# Improving Adherence in Hypertension Management

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### **Three Main Causes of The Low Rate of BP Control**



# Patients' adherence in various therapeutic area

Therapeutic Area	No. of Reports	Mean Compliance Rate (%)	Range (%)
Cancer <sup>14-18</sup>	5	80	35-97
Cardiovascular-all <sup>19-43</sup>	26	71	39-93
Hypertension only	17	73	39-93
Other cardiovascular	9	71	64-93
Epilepsy <sup>4,44,45</sup>	3	70	46-88
Fertility <sup>46-50</sup>	5	71	34-97
Glaucoma <sup>9,10</sup>	2	78	76-80
Infectious disease <sup>13,51-57</sup>	8	74	40-92
Medical, general-all <sup>66-78</sup>	14	75	51-85
Diabetes only	3	73	66-85
Thalassemia only	3	79	72-85
Other medical only	8	74	51-84
Medical education <sup>83</sup>	1	47	
Psychiatry <sup>79-82</sup>	4	78	75-83
Respiratory-all <sup>58-65</sup>	10	54	37-92
Asthma only	7	55	37-92
Chronic obstructive			
pulmonary disease only	3	51	50-52

Claxton et al. Clin Ther 2001:23:1296-1310

## Poor Adherence and Persistence with Antihypertensive Treatment



# Adherence to Antihypertensive Treatment Has Been Found to Decrease Risk of Acute CV Events

Hazard Ratio for Acute CV Event

- 18,806 newly diagnosed hypertensive patients aged ≥35 years (mean age at entry, 62 years)
- Newly treated for HTN and initially CVD free
- Adherence:
  - High: ≥80% of days covered
  - Intermediate: 40–79% of days covered
  - Low: ≤40% of days covered
- Mean follow-up: 4.6 years



#### Adherence

CVD=cardiovascular disease; HTN=hypertension. Mazzaglia G, et al. *Circulation.* 2009;120:1598-1605.

### Adherence Has Been Found to Decrease Risk of Hospitalization



\*Adherence was defined as the percentage of days during the analysis period that patients had a supply of ≥1 maintenance medications for the condition. Sokol MC, et al. *Med Care.* 2005;43:521-530.

# Adherence to Antihypertensive Treatment Has Been Found to Decrease Mortality Risk

 Retrospective cohort study included all chronic medication-treated patients with HTN enrolled in Tennessee's Medicaid program (TennCare) for an average of 4.7 years during the period 1994–2000 (N=49,479)



Adjusted Kaplan-Meier survival curves demonstrate that  $\geq$ 80% baseline refill adherence was associated with better 5-year estimated survival than <80% refill adherence for a combined outcome of stroke or death (*P*<0.001)

Medication Refill Adherence (MRA) was calculated as the percentage of eligible prescription days filled (total days' supply for all qualifying drug classes/ total number of days from the first to the last fill in the interval × 100, capped at 100%) for all antihypertensive medications taken in the time period.

HTN=hypertension; MRA=medication refill adherence.

Bailey JE, et al. J Gen Intern Med. 2010;25:495-503.

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### Poor Adherence Has Been Found to Increase Cost of Care



ED=emergency department; MPR=medication possession ratio.

Pittman DG, et al. Am J Manag Care. 2010;16:568-576.

Annual Cost of Care (\$)



STUDY OF COMPLIANCE TO ANTIHYPERTENSIVE MEDICATION IN KOREAN HYPERTENSIVE PATIENTS USING MEDICATION EVENT MONITORING SYSTEM

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# Methods of measuring adherence

- In practice
  - Attendance at appointments
  - Clinical response to medications
  - Patient self-report
- In research
  - Pill count at home visits
  - Monitoring prescription refills
  - Drug Assays in body fluids
  - Tracers
  - "Memory" pill containers

# Medication Event Monitoring System (MEMS)



Considered to be gold standard in measuring adherence

# **MEMS-HTN study**

- Inclusion and exclusion

- Inclusion
  - Diagnosed HTN
  - Both drug-naïve and in ongoing treatment
  - In or about to start monotherapy
- Exclusion
  - Who needs more than two drugs to control BP
  - >= Twice a day medication
  - Hypertensive emergency or urgency
  - Comorbidity is not a limiting factor unless it necessitate co-administration of other drugs
  - Patient's refusal

## MEMS-HTN study – Subjects

- N=80 (M:F=52:38%), Age: 53  $\pm$  10 yrs
- <= Stage I HTN: 77%
- Total duration of hypertensive medication: median 11 months (range: 0-204 months)
- Drug-naïve: 15%
- No medication in recent 1 month: 30%
- History of self discontinuation of medication within 1 year: 5%
- Education level: >= college-graduated 63%

# Near-perfect adherence

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# Poor adherence

#### - due to psychological resistance



# 'Random' non-adherence



# 'White coat adherence'

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## **Overall compliance parameters**



## Predictors of poor compliance (1)

Percent of dose taken	<80%	80-99%	>=90%	p for trend
Previous history of medication discontinuation	15%(2/13)	13% (1/8)	3% (2/59)	0.04
Currently not in drug treatment	46% (6/13)	38% (3/8)	25% (15/59)	0.06
Percent of dose taken correctly				
Previous history of medication discontinuation	15% (2/13)	9% (2/22)	2% (1/45)	0.03
Currently not in drug treatment	46% (6/13)	35% (8/22)	22% (10/45)	0.04

## Predictors of poor compliance (2)



## Methods to Improve Adherence

Patient level					
Information combined with motivational strategies	Health system level				
(see Section 5.1.6 on smoking cessation).	Intensified care (monitoring, telephone follow-u reminders, home visits, telemonitoring of home blood pressure, social support, computer-aided				
Group sessions.					
Self-monitoring of blood pressure	counseling and packaging).				
Self-management with simple patient-guided system.	Interventions directly involving pharmacists.				
Complex interventions.	Reimbursement strategies to improve general				
Drug treatment level	practitioners' involvement in evaluation and treatment of hypertension				
Simplification of the drug regimen					
Reminder packaging					

# Trials in Which Multiple Antihypertensive Medications Were Required

Number of Drugs

Trial	and SBP achieved (mm Hg)	0	1	2	3	4
	ALLHAT <sup>1</sup> , 138	+	I			
HTN	HOT <sup>1</sup> , 138					
	ASCOT <sup>2</sup> , 137					
Diabetes	ACCORD BP (Intensive)*3, 119					
	ACCORD BP (Standard)*3, 134					
Diabetes With	IDNT <sup>1</sup> , 138					
and Without	RENAAL <sup>1</sup> , 141					
<b>Renal Disease</b>	ABCD <sup>1</sup> , 132					
	UKPDS <sup>1</sup> , 144					
Kidney Disease	AASK <sup>1</sup> , 128					
	MDRD <sup>1</sup> , 132					

\*Target BP control groups in ACCORD defined as <120 mm Hg (intensive) and <140 mm Hg (standard).

1. Bakris GL. Am J Med. 2004;116:30S-38S. 2. Dahlof B, et al. Lancet. 366:895-906. 3. Cushman WC, et al. N Engl J Med. 2010;362:1575-1585.

Advantages of combination therapy - esp. single-pill combination (SPC)

- Additive antihypertensive efficacy

   complementary mechanisms of action
- Higher patient response rates
- Simple titration and dosing schedules
- Maintained or improved tolerability
- Improved patient adherence
- Attenuation of adverse effects / metabolic effects
- Cost effective

## Improved Persistence Found With Fixed-Dose Combination vs Free-Dose Components





Improved Compliance with Single-pill Combination Therapy Compared with Free-combination Therapy



<sup>†</sup>Defined as the total number of days of therapy for medication dispensed/365 days of study follow-up

Gerbino & Shoheiber. Am J Health System Pharm 2007;64:1279-83

## Single-pill Combinations Improve Compliance Regardless of Concomitant Medications

Medication-possession ratio



\*p<0.0001

Gerbino & Shoheiber. Am J Health System Pharm 2007;64:1279-83

# Fixed-Dose Combinations Resulted in Increased Persistence and Compliance



### **Meta-analysis of 6 Studies**

CI=confidence interval; FDC=fixed-dose combination; OR=odds ratio.

Gupta AK, et al. Hypertension. 2010;55:399-407.

# Fixed-Dose Combinations Resulted in Increased Normalization of BP

## **Meta-analysis of 3 Studies**



BP=blood pressure; CI=confidence interval; FDC=fixed-dose combination; OR=odds ratio.

Gupta AK, et al. Hypertension. 2010;55:399-407.

Fixed-Dose Combinations Decreased Risk of AEs

### **Meta-analysis of 5 Studies**



AEs=adverse events; CI=confidence interval; FDC=fixed-dose combination; OR=odds ratio.

Gupta AK, et al. Hypertension. 2010;55:399-407.

## Guideline for Fixed-Dose Combination

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension.	IIb	B

## **Recommended Combination Therapy on Guidelines**



ESH-ESC Guidelines. J Hypertens. 2013, 31:1281-1357

### We need to understand the feelings generated by hypertension

- Our patients
  - reaction to being diagnosed with hypertension and facing a lifetime of treatment
  - worries about side effects of drugs and interactions
  - difficulties with complex regimens





- Ourselves, as physicians
  - frustrations over poor BP control
  - concerns about poor adherence
  - personal and patient motivation

# Triple Therapy with High Dose Olmesartan/AML/HCTZ in the TRINITY Study



Oparil et al. Clin Ther 2010;32:1252-69

High Dose OLM/AML/HCTZ Triple Combination Therapy is Superior to Dual Combination at Lowering BP (TRINITY study)



\*p<0.001 vs. baseline \*p<0.001 for triple vs. each dual combination

In patients with baseline mean SeBP 168.5/100.9 mmHg, af ter 12 weeks of treatment

Oparil et al. Clin Ther 2010;32:1252–69

### Take-home Messages

- Barriers to good BP control
  - Physicians' side: clinical inertia
  - Patients' side: poor persistence and/or adherence
- Poor persistence/adherence is not uncommon and has significant influence on prognosis.
- There is no short answer in improving persistence/adherence.

Patient's health belief

# However,

Simplifying regimen using singlepill combination is the easiest and the most feasible way to improve patient's adherence.