Are initial fixed-dose combination antihypertensive medications cost-effective?

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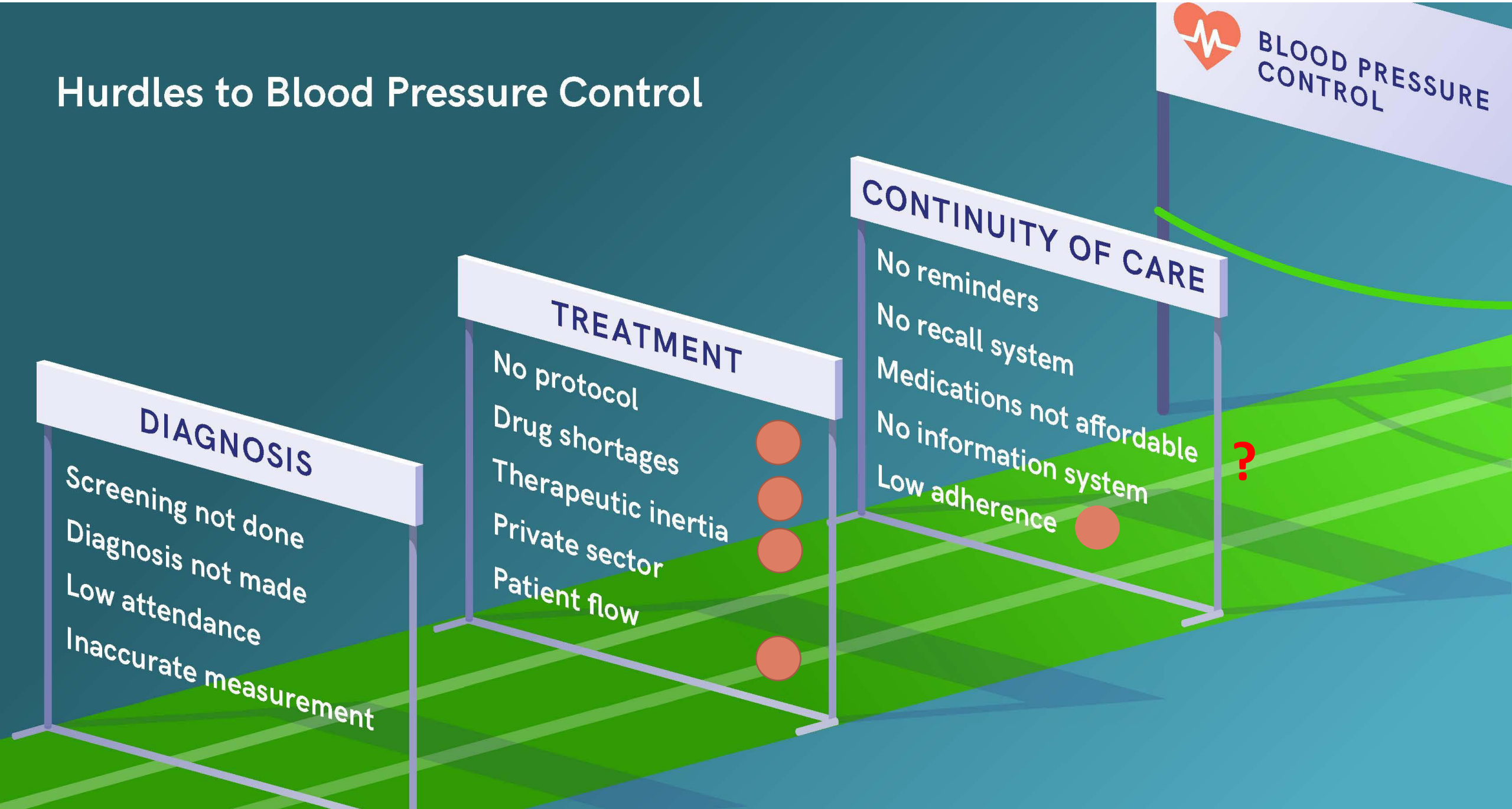
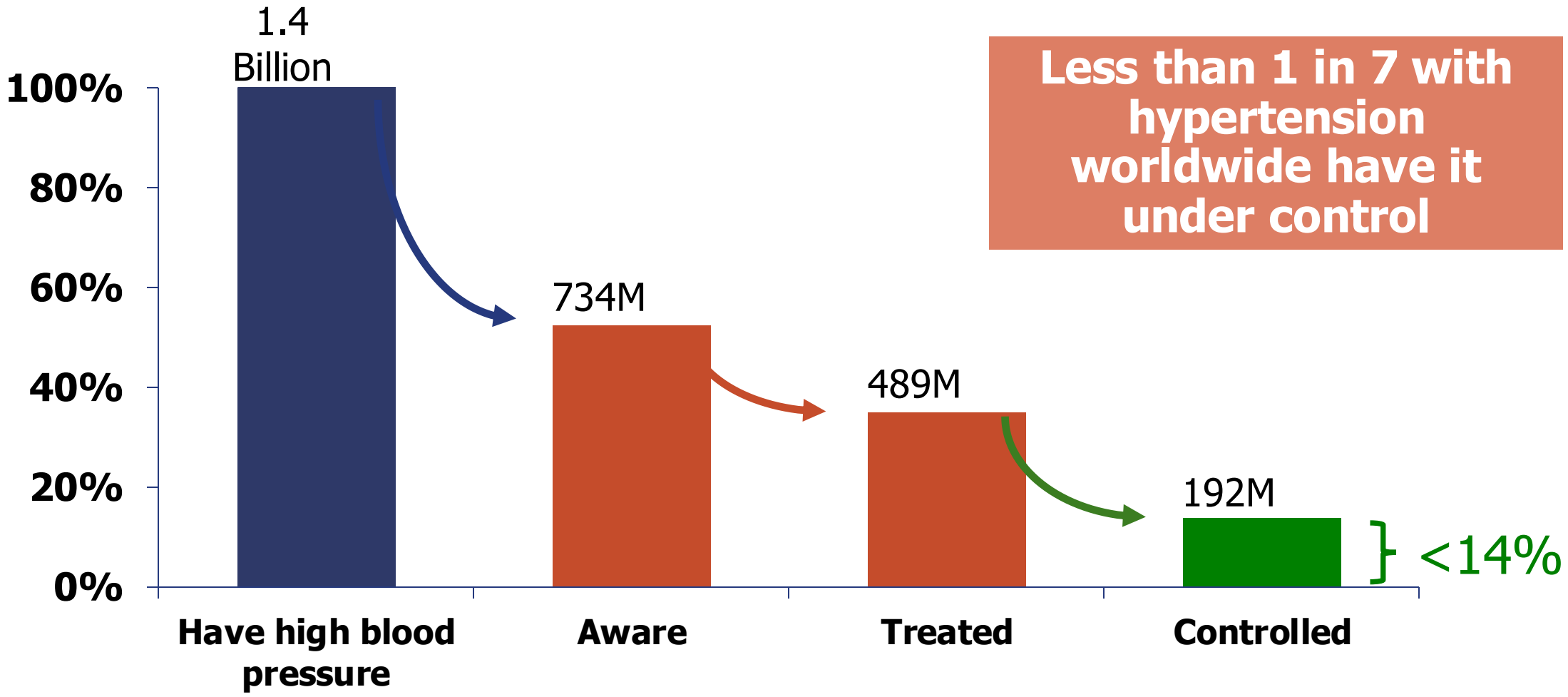
Hurdles to Blood Pressure Control



Most People With Hypertension Globally Do Not Have It Under Control

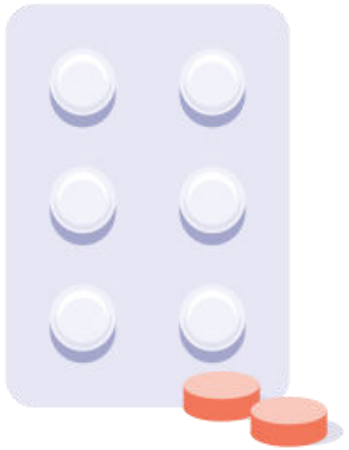


Mills KT et al. Circulation. 2016 Aug 9;134(6):441-450.

Effective Hypertension Care As Pathfinder for Primary Health Care

Simple, Practical Protocol

Manage other chronic conditions; improve evidence-based care; reduce costs



Medication and Equipment Supply

Improve purchasing and supply chain management

Team-Based Care

Applicable to wide range of chronic health conditions

Patient-Centered Services

Improve patient support; access to and confidence in primary care; reduce reliance on hospital care; reduce financial and other barriers

Information Systems

Create feedback loops applicable to other conditions; strengthen data-driven culture of accountability and quality improvement

Advantages of single pill FDC antihypertensive medications

Single pill FDCs simplify the treatment regimen by:

1. Decreasing daily pill burden
2. Improved medication adherence (in terms of execution and persistence)
3. Faster BP control
4. Less time exposed to CVD-risk

Improved efficacy… at what price? *(JAMA 2018)*

- In the United States, like in many countries, single pill FDCs more expensive than their own constituents even in generic form
- Potential reduction in Medicare spending (relative to decreasing the price of SPC) would amount to millions of dollars (~$925)
- Using equally safe and effective lower-cost generic drugs represents an important opportunity to reduce unnecessary expenditures

Comparison of single pill FDC medications with free dose equivalent components

JAMA | Original Investigation

Medicare Spending on Brand-name Combination Medications vs Their Generic Constituents

Chana A. Sacks, MD, MPH; ChangWon C. Lee; Aaron S. Kesselheim, MD, JD, MPH; Jerry Avorn, MD

Table 2. Reported Spending by Medicare Part D on Brand-name Combination Drugs and Estimated Potential Reduction in Spending by Substituting Generic Constituents in 2016

Brand-name Combination Drug	Generic Constituents	List Price, $[a]		Total Reported Spending on Brand-name Product, $[c]	Price of Generic Constituents/Price of Combination Product, %[d]	Estimated Potential Reduction in Spending, $[c,e]
		Per Pill[b]	Generic Constituents			
Constituents Available as Generic Medications at Identical Doses Category						
Epzicom	Abacavir, lamivudine	42.85	14.01	157 504 662	33	106 008 707
Percocet	Oxycodone, acetaminophen	14.23	0.38	43 993 029	3	42 832 272
Zegerid	Omeprazole, sodium bicarbonate	86.29	0.47	28 255 198	1	28 106 005
Diovan HCT	Valsartan, hydrochlorothiazide	7.79	0.93	14 985 874	12	13 190 005
Bidil	Isosorbide dinitrate, hydralazine	2.93	0.88	13 866 434	30	9 700 493
Exforge	Amlodipine, valsartan	8.21	0.96	7 755 807	12	6 845 024
Lotrel	Amlodipine, benazepril	8.27	0.25	5 589 369	3	5 419 066
Pylera	Bismuth, metronidazole, tetracycline	5.86	5.27	4 234 402	90	425 805
Caduet	Amlodipine, atorvastatin	11.92	0.42	4 086 377	4	3 942 761
Micardis HCT	Telmisartan, hydrochlorothiazide	5.76	1.28	3 554 664	22	2 764 368
Hyzaar	Losartan, hydrochlorothiazide	4.47	0.25	3 501 615	6	3 303 564
Actoplus Met XR	Pioglitazone, extended-release metformin	12.16	1.35	2 754 836	11	2 421 828
Exforge HCT	Amlodipine, valsartan, hydrochlorothiazide	8.36	1.05	2 010 417	13	1 756 307
Avalide	Irbesartan, hydrochlorothiazide	6.81	0.46	1 959 401	7	1 826 769
Fosamax Plus D	Alendronate, vitamin D_3	39.05	1.25	1 875 014	3	1 814 983
Arthrotec 75	Diclofenac, misoprostol	5.88	1.40	1 720 942	24	1 310 946
Tarka	Trandolapril, extended-release verapamil	4.22	0.78	1 671 759	18	1 362 704
Stalevo 100	Carbidopa, levodopa, entacapone	6.13	2.65	1 509 886	43	856 799
Simcor	Extended-release niacin, simvastatin	5.53	2.68	1 023 636	48	536 956
Advicor	Extended-release niacin, lovastatin	6.82	2.71	723 072	40	434 939
Subtotal				302 576 394		234 860 301

Cost-effectiveness of single pill FDCs: objectives

- Initiating HT treatment with single-pill combination medications reduces time-to-BP control while not increasing adverse medication event risk.
- We hypothesized that initiating treatment with a single-pill combination will increase medication costs, but that these may be offset by reducing number of office visits dedicated to BP monitoring and medication titration.

Cost-effectiveness of single pill FDC antihypertensive meds

Study design

- **Time-horizon:** 10 years
- **Cohort:** U.S. adults with uncontrolled hypertension that have never been treated bef**ore**
- **Methods:** cardiovascular disease simulation model within TreeAge 2019 decision analysis software
- **Treatments:** initial monotherapy with subsequent FEC (also known as usual care), which involved a "start-low-go-slow" approach compared against initial and subsequent SPC therapy
- **Outcomes:** time-to-control BP, percentage of patients controlled, total costs
- **BP goals:** JNC-7 and 2017 AHA/ACC guidelines

Cost-Effectiveness Analysis

- **Cost-effective analysis (CEA):** evaluates the effectiveness of two or more treatments relative to their cost. Multiple alternatives each have their own costs and health effects, through which it is possible to calculate cost-effectiveness (change in costs/change in health, or *investment needed to gain health*)
- **Primary outcomes for this analysis:**
  - % of controlled hypertensive patients at 1, 5 and 10 years
  - Med costs, monitoring costs, total costs (med costs + monitoring cost)
  - Cost per patient with controlled hypertension

Study treatment groups

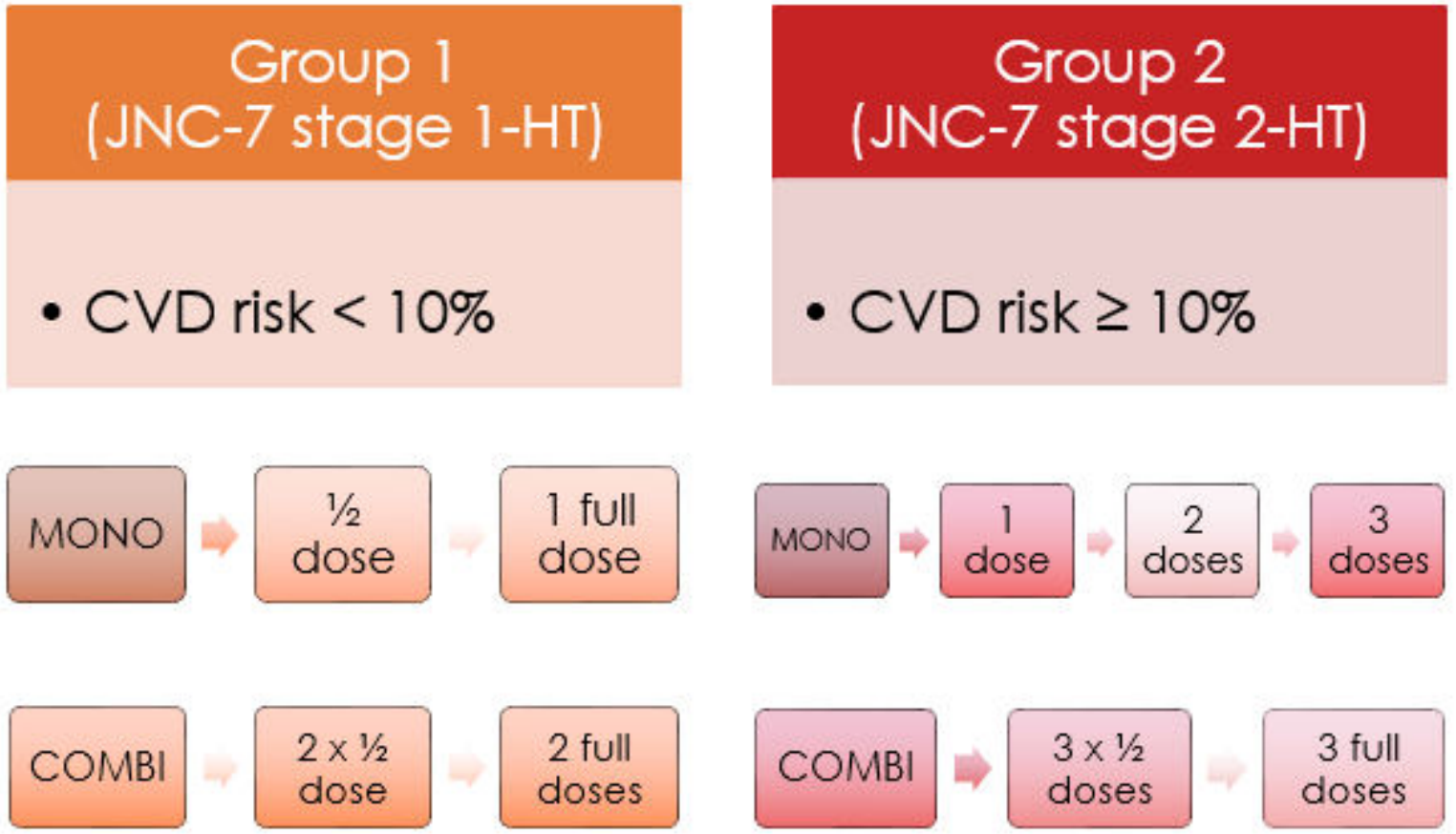


Figure 1. Treatment Strategies – in all four strategies the up-titration process will increase to a maximum of 5 doses for every group if BP is not under control.

Single pill combinations: titration steps

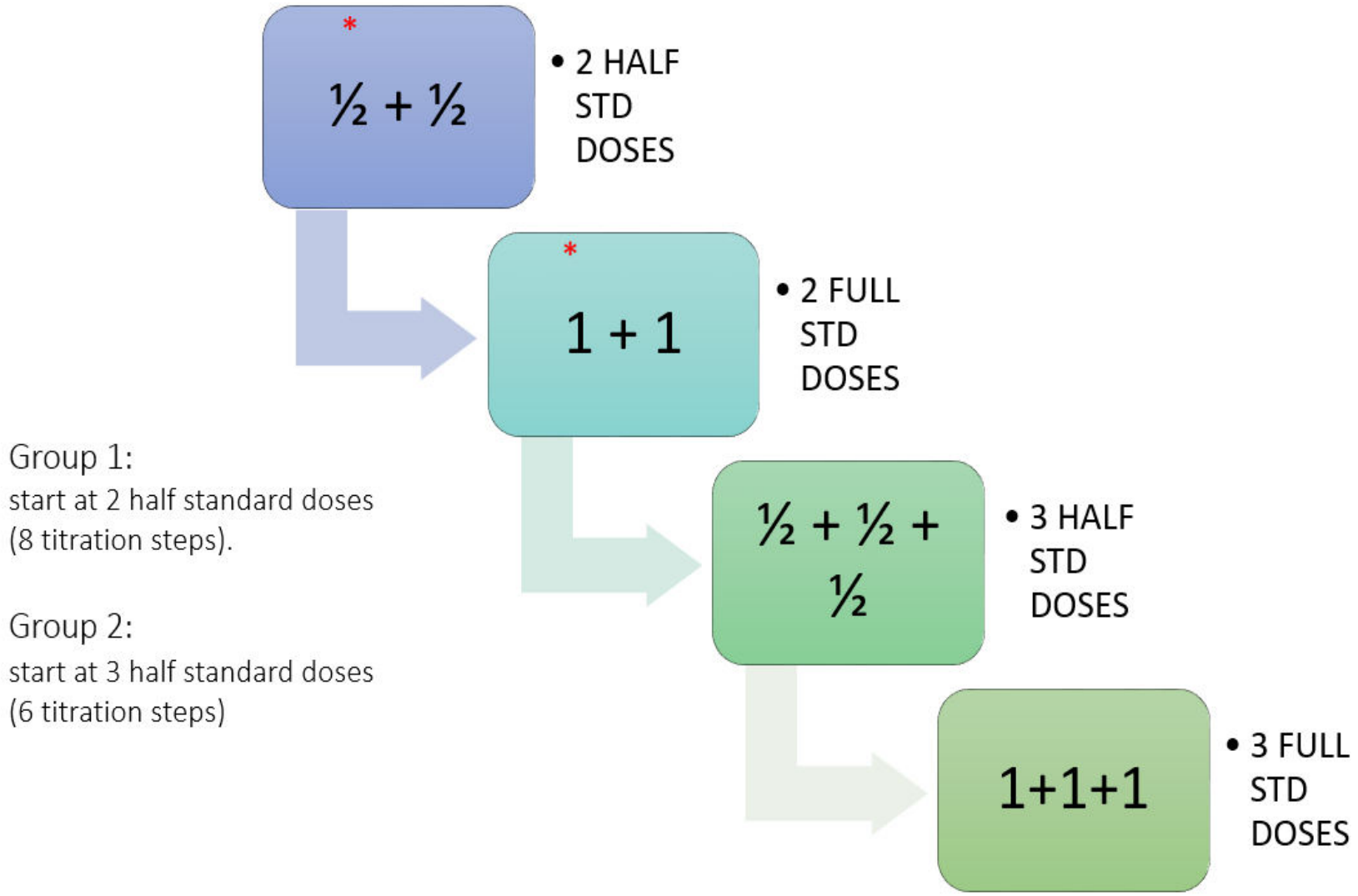
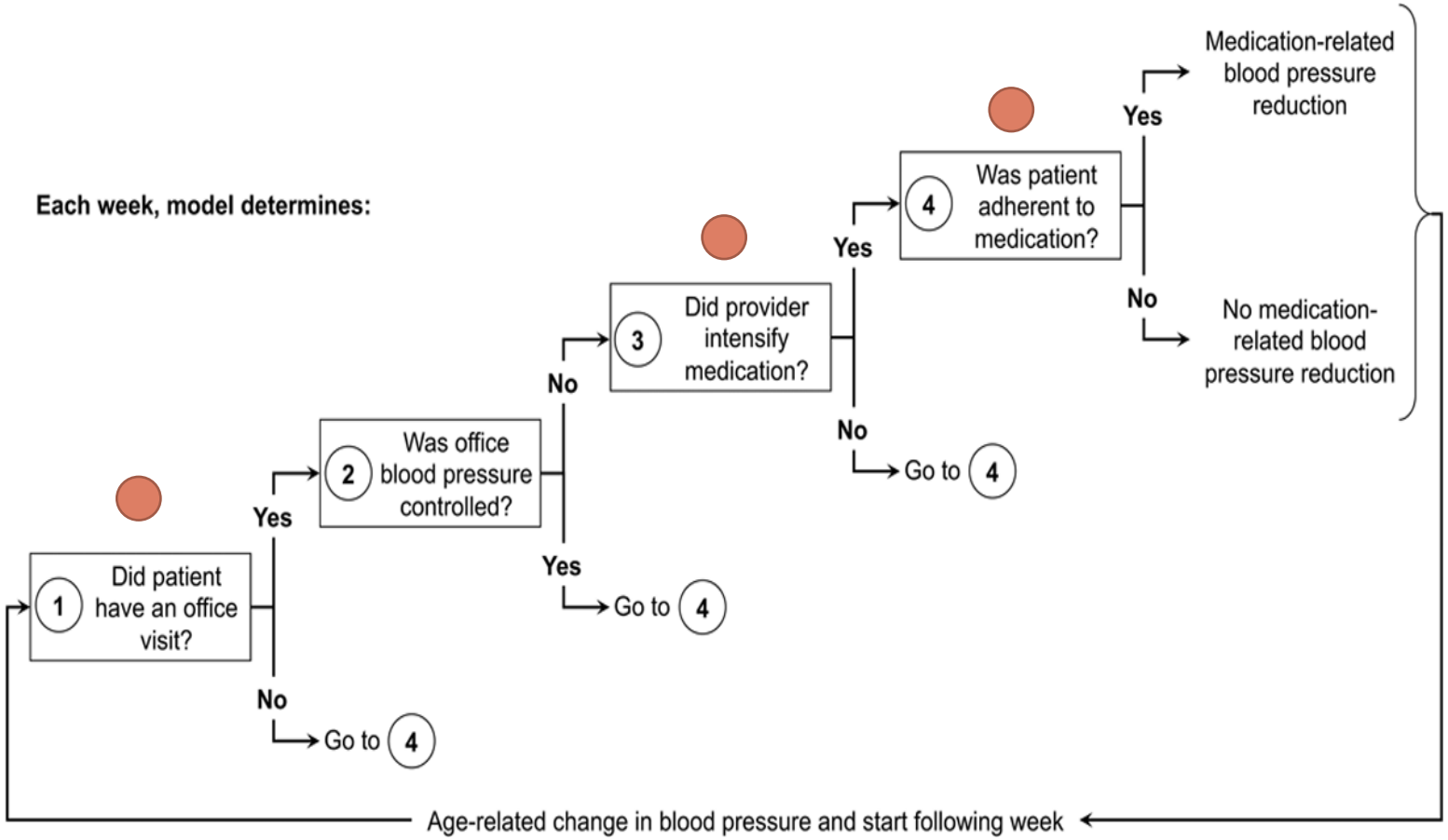


Figure 2. Treatment Strategies – in all four strategies the up-titration process will increase to a maximum of 5 doses for every group if BP is not under control.

Blood Pressure Control Model (computer simulation model)



Brandon K. Bellows. Circulation: Cardiovascular Quality and Outcomes. Clinic-Based Strategies to Reach United States Million Hearts 2022 Blood Pressure Control Goals, Volume: 12, Issue: 6, DOI: (10.1161/CIRCOUTCOMES.118.005624)

Tables of BP predicted reductions

Patients	Baseline BP Range (mmHg)	½ drug ΔBP	1 drug ΔBP	2 drugs ΔBP	3 drugs ΔBP
Group 1					
SBP	130-149	5.1 (2.55-7.65)	6.7 (6.1-7.2)	12.7 (6.35-19.05)	18.2 (9.1-27.3)
DBP	80-99	3.7 (3.1 to 4.3)	4.7 *		
Group 2					
SBP	150-159	6.7 (6.1-7.2)	8.7 (4.35-13.05)	16.5 (8.25-24.75)	23.6 (11.8-35.4)
DBP	95-100				

Monotherapy BP Changes
Source: From Law et al. BMJ. 2009; 338:b1665 and Law et al. BMJ 2003; 326:1427
Standard Deviation in parenthesis
*The SD for this estimate (from Law et al. BMJ. 2009;338:b1665) is not available; therefore, we are will use the mean of the SDs for 1 and 2 half-standard doses.

Patients	Baseline BP Range (mmHg)	2 x ½ drug ΔBP	3 x ½ drug ΔBP
Group 1			
SBP	130-149	6.7 (6.1-7.2)	15.2 (N/A)
DBP	80-99	7.3 (6.2 to 8.3)	10.7 (9.1 to 12.4)
Group 2			
SBP	150-159	13.3 (12.4-14.1)	19.9 (18.5-21.3)
DBP	95-100	7.3 (6.2-8.3)	

Combination Therapy (SPC) BP Changes
Source: Law et al. BMJ 2003; 326:1427
Standard Deviation in parenthesis

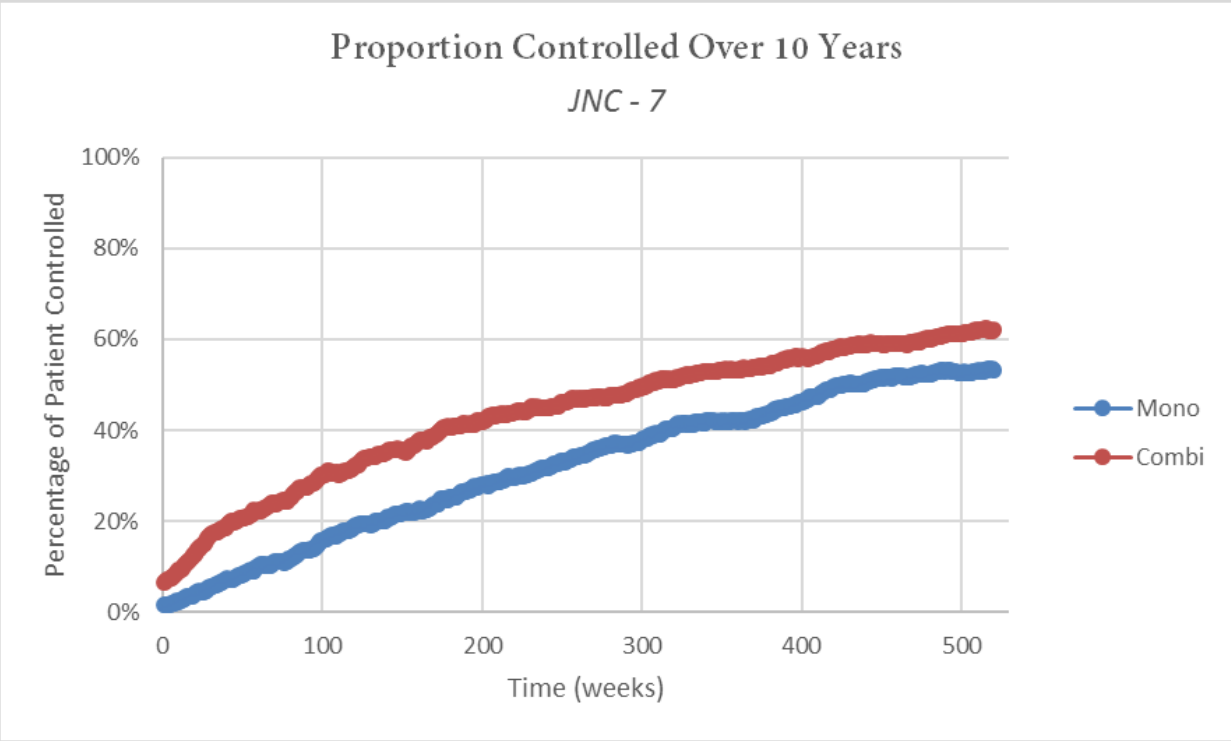
Summary table of Medication Cost and Persistence Rates Table

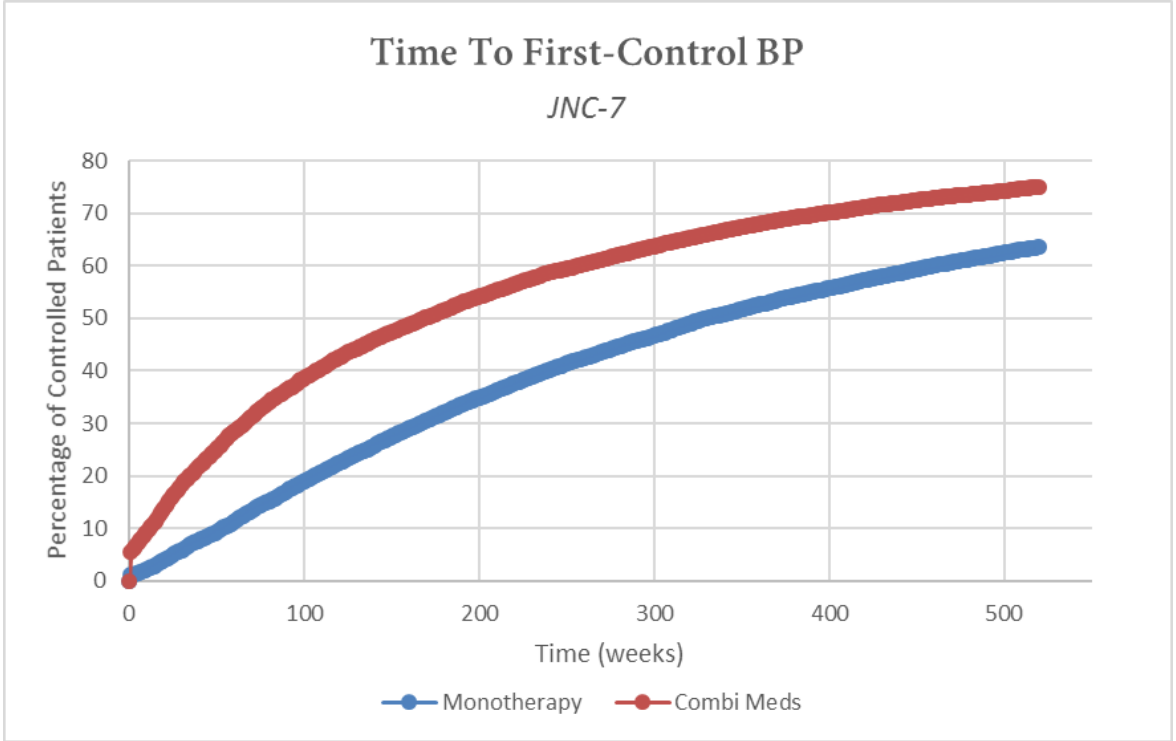
MEDICATION COST

Therapy	Monthly Avrg Cost	Total Cost
Mono	$ 5.16	$ 7.66
Combi - 2 agents	$ 13.03	$ 15.53
Combi - 3 agents	$ 53.40	$ 55.90
Dispensing Fee	$ 2.50	

PERSISTENCE WITH SPC (%)	SPC	N (SPC)	FREE-EQ.	N (FREE)	Total N	Follow-up	Weighted AVRG SPC	Weighted AVRG FREE
Dezii CM.15 2000	68.7	1644	57.8	624		365 days	112942.80	36067.20
Bristol-Myers Squibb Company	70	969	57.7	705	3942	366 days	67830.00	40678.50
Brixner et al.16 2008								
Novartis Pharmaceuticals	54	8150	19	561	8711	365 days	440100.00	10659.00
Zeng et al. 2010, Novartis	40	2213	30	2312	4525	365 days	88520.00	69360.00
Baggarly et al. 2014 Takeda								
	11	383	15	148	4544	365 days	4213.00	2220.00
Machnicki et al. 2015 Novartis	46.8	1884	23.6	1884	3768	365 days	88171.20	44462.40
							52.60	**32.64**

JNC- 7


Proportion Controlled Over 10 Years
JNC - 7
Percentage of Patient Controlled
100%
80%
60%
40%
20%
0%
0
100
200
300
400
500
Time (weeks)
Mono
Combi


Time To First-Control BP
JNC-7
Percentage of Controlled Patients
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
Time (weeks)
Monotherapy
Combi Meds

Primary Outcomes

Observed Parameter	Initial mono	Single pill FDC
Analysis	BP goal < 140/90 mmHg	
% of controlled patients at 10 years	51.8 %	61.7 %
COST-EFFECTIVENESS		
Medication cost (US dollars)	$ 1,781	$ 3,376
Office visit cost (US dollars)	$ 5,020	$ 4,877
Total cost (US dollars)	$ 6,802	$ 8,254
Incremental Cost Per Patient Controlled*		**$ 14,773**

Conclusions

- **More people achieved BP control with initial single pill FDC compared with initial monotherapy**
- **Patients on SPC had fewer office visits and achieved a faster BP-control at 1 year**
  - 12% more controlled patients (JNC-7)
  - 6% more controlled patients (2017 AHA/ACC)
- **Total costs were higher for SPC patients**
  - $1,400 more for SPC (JNC-7)
  - $2,170 more for SPC (2017 AHA/ACC)
- **However, SPC patients "saved up" on office visit cost because they got controlled in a shorter time-frame**
- **SPC can be made more cost-effective by controlling drug price**

Cost: Global Analysis – ARB + CCB FDC (Quintiles IMS)

	2013		2014	
	Medicine units (pills) sold (in Millions)	Average Median price per pill (Euro)	Medicine units (pills) sold (in Millions)	Average price per pill (Euro)
Australia	1,245,306	0.12	1,557,842	0.11
Brazil	4,214,477	0.16	4,570,294	0.15
China	6,413,435	0.06	9,577,657	0.06
France	3,730,504	0.26	3,844,684	0.27
Germany	2,339,436	0.52	2,484,979	0.51
India	61,204,872	0.01	69,116,835	0.01
Italy	1,820,286	0.19	2,311,639	0.17
Mexico	908,476	0.29	1,029,660	0.31
Turkey	2,853,299	0.04	3,244,745	0.04
UK	77,594	0.26	79,040	0.26
USA	4,540,755	1.50	4,169,954	1.73
Median of average price per pill		0.19		0.17

Salam A, Kanukula R, Esam H, et al. An application to include blood pressure lowering drug fixed dose combinations to the model essential medicines list for the treatment of essential hypertension in adults.

Cost of FDC Is Similar to or Lower than Cost of Monotherapy with Constituent Pills (India)

	Median (range) unit price per pill (2018, Euros)
Fixed dose combination	
Lisinopril 5 mg + Hydrochlorothiazide 12.5 mg	**0.060** (0.013 – 0.087)
Constituent monotherapy pills	
Lisinopril 5 mg	0.045 (0.031-0.130)
Hydrochlorothiazide 12.5 mg	0.013 (0.008-0.026)
Sum of median prices of two monotherapy pills	**0.059**
Fixed dose combination	
Telmisartan 40mg + Amlodipine 5 mg	**0.090** (0.004-0.120)
Constituent monotherapy pills	
Telmisartan 40mg	0.079 (0.038-0.100)
Amlodipine 5 mg	0.026 (0.013-0.053)
Sum of median prices of two monotherapy pills	**0.11**
Fixed dose combination	
Telmisartan 40 mg + Hydrochlorothiazide 12.5 mg	**0.09** (0.004-0.190)
Constituent monotherapy pills	
Telmisartan 40 mg	0.088 (0.038-0.100)
Hydrochlorothiazide 12.5 mg	0.013 (0.008-0.026)
Sum of median prices of two monotherapy pills	**0.093**
Note: A full listing of retail and procurement prices is provided (Exhibit A) and manufacturers (Exhibit B) for one country (India)	

Salam A, Kanukula R, Esam H, et al. An application to include blood pressure lowering drug fixed dose combinations to the model essential medicines list for the treatment of essential hypertension in adults.

Acknowledgments

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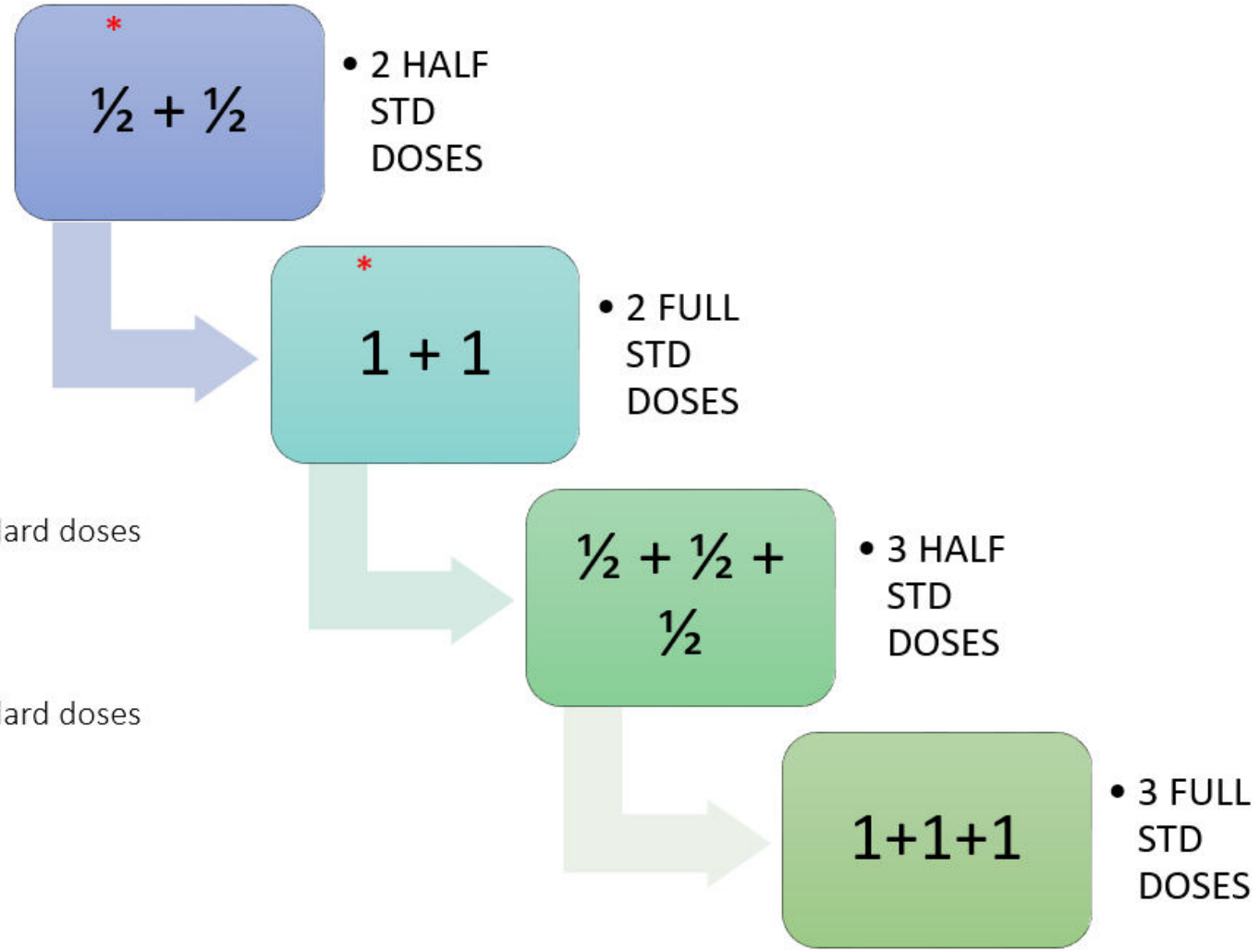
Clinical trial evidence about SPC

- Efficacy of drugs in combination is additive *(Law et al. 2003)*
- Prevalence of adverse drug reactions (ADR) is less than additive *(Law et al. 2003)*
- Mono, FEC or SPC?
  "Single-pill combinations were 53% and on free combination 34% more likely than those started on monotherapy to attain BP control in the first year" *(Egan et al. 2012)*
- "The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug" *(Wald et al. 2009)*

Combi meds regimen graphical representation



Group 1:
start at 2 half standard doses
(8 titration steps).

Group 2:
start at 3 half standard doses
(6 titration steps)

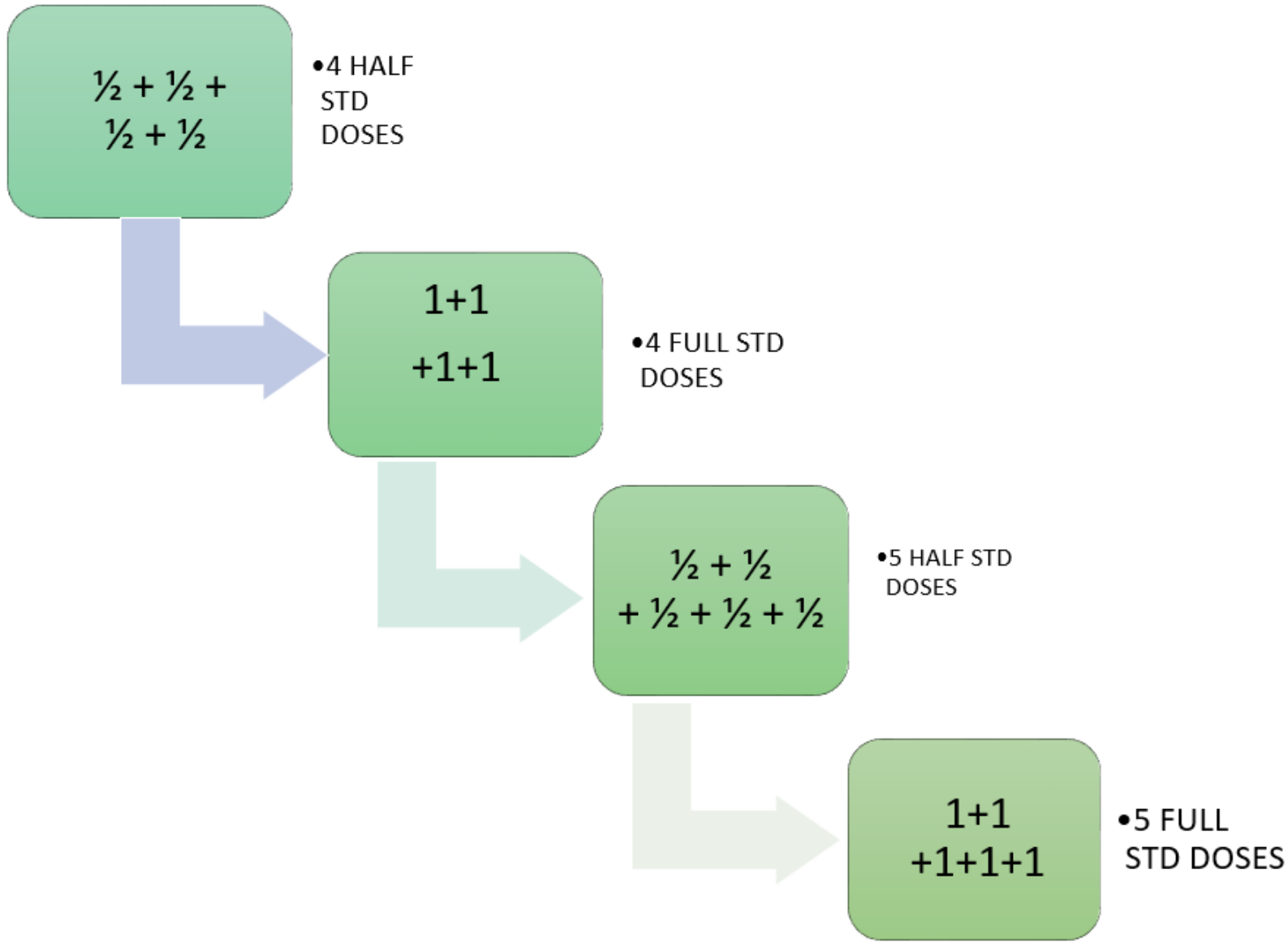
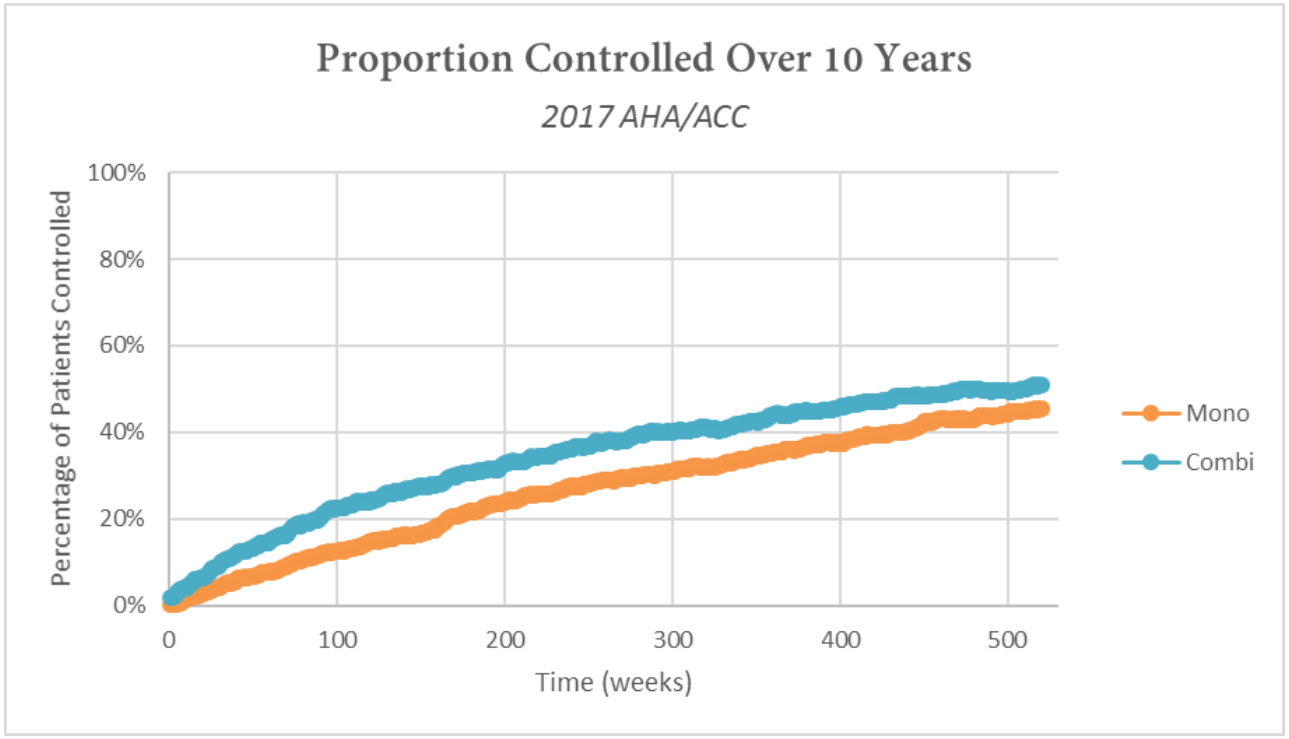

½ + ½ +
½ + ½
•4 HALF STD DOSES
1+1
+1+1
•4 FULL STD DOSES
½ + ½
+ ½ + ½ + ½
•5 HALF STD DOSES
1+1
+1+1+1
•5 FULL STD DOSES

Table of Inputs

BP Control Model Parameter	Base-Case Value	SD	Min	Max	Distribution	Data Sources
Time Horizon	10 years	-	-	-	-	Assumed
BP Control Definition - Goals						2003; 2014 Joint National Commission or ACC/AHA 2017
Population Characteristics						
Group 1 (mild HT) - Baseline SBP mmHg mean	130-149		130	149	Normal	U.S. NHANES adults with uncontrolled HT
Group 1 (mild HT) - Baseline DBP mmHg mean	80-95		80	95	Normal	U.S. NHANES adults with uncontrolled HT
Group 2 (moderate HT) - Baseline SBP mmHg mean	150-159		>150	-	Normal	U.S. NHANES adults with uncontrolled HT
Group 2 (moderate HT) - Baseline SBP mmHg mean	95-100		>95	-	Normal	U.S. NHANES adults with uncontrolled HT

BP Control Model Parameter	Base-Case Value	SD	Min	Max	Distribution	Data Sources
Office Visit Frequency (~ weeks)	4	-	-	-		From Fontil et al. J Gen Intern Med. 2015
SBP Measurement Visit-To-Visit Variability	10.5	4.5	1.68	19.32	Normal	Derived from Kronish et al. and US-based ALLHAT trial
DBP Measurement Visit-To-Visit Variability	6.2	2.6	1.104	11.296	Normal	Derived from Kronish et al. and US-based ALLHAT trial
Probability of Discontinuing over the first year	0.430	SD = range (based on poor and good correct dose taking)/4	0.34	0.535	Normal	Derived from literature review and pooled weighted estimates of discontinuation rates at one year by class. The classes were then weighted by use in the NHANES 2013-2014 exam.
Treatment Intensification Probability (when BP is poorly controlled)	0.332	0.0775	0.130	0.440	-	Pooled estimate from 4 US studies of treatment intensification

2017 AHA/ACC


Proportion Controlled Over 10 Years
2017 AHA/ACC
Percentage of Patients Controlled
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80%
60%
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0
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200
300
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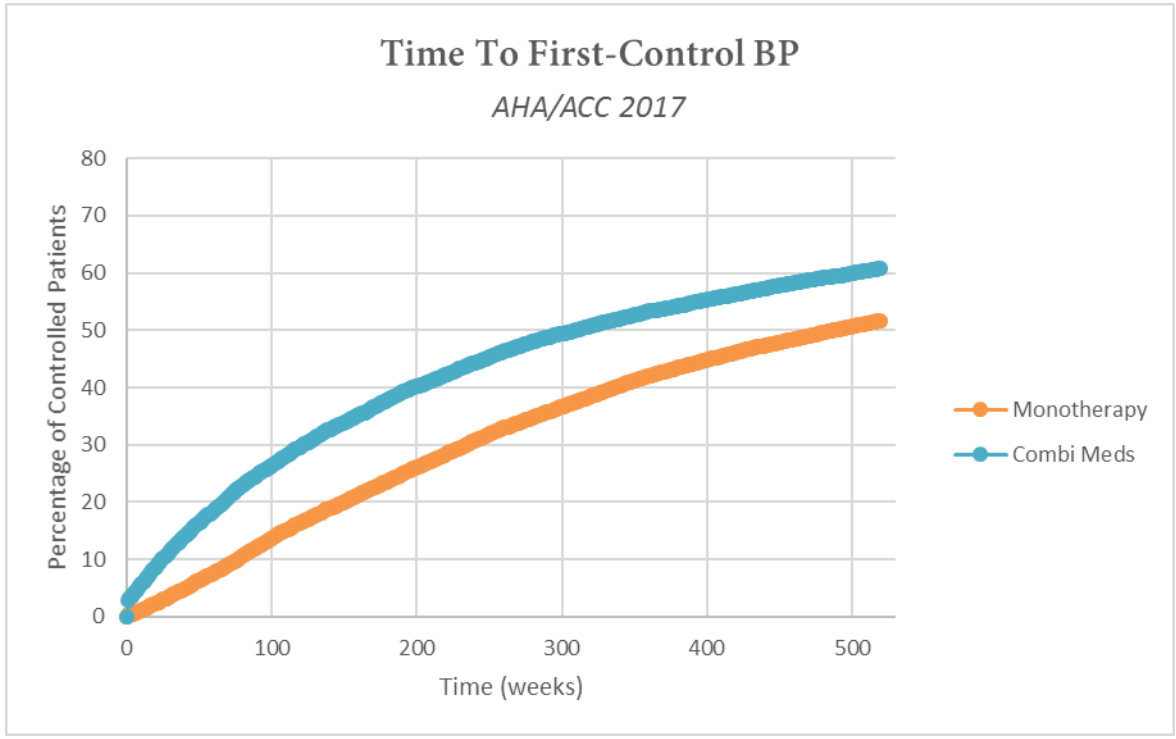
Time (weeks)
Mono
Combi


Time To First-Control BP
AHA/ACC 2017
Percentage of Controlled Patients
80
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Time (weeks)
Monotherapy
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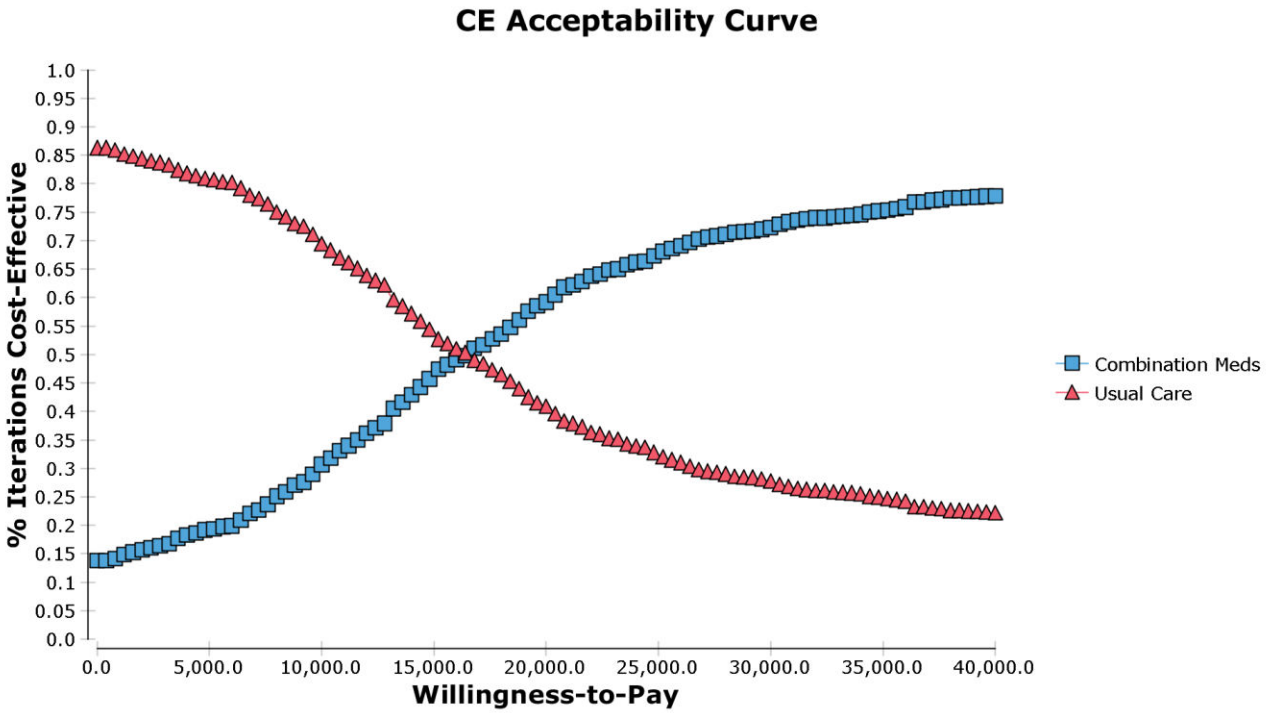
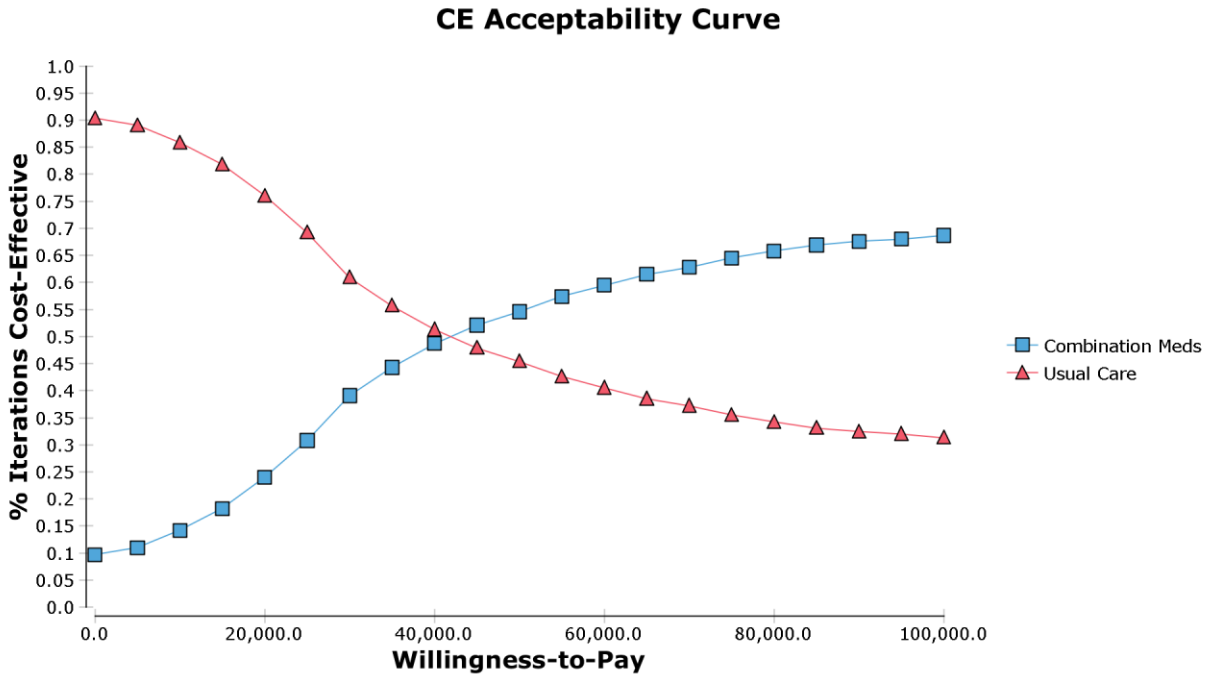
Probabilistic Sensitivity Analysis (PSA)

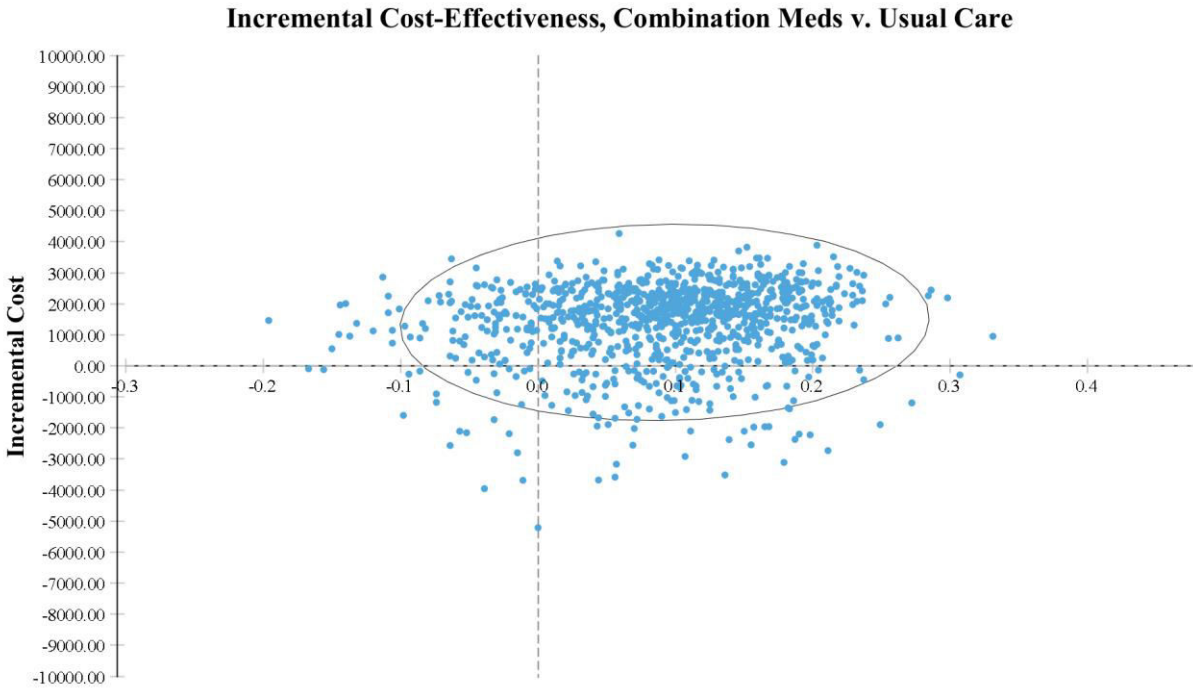


JNC-7

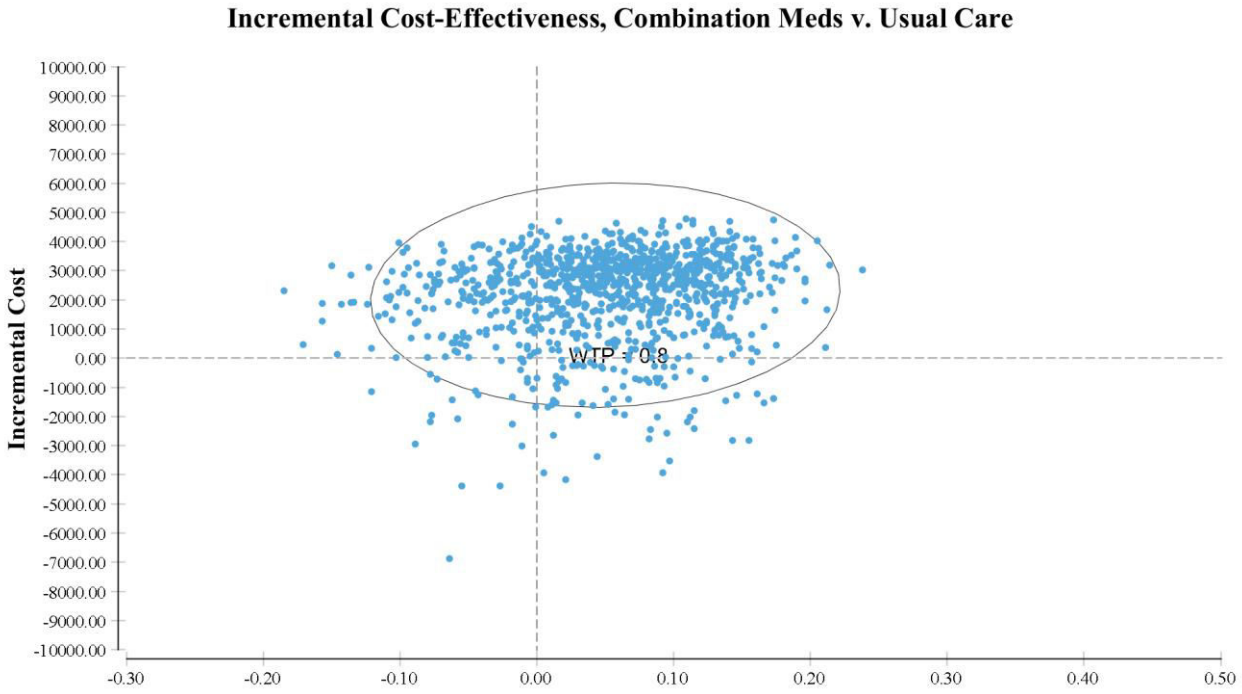


2017 AHA/ACC

Incremental CE: Combi vs Usual care



JNC-7



2017 AHA/ACC

Limitations of this study

- Individuals can only discontinue during the first year on treatment, after that everybody is supposed to be 100% persistent
- Model assumes if a patient discontinues at any point, their medication cost will be accounted for the whole month they are in
- No variable accounting for lifestyle modifications
- No regression to mean
- Not accounting for ADR resulting from the use of SPC
- Lack of CVD outcomes

Lifestyle Modifications BP-Related Changes

Lifestyle Modification	BP reduction (mmHg)
Weight Loss	5
Healthy Diet	11
Reduced NA Intake	5.5
Enhanced K intake	4.5
Physical Activity	5.166
Alcohol decrease	4
Average Reduction	5.86111

Source: 2017 Guidelines HTN AHA/ACC

Extra slides

What we know so far:

- **From SPRINT trial CEA by Bress et al. 2017, a patient treated with the intensive vs standard BP control would gain 0.27 QALYs**

Note:
(CE)ICER = Δc/Δh < k

So we made:

- **10 different assumptions of QALYs gained (using SPC)**

JNC-7: Cost-per-Patient Controlled = $14,774, AHA/ACC: Cost-per-Patient Controlled= $35,591

		Assumed QALYs Gained per Patient Controlled										
		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
ICER ($/QALY)	JNC-7	Dominated	147,738	73,869	49,246	36,934	29,548	24,623	21,105	18,467	16,415	14,774
	ACC/AHA	Dominated	355,910	177,955	118,637	88,978	71,182	59,318	50,844	44,489	39,546	35,591

Incremental Cost-per-QALY for combination therapy versus monotherapy in hypertensive patients, assuming different values of QALYs gained per patient controlled; assumes no difference in future health care costs between patients

Extra slides - Medication costs

MEDICATIONS TAKEN INTO CONSIDERATION (i.e. the most prescribed ones in terms of frequency)

MONOTHERAPY		NADAC cost	Daily Freq.	AHA half-dose	AHA full-dose	Monthly Cost
ACE	Lisinopril	10mg=$0.02	1	5	10	$ 0.60
	Enalapril (Maleate)	5mg=$0.21	1	2.5	5	$ 6.30
	Benazepril (HCl)	10mg=$0.05	1	5	10	$ 1.50
ARBs	Losartan (Potassium)	50mg=$0.03	1	25	50	$ 0.90
	Valsartan	80mg=$0.07	1	40	80	$ 2.10
THZ	Chlorthalidone	25mg=$0.73	1	6.25	12.5	$ 10.95
	Hydrochlorothiazide	25mg=$0.01	1	12.5	25	$ 0.30
CCB	Amlodipine (Besylate)	2.5mg=$0.02	1	1.25	2.5	$ 0.60
	Nifedipine	10mg=$0.6	1	15	30	$ 18.00
	Diltiazem SR	90mg=$2.92	2	90	180	$ 350.40
BB	Metoprolol Tartrate	100mg=$0.03	2	50	100	$ 1.80
	Atenolol	25mg=$0.04	1	12.5	25	$ 1.20
	Carvedilol	12.5=$0.03	2	6.25	12.5	$ 1.80
α-AGO	Clonidine (HCl)	0.1mg=$0.02	2	0.05	0.1	$ 1.20
α-ANTA	Doxazosin (Mesylate)	1mg=$0.24	1	0.5	1	$ 7.20
	Terazosin	1mg=$0.13	1	0.5	1	$ 3.90
Vasodil.	Hydralazine	100mg=$0.10	2	100	200	$ 6.00
					AVERAGE	$ 24.40
					AVRG	$ 4.02
					(NO DLTZEM)	

	SPC 2 AGENTS	NADAC cost	AHA full-dose (mg)	AHA half-dose (mg)	Daily Freq	Monthly Cost
ACE+THZ	LSNPR-HYDCLTHZ	$ 0.03	10/12.5	5/6.25	1	$ 0.90
	CAPTOPRIL-HYDRCLTHZ	50/25mg=$1.59	25/15	12.5/7.5	2	$ 48.00
ARB+THZ	LOSARTAN-HYDCLTHZ	$ 0.07	50/12.5	25/6.25	1	$ 2.10
BB+THZ	ATENOLOL-CHLORTHALIDONE	$ 0.42	50/25	25/12.5	1	$ 12.60
	BISOPROLOL-HYDCLTHZ	$ 0.07	2.5/6.25	1.25/3.125	1	$ 2.10
CCB(DHP)+ACEi	AMLODIPINE-BENZPRIL	$ 0.22	2.5/10	1.25/5	1	$ 6.60
CCB(DHP)+ARB	AMLODIP-OLMESART.	$ 0.63	5 20	2.5/10	1	$ 18.90

	SPC 3 AGENTS	NADAC cost	Daily Freq.	AHA half-dose (mg)	AHA full-c	Monthly Cost	Half-dose Monthly Cost
CCB	Amlodipine 10mg	$1.25	1	5	10	$ 37.50	$ 18.75
ARBs	Valsartan 160mg			80	160		
THZ	Hydrochlorothiazide 25mg			12.5	25		
ARBs	Olmesartan 40mg	$2.31	1	20	40	$ 69.30	$ 34.65
CCB	Amlodipine 5mg			2.5	5		
THZ	Hydrochorothiazide 12.5mg			6.25	12.5		

Extra slides - Medication costs

	MONO 1					MONO 2		
Tot. steps	Standard dose		Cost x Step		Tot. steps	Standard dose		Cost x Step
1	1/2		$ 1.27		1	1		$ 1.91
2	1		$ 1.91		2	2		$ 3.20
3	1 1/2		$ 2.56		3	3		$ 4.49
4	2		$ 3.20		4	3 1/2		$ 5.14
5	2 1/2		$ 3.85		5	4		$ 5.78
6	3		$ 4.49		6	4 1/2		$ 6.43
7	3 1/2		$ 5.14		7	5		$ 7.07
8	4		$ 5.78		8			
9	4 1/2		$ 6.43					
10	5		$ 7.07					
11								
	COMBI 1					COMBI 2		
Tot. steps	Standard dose		Cost x Step		Tot. steps	Standard dose		Cost x Step
1	2 x 1/2		$ 1.94		1	3x 1/2		$ 4.20
2	2 full		$ 3.88		2	3 full		$ 13.98
3	3x 1/2		$ 4.20		3	4x 1/2		$ 14.29
4	3 full		$ 13.98		4	4 full		$ 14.45
5	4x 1/2		$ 14.29		5	5 x 1/2		$ 14.61
6	4 full		$ 14.45		6	5 full		$ 14.78
7	5 x 1/2		$ 14.61		7			
8	5 full		$ 14.78					
9								