mail, email, or phone
- ▶ 2nd letter informing them of treatment assignment (only intervention group). Letter included information about (2 pages):
 - ▶ Dosage change, need for pill splitting
 - ▶ Date of switch, pharmacy location
 - ▶ Likelihood of higher cost, debit card
 - ▶ Ability to opt out, PCP may change medications at any time after switch

PCP and Patient Recruitment

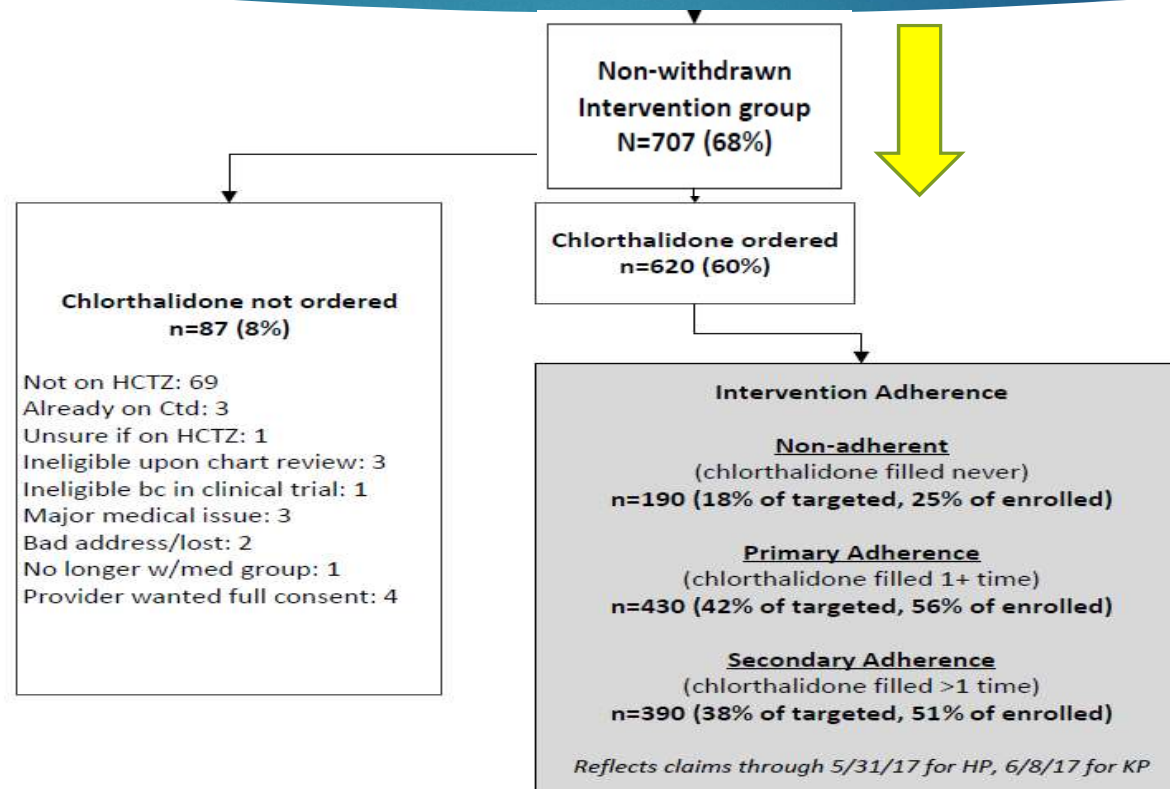


- ▶ 316 PCPs contacted
- ▶ 78 (25%) PCPs agreed to participate
 - ▶ 40 at HP and 38 at KPNW
- ▶ Average cluster size ~26 (smaller than in preliminary data due to increasing use of combination drugs)

Post-randomization Withdrawals



Intervention Adherence (Aim 1)



Eligible & Enrolled Patient Characteristics

	Eligible Patients (N=2027)	Enrolled Patients (N=1555)
Age, mean	65.9	64.5
Female, %	59.2	56.1
White, %	82.7	81.5
BP, mm Hg	132/75	132/76
Diabetes, %	27.4	27.2

- ▶ Eligible patients were older (65.9 years) and more likely to be female (59%)
- ▶ Similar racial/ethnicity, BP, labs, comorbidities in enrolled and eligible population
- ▶ Similar characteristics across sites and randomized groups (randomization worked!)

Blood Pressure Data (Aim 2)

	Total			
	Total	UC	Inter- vention	Inter- vention 2° Adherent
Data cumulative through June 1, 2017				
Denominator: All ENROLLED patients	1555	788	767	390
Blood Pressure				
Patients with BP in record after index date (y/n), %	96.5	97.1	95.8	96.4
SBP post-index date, mean mmHg	134	134	133	134
DBP post-index date, mean mmHg	73	74	72	72
SBP post-index date, most recent mmHg	133	132	133	134
DBP post-index date, most recent mmHg	75	76	75	75

Safety Data (Aim 2)

	Total			
	Total	UC	Inter- vention	Inter- vention 2° Adherent
Data cumulative through June 1, 2017				
Denominator: All ENROLLED patients	1555	788	767	390
Serum K+ values available, %	90.8	90.5	91.1	92.5
K+, avg most recent (mEq/L)	4.0	4.0	4.0	3.9
K+ <3.5 mEq/L, %	12.2	11.0	13.5	14.5
K+ <3.0 mEq/L, %	0.8	0.7	1.0	1.1
Serum Na+ values available, %	75.7	76.3	75.1	75.6
Na+, avg most recent (mEq/L)	140.2	140.2	140.1	140.0
Na+ <135 mEq/L, %	6.4	6.1	6.7	7.0
Na+ <130 mEq/L, %	0.8	1.0	0.5	0.3

Safety Data (Aim 2)

	Total			
	Total	UC	Inter- vention	Inter- vention 2° Adherent
Data cumulative through June 1, 2017				
Denominator: All ENROLLED patients	1555	788	767	390
eGFR values available, %	90.6	91.2	91.7	92.1
eGFR, % <60 (mL/min/1.73 m2)	23.8	24.1	23.1	20.9
ICD-10 Incident diagnosis codes - safety, %				
Hypotension, %	2.0	1.6	2.3	1.5
Hypokalemia, %	6.7	5.6	7.8	7.2
Hyponatremia, %	2.1	2.0	2.1	1.5

PCP and Patient Survey (Aim 3)

- ▶ 13 responses from 39 intervention PCPs
- ▶ Most agreed that they would participate in a similar study again
- ▶ Less time spent than expected reviewing patient list and answering patient questions
- ▶ Agree or neutral: “Patients did well after switch to chlorthalidone”
- ▶ Confusion about opt-in vs. opt-out
- ▶ Confusion about logistics of medication switch
- ▶ Dislike of reimbursement method and increased co-pays
- ▶ Some reported difficulty with pill-splitting (although most did not)
- ▶ Main reasons for not filling chlorthalidone: higher cost, inconvenience, satisfaction with HCTZ

Lessons Learned - 1

- ▶ Cluster-randomized design at physician level worked well
- ▶ Physicians are surprisingly willing to participate in this kind of research and even be inconvenienced by it
- ▶ Enrolled patients very similar to eligible population
- ▶ Relatively high proportion of eligible patients received intervention
- ▶ EHR data on BP and safety labs were quite complete, could be extracted and compiled with relative ease
 - ▶ Method used for common “index date” did not make it simple to determine post-intervention data
 - ▶ Some indication of increased risk of hypokalemia, but not other adverse effects of chlorthalidone

Lessons Learned - 2

- ▶ Mailed information with opt-out is not a viable method for a large-scale trial (despite its similarity to routine formulary therapeutic substitution)
 - ▶ Patients too often did not receive, read, or understand mailings
 - ▶ 25% of enrolled patients never filled chlorthalidone
- ▶ Patient understanding critical given inability to e-discontinue HCTZ
 - ▶ Co-administration of HCTZ and chlorthalidone an important safety concern
- ▶ Pharmacy claims do not provide good enough real-time data to closely monitor adherence (KP pharmacy dispensing records are much better)
- ▶ High out-of-pocket costs for chlorthalidone a major obstacle
 - ▶ Debit cards not a good solution
 - ▶ Central pharmacy if out-of-pocket costs cannot be waived at point-of-care

Practical Considerations

- ▶ VA Diuretic Comparison Project incorporates some of the design changes that we would make to full-scale THIAZIDES
 - ▶ Opt-in consent with direct communication between patients and research team
 - ▶ Eliminate out-of-pocket cost differences between HCTZ and CTD
 - ▶ Ensure HCTZ stopped before CTD started
 - ▶ Do not include 12.5 mg HCTZ or consider monitoring K+ more actively

VA DCP Challenges

- ▶ No local site investigator to push the study at each site. Has been difficult to get sites to agree to participate
 - ▶ Worry about additional burden on PCPs
 - ▶ Competing interests from other high priority items – so feel DCP would be a distraction to leadership
- ▶ Getting PCPs to agree to participate – worry about view alert burden
 - ▶ Have changed the messaging to highlight that the average PCP gets 8 total additional view alerts over a 3-6 month period
- ▶ We relied on a VA contracted call center to call and consent Veterans
 - ▶ Call center was tasked with other VA priorities – and their dedication to the study substantially decreased
 - ▶ Call center callers were not fully engaged with the study and had a very low consent rate
 - ▶ Hiring callers in Minneapolis now to make the calls so we can
 1. Provide the volume of calls needed
 2. We have a greater consent rate than the contracted call center