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A:CARE CONGRESS

Acting on the unseen: How do we help patients to remain adherent when they are asymptomatic?

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ACTING ON THE UNSEEN: HOW DO WE HELP PATIENTS TO REMAIN ADHERENT WHEN THEY ARE ASYMPTOMATIC?

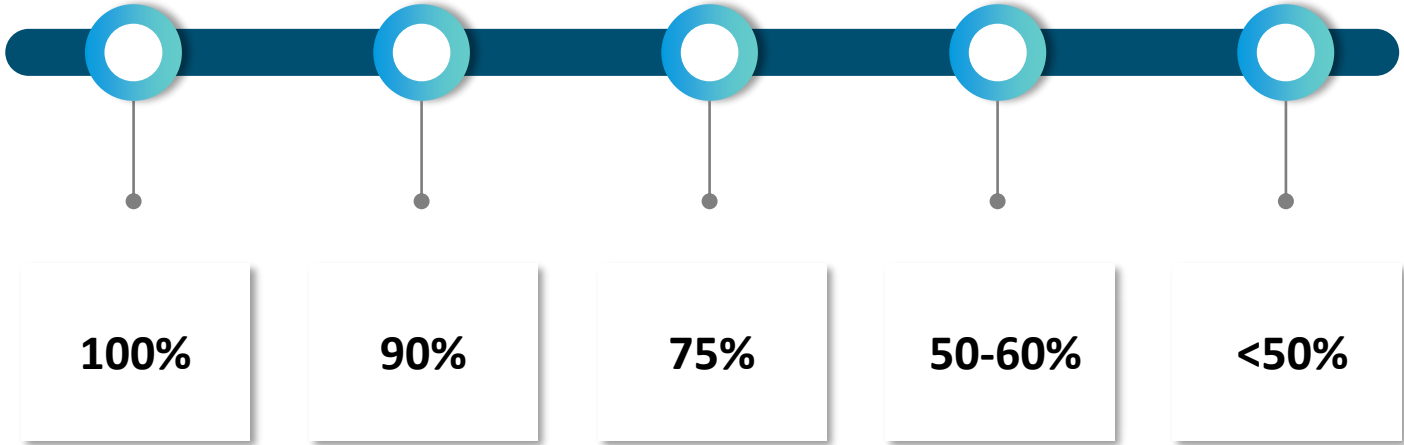
Is Doctor's prescribing the first step in setting the asymptomatic patient up for failure? – Lessons from management of hypertension

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University of Western Australia – Royal Perth Hospital
Perth, Australia

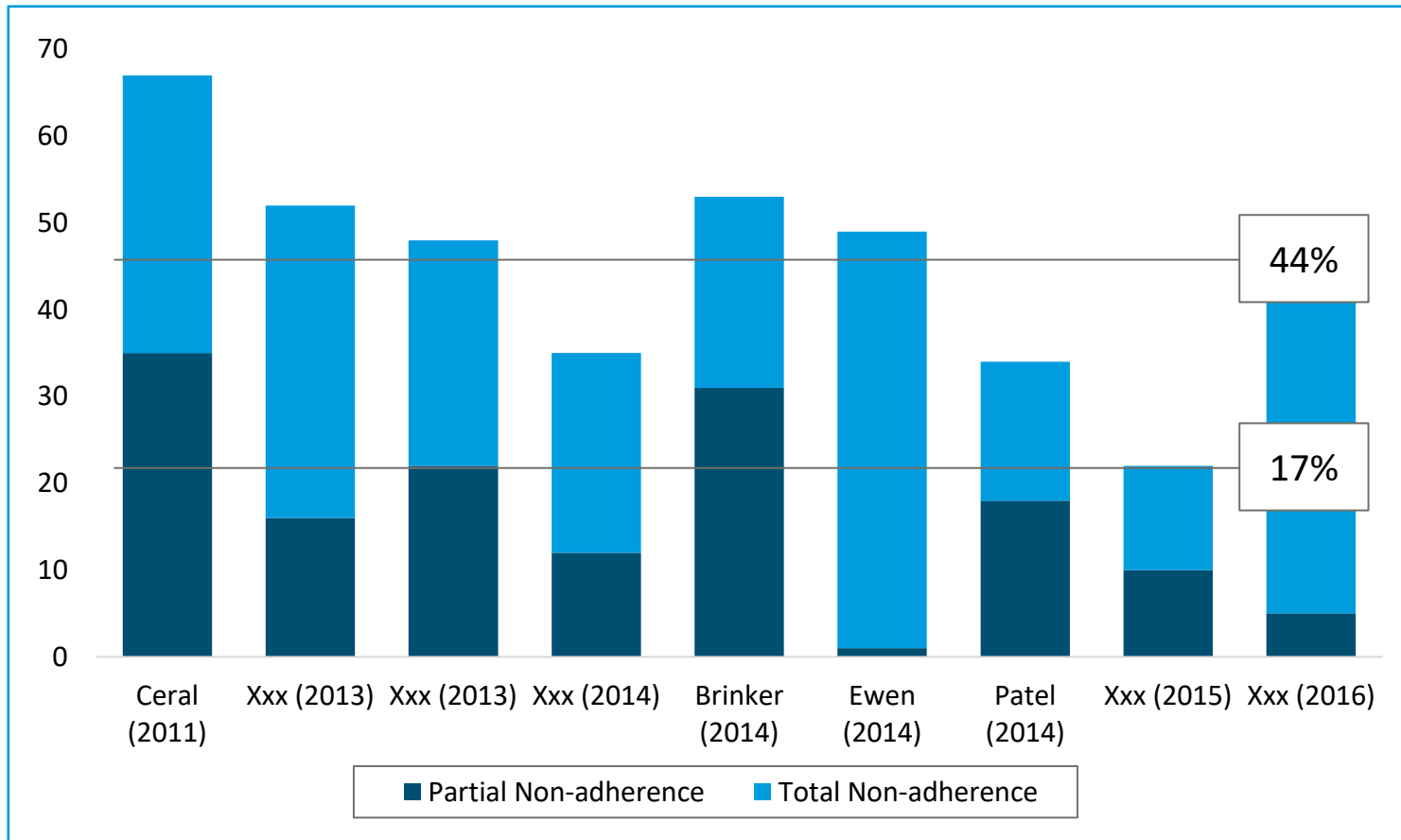
Adherence with prescribed medication in randomized controlled trials (RCTs):



What percentage of patients do you think are adherent with medication in RCTs?



Non-adherence with prescribed antihypertensive drug in clinical studies



30 to 50% non-adherence rate is consistent between clinical trials and medical practice

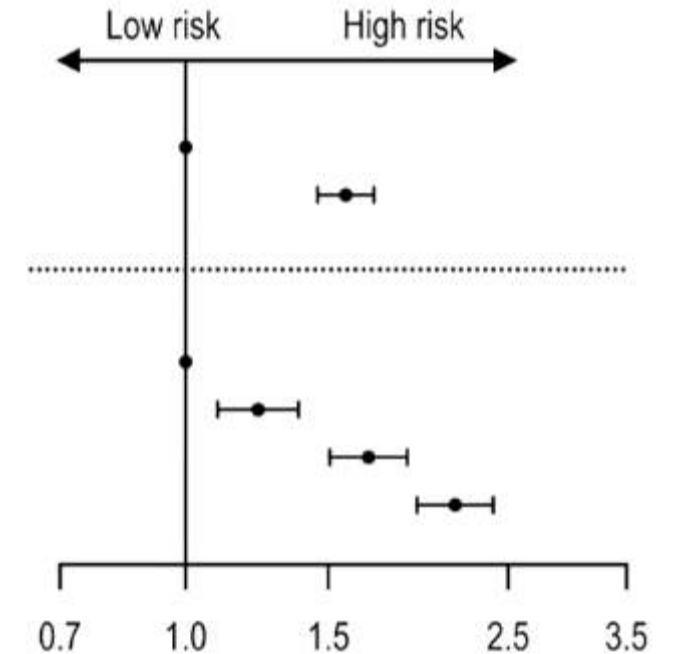
Poor and dynamic adherence introduces variability to trial endpoints

Not easily controlled, even with rigorous trial design

Berra E, Azizi M, Capron A, Høieggen A, Rabbia F, Kjeldsen SE, Staessen JA, Wallemacq P, Persu A. Evaluation of Adherence Should Become an Integral Part of Assessment of Patients With Apparently Treatment-Resistant Hypertension. *Hypertension*. 2016 Aug;68(2):297-306

Adherence to antihypertensive medication and incident CV events in young adults with hypertension

COMPOSITE CVD EVENTS				
Group	Events	Person-yrs	Rate ¹	HR (95% CI)
Adherence group				
Adherent	855	447,564	191.0	1.00 (reference)
Nonadherent	2,147	761,129	282.1	1.58 (1.45-1.71)
Proportion of days covered, quartile				
Q4, highest	522	300,596	173.7	1.00 (reference)
Q3	662	307,239	215.5	1.23 (1.10-1.38)
Q2	841	300,825	279.6	1.68 (1.51-1.88)
Q1, Lowest	977	300,034	325.6	2.15 (1.93-2.40)

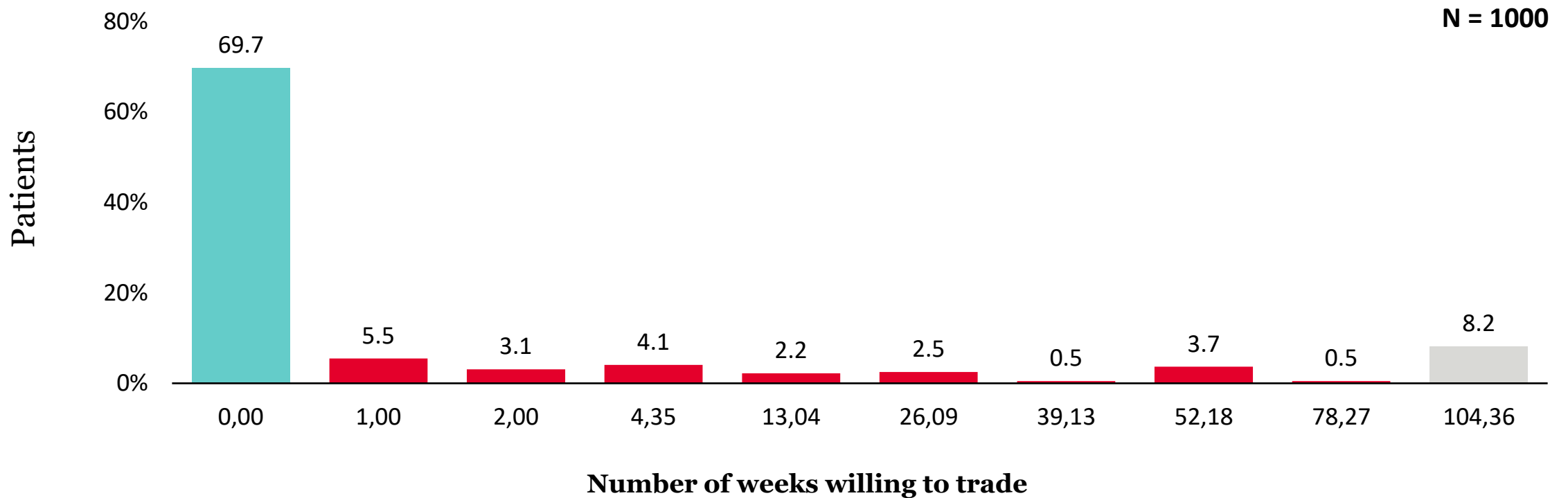


Cardiovascular disease (CVD) risk associated with nonadherence to antihypertensive medication

Lee H, Yano Y, Cho SMJ, Heo JE, Kim DW, Park S, Lloyd-Jones DM, Kim HC. Adherence to Antihypertensive Medication and Incident Cardiovascular Events in Young Adults With Hypertension. *Hypertension*. 2021 Apr;77(4):1341-1349

~30% of Adults Would Rather Die Early than **Take** Lifelong Polypharmacy

8.2% OF ADULTS WOULD GIVE UP 2 YEARS OF THEIR LIFE TO AVOID ADDING 1 DAILY PILL



Adherence is a Behavior ...

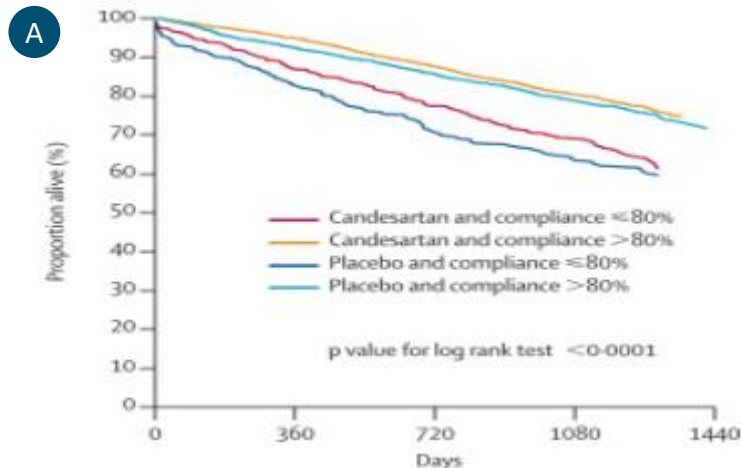
Adherence to Placebo is a good Behavior!



Good adherence was associated with lower all-cause mortality in all patients
HR 0.65, 95% CI 0.57–0.75)



The adjusted HR for good adherence was similar in the candesartan (0.66) and placebo (0.64) groups.



Numbers at risk

Candesartan and compliance ≤ 80	493	426	380	249
Candesartan and compliance > 80	3310	3137	2891	1967
Placebo and compliance ≤ 80%	435	359	306	209
Placebo and compliance > 80%	3361	3106	2864	1951

Granger BB, *et al.* Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM program: double-blind, randomized, controlled clinical trial. *Lancet.* 2005 Dec 10;366(9502):2005-11

Reasons for poor adherence to antihypertensive therapy – Patient perspective

PATIENT

- Lack of symptoms
- Lack of understanding of disease and of treatment need
- Fear of possible/experienced adverse effects
- Actual/perceived lack of treatment benefits
- Fear of stigma associated with disease
- Treatment interference with patient's daily schedule
- Outright refusal
- Regimen complexity, polypharmacy/high pill burden
- Forgetfulness
- Comorbidities, including depression
- Physical (e.g., visual, hearing) or cognitive impairments influencing ability of patient to take the treatment
- Sociodemographic factors (e.g., age, sex, education, employment, income, family support, health literacy)



Reasons for poor adherence to antihypertensive therapy – Practitioner and Health Care perspective

PRACTITIONER

- Physician inertia
- Inadequate prescription/Regimen complexity
- Lack of guideline knowledge/lack of training for hypertension treatment
- Communication skills
- Patient-provider relationship
- Time constraints

HEALTHCARE SYSTEM

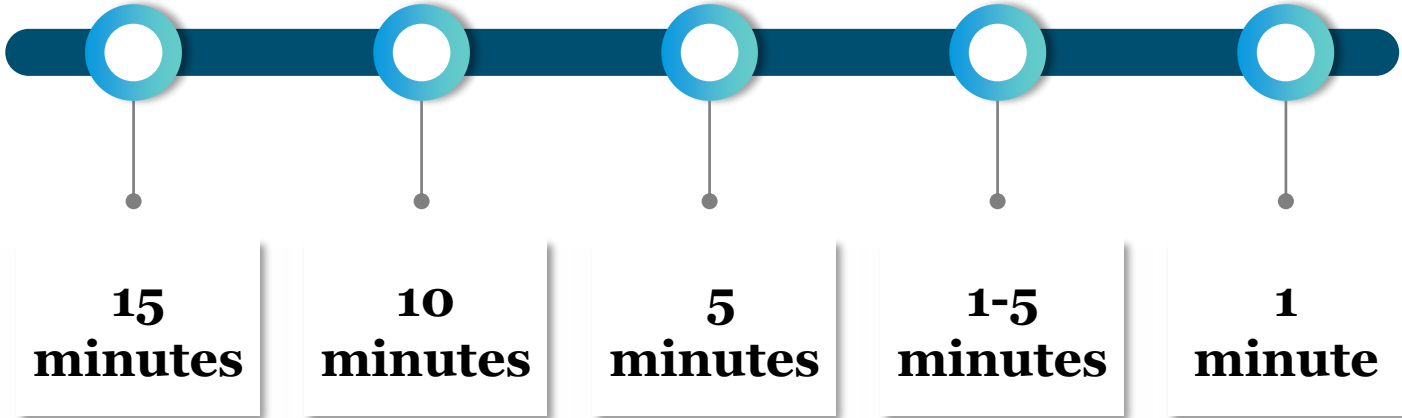
- Access to care
- Medication cost/affordability
- Guideline inertia/overcomplicated guidelines
- Barriers to the use of single-pill combinations (e.g., limited reimbursement)



Time spent discussing use of medication in hypertension centers:

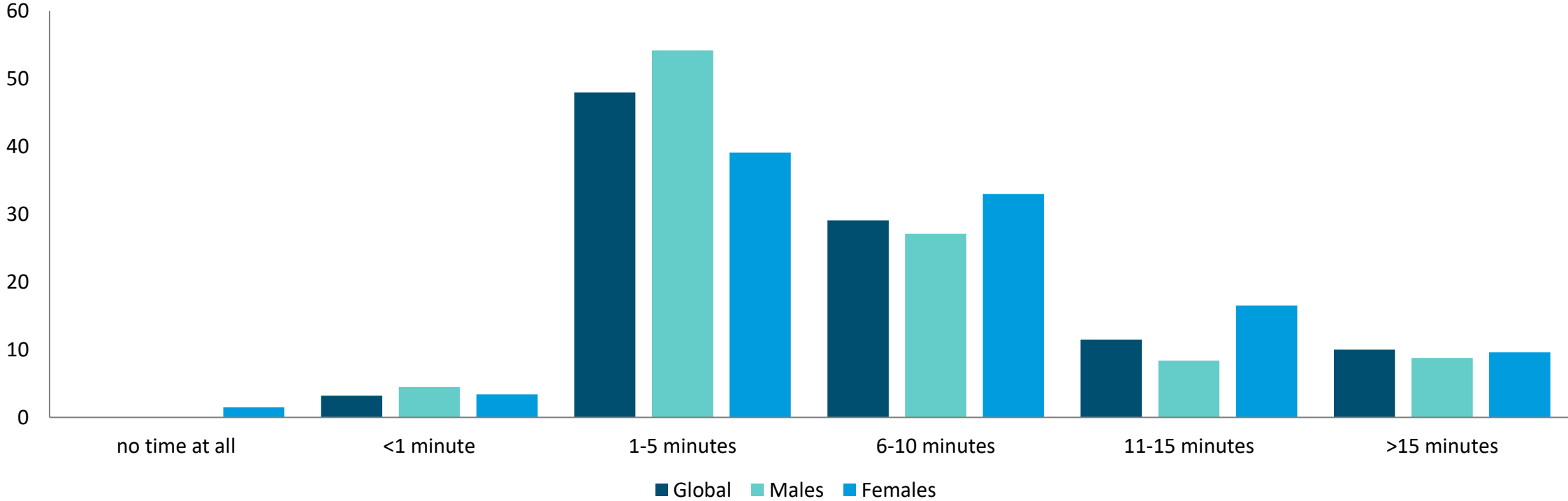


How much time do you think doctors in hypertension centers on average spend discussing use of medication with patients?



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Time spent by physicians talking with patients about their use of medications - a survey of ESH Centers of Excellence



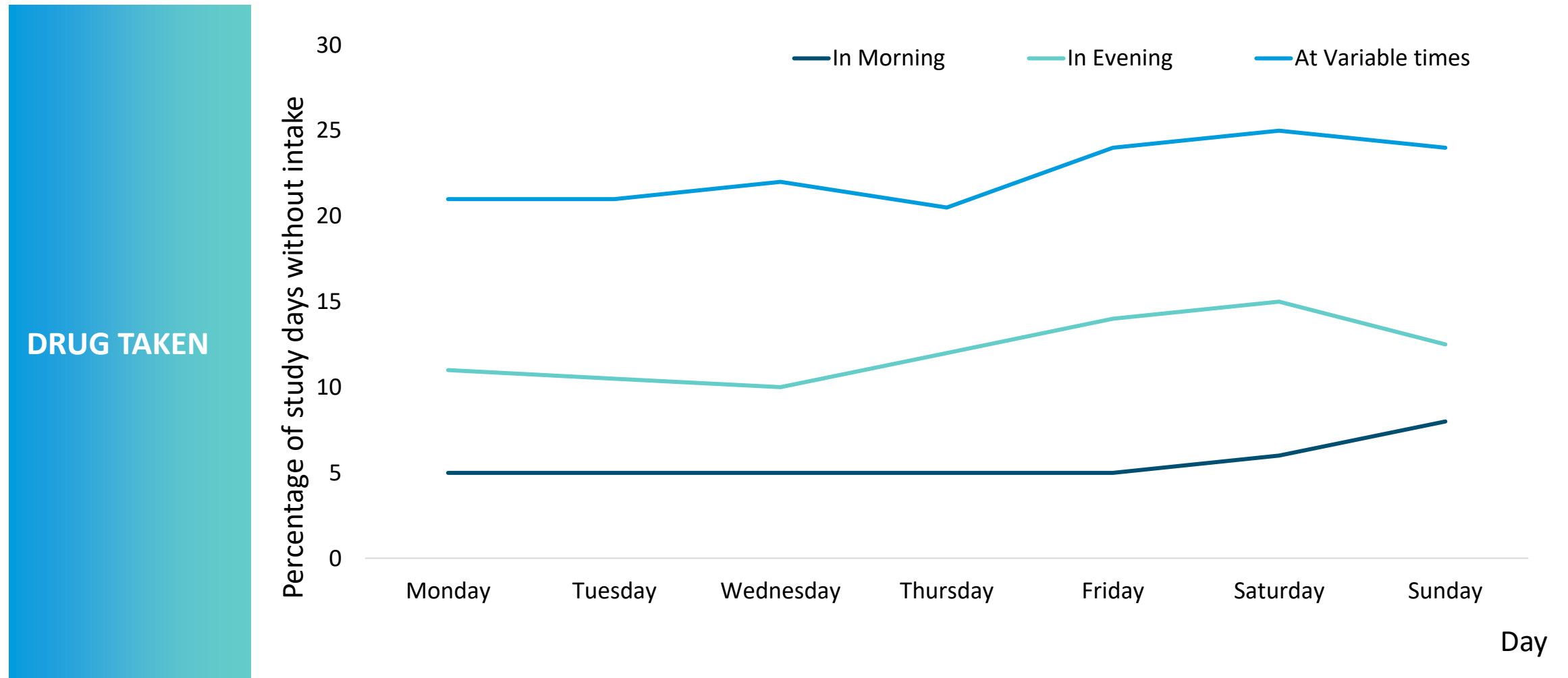
Burnier M, Prejbisz A, Weber T, et al. Hypertension healthcare professional beliefs and behaviour regarding patient medication adherence: a survey conducted among European Society of Hypertension Centres of Excellence. *Blood Pressure*. 2021 Oct;30(5):282-290.

Interventions to improve adherence

- Assess each patient's needs and offer individualized solutions
- Make pill-taking easier for the patient
- Improve patient-practitioner communication in a blame-free environment
- Educate patients
- Offer motivational interviewing
- Involve patient in decision-making/empower the patient
- Implement guideline recommendations
- Use single-pill combinations
- Establish a collaborative team-based care approach, including nurses and pharmacists
- Use reminders (memory cues, blister packaging, pill counters, MEMS)
- Use e-Health technology as a supportive tool

MEMS, medication event monitoring systems.

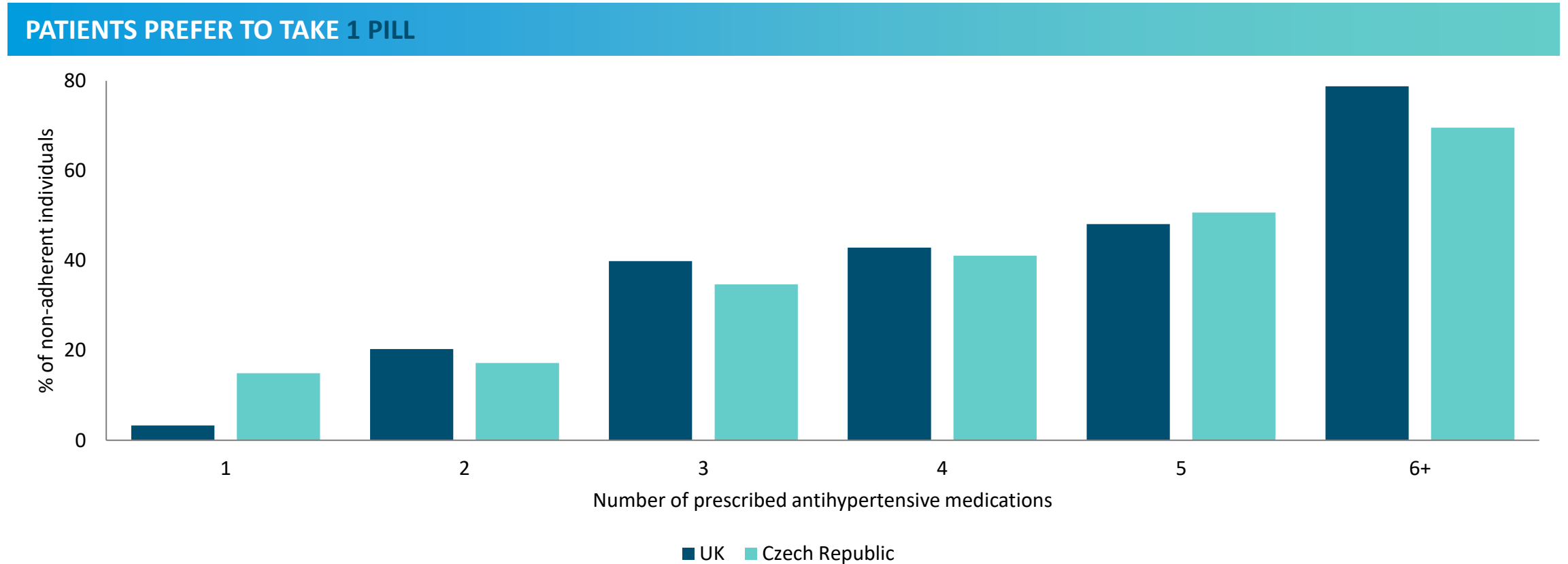
Relevance of timing of antihypertensive therapy



Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ*. 2008 May 17;336(7653):1114-7.

Patients prefer to take less pills

Non-adherence to antihypertensive medicines in the real world- according to number of medicines





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ACTING ON THE UNSEEN: HOW DO WE HELP PATIENTS TO REMAIN ADHERENT
WHEN THEY ARE ASYMPTOMATIC?

Monitoring adherence in chronic cardiovascular disease

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Disclosures

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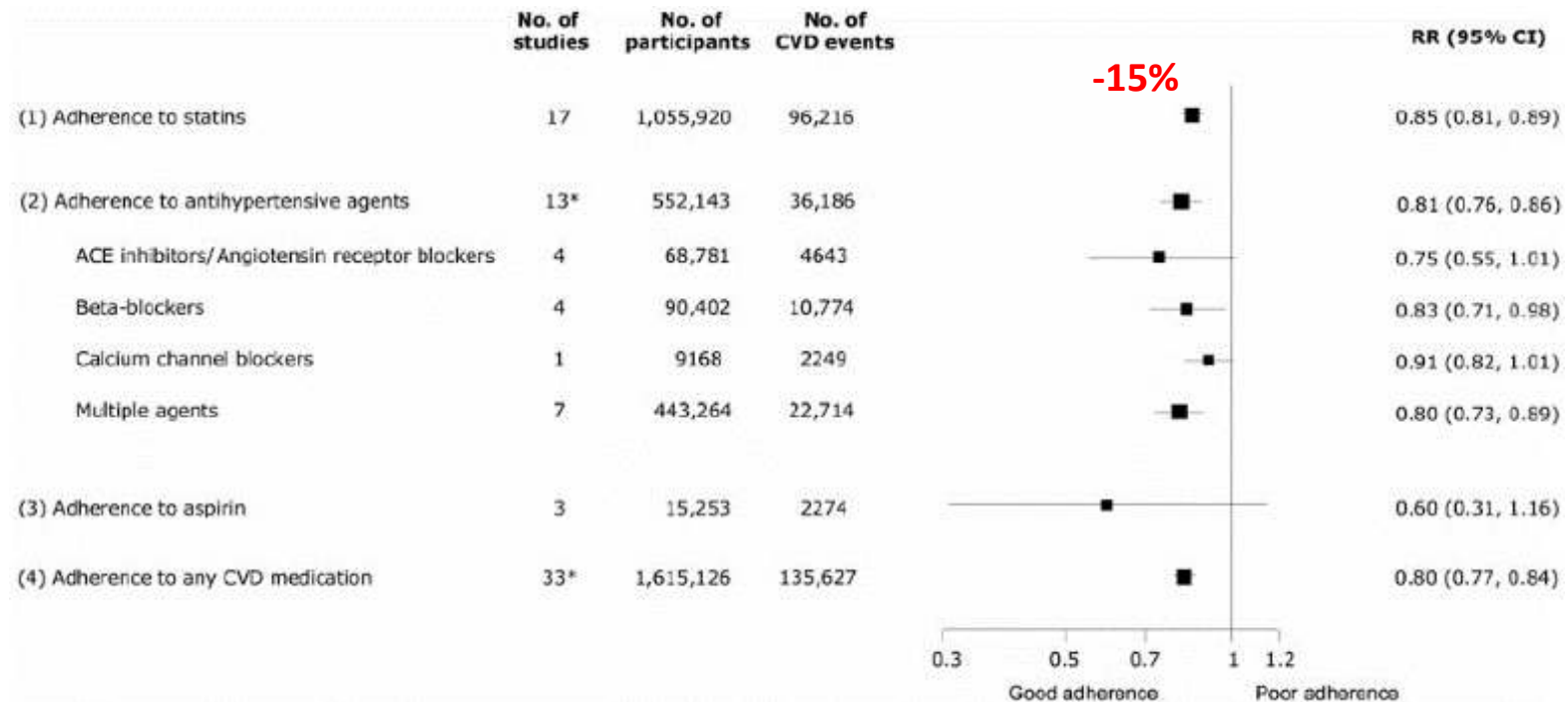
Recordati

Sanofi

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Relative risks for any cardiovascular disease in good vs. poor (<80%) adherence

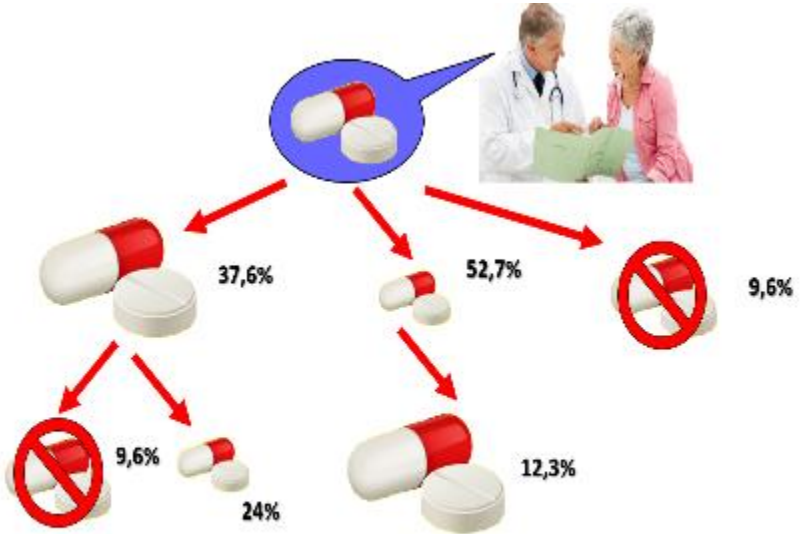
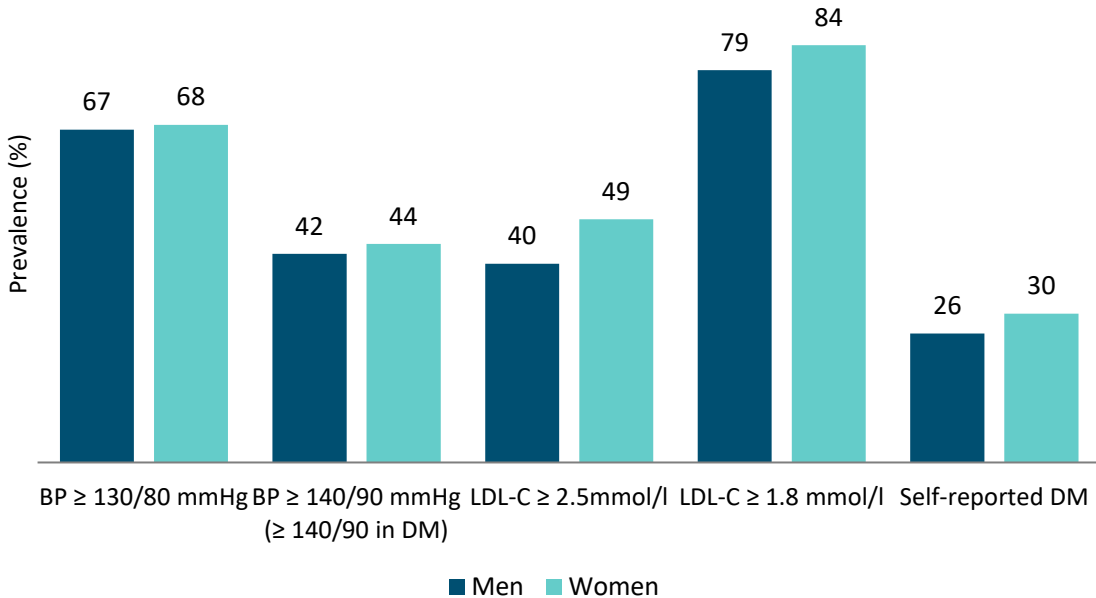
META-ANALYSIS OF 44 STUDIES, N= 1 978 919; 135 627 CVD EVENTS; 94 126 CASES OF ALL-CAUSE MORTALITY



Achieving treatment targets in patients with coronary artery disease






ATTAINING TARGETS IN CAD PATIENTS FROM 24 EUROPEAN COUNTRIES¹ EA IV

EUROASPIRE IV STATIN THERAPY AT DISCHARGE: INSTEAD OF ESCALATING RX TO GET TO GOAL, DE-ESCALATE AT FU







1. 24 European countries: Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Ireland, Latvia, Lithuania, the Netherlands, Poland, Romania, Russia, Serbia, Slovenia, Spain, Sweden, Turkey, Ukraine and the UK. Note: Kotseva & Makedou, Kali. (2016). EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *European Journal of Preventive Cardiology*. 23. 636-648. 2. Ž. Reiner, G. De Backer, Z. Fras, K. Kotseva, L. Tokgözoğlu, D. Wood, D. De Bacquer. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries – Findings from the EUROASPIRE IV survey. *Atherosclerosis*, Volume 246, 2016, Pages 243-250, ISSN 0021-9150.

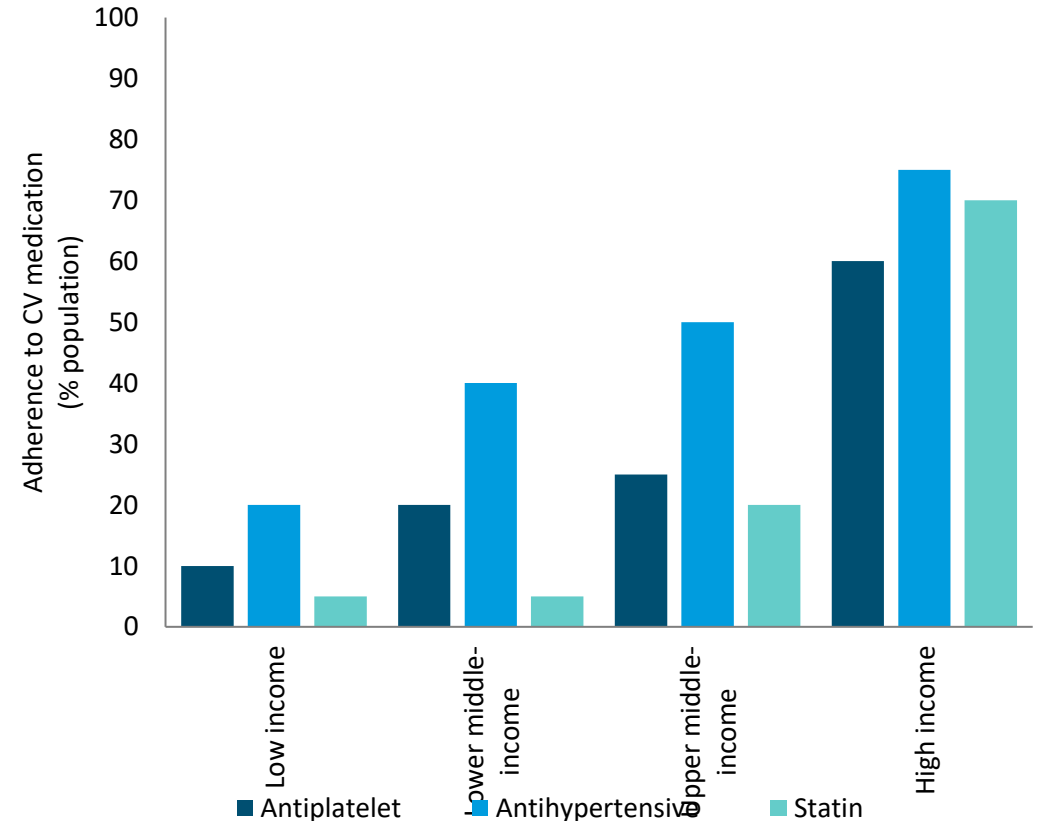
How to measure adherence ?

Method	Advantages	Disadvantages
 Self –report	<ul style="list-style-type: none"> • Simple • Low cost • May reveal reasons for non- adherence 	<ul style="list-style-type: none"> • Subject to recall bias • Poor-to-moderate correlation with objective measures
 Physiologic or laboratory markers	<ul style="list-style-type: none"> • Objective 	<ul style="list-style-type: none"> • Only pertain to most recent dosing • May reflect only pharmacodynamics/pharmacokinetics • Unavailable for all medications • Expensive
 Pharmacy refill	<ul style="list-style-type: none"> • Objective • Quantifiable • Unobtrusive • Inexpensive for large populations 	<ul style="list-style-type: none"> • Difficult to obtain outside a closed pharmacy system • No information of medications are being ingested • Over-the-counter and generic refills not always captured
 Pill count	<ul style="list-style-type: none"> • Objective • Quantifiable 	<ul style="list-style-type: none"> • Time-consuming • Data easily altered by patients (ie: pill-dumping) • No information on daily behavior
 Electronic medication monitor	<ul style="list-style-type: none"> • Objective • Quantifiable • Provides data on daily pattern of pill taking • Access data remotely 	<ul style="list-style-type: none"> • Cost • Requires adherence to pill monitoring technology • Generally, cannot confirm pills are ingested • Not readily integrated into clinical care pathways

Self-reported measures tend to overestimate medication adherence

-  Self-reported medication adherence measures vary in their question phrasing, recall periods, and response items.
-  Tend to overestimate adherence behavior compared with other assessment methods and generally have high specificity but low sensitivity.
-  Self-report adherence measures show moderate correspondence to other adherence measures and can predict clinical outcomes.
-  The quality of self-report adherence measures may be enhanced through efforts to use validated scales, assess the proper construct, improve estimation, facilitate recall, reduce social desirability bias, and employ technologic delivery

NON-ADHERENCE HIGHER IN LMIC: EXPENSIVE MEASURES NOT REALISTIC



Stirratt MJ, *et al.* Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med.* 2015 Dec;5(4):470-82. 2.Kolandaivelu K, Leiden BB, O'Gara PT, Bhatt DL. Non-adherence to cardiovascular medications. *Eur Heart J.* 2014 Dec 7;35(46):3267-76.

Medication Adherence Interventions for Cardiovascular Disease in Low- and Middle-Income Countries: A Systematic Review



Multi-component interventions were more effective than unifocal interventions.

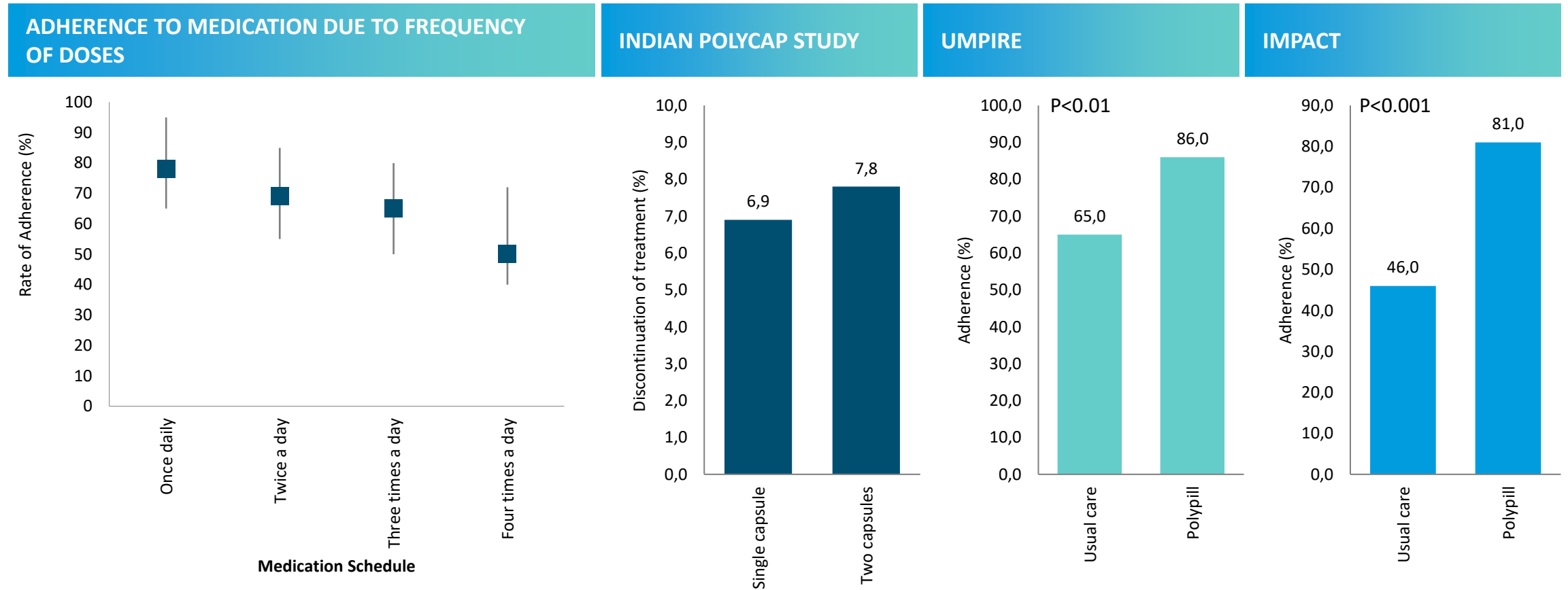


Interventions involving technology, such as mobile phone calls, electronic pillboxes, and interactive phone SMS reminders, were more effective than generic reminders.



When interventions were implemented at both the patient level, such as reminders, and at the provider level, such as **team-based care**, the effect on medication adherence was larger.

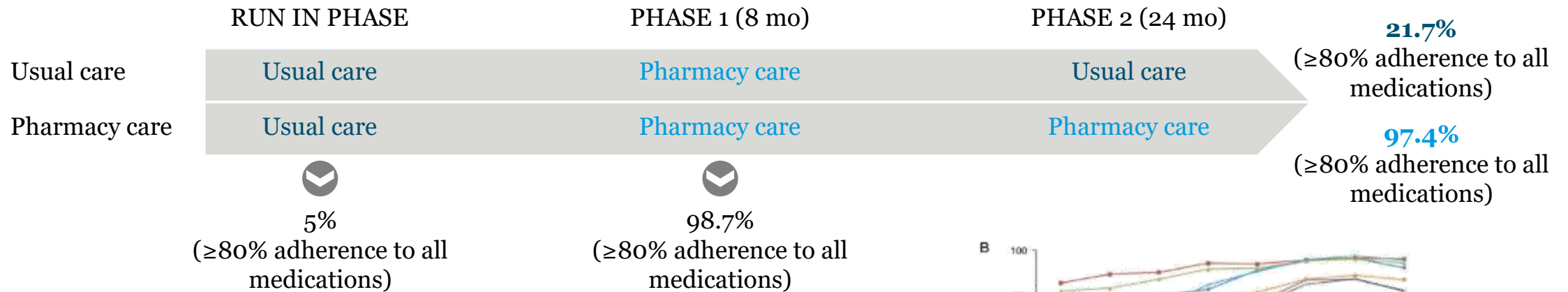
Polypill: Possible to track by biomarkers; increases adherence significantly-Solution for LMIC



Coca, Antonio & Agabiti-Rosei, Enrico & Manolis, Athanasios & Redón, Josep & Mancia, Giuseppe. (2017). The polypill in cardiovascular prevention: Evidence, limitations and perspective-position paper of the European Society of Hypertension. *Journal of Hypertension*. 35. 2. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005 Aug 4;353(5):487-97.

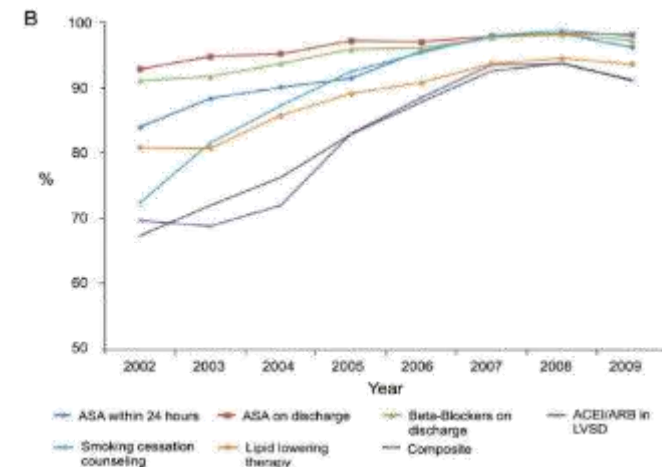
Pharmacy care improves adherence: In FAME, elderly patients with coronary risk factors were randomized to usual care vs. a multi-component program

FAME STUDY



Interventions:

- Individualized medication education (using standardized scripts)
- Medications dispensed using an adherence aid (blister packs)
- Regular follow-up with clinical pharmacists every 2 months

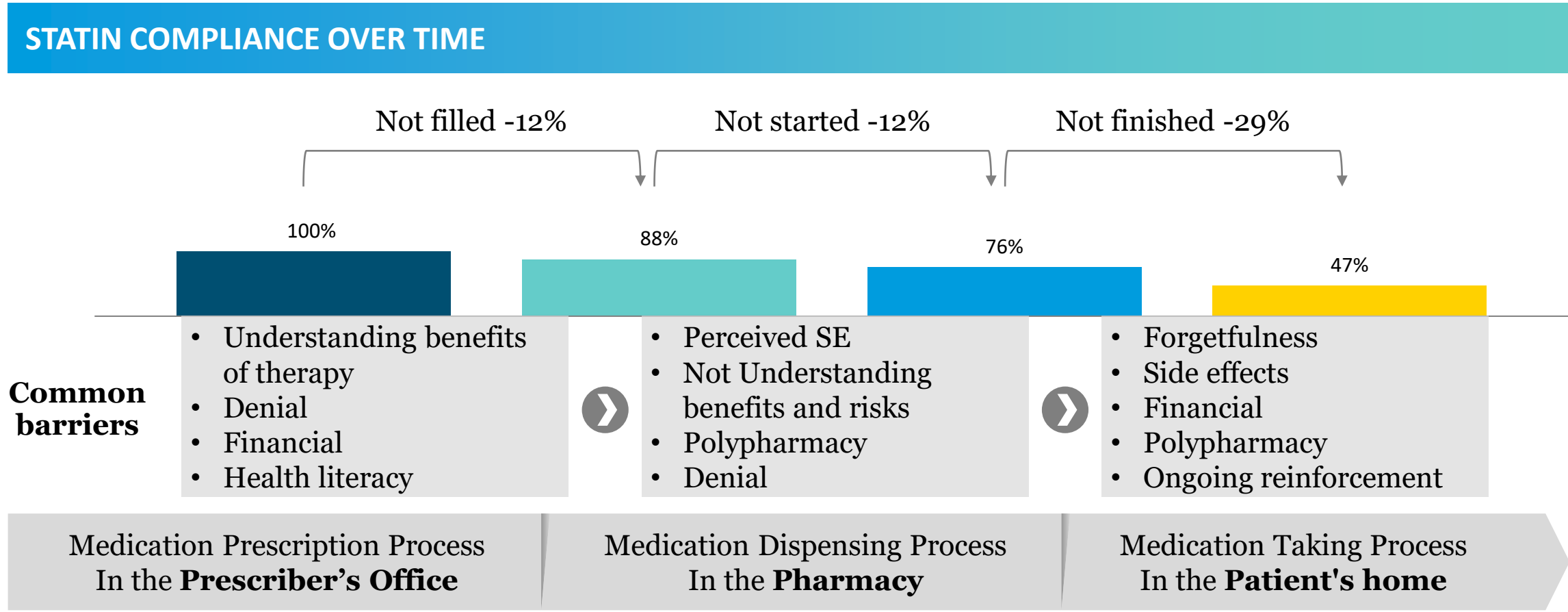


Patient engagement essential even for pharmacy care and for most other methods to work ! (1/2)

TECHNOLOGY BASED PROGRAMS INCREASE PATIENT ENGAGEMENT				
	Measurement	Intervention arm	Control arm	P-value
SMS and automated behavioral education response	≥80% PDC	62.8%	49.4%	<0.001
SMS, automated education response and optional interactive personalized message	≥80% PDC	60.0%	49.4%	0.002
Automated telephone call followed by education letter	Proportion of dispensed medication	42.3%	26.0%	<0.001
Automated text reminders	≥80% medication use	91.0%	75.0%	<0.001

1. Cohen, J.D., Aspary, K., Brown, A.S., Foody, J.A., Furman, R., Jacobson, T.A., Karalis, D.G., Kris-Etherton, P.M., Laforge, R., O'Toole, M.F., Scott, R.D., Underberg, J.A., Valuck, T., Willard, K., Ziajka, P.E., & Ito, M.K. (2013). Use of health information technology (HIT) to improve statin adherence and low-density lipoprotein cholesterol goal attainment in high-risk patients: proceedings from a workshop. *Journal of clinical lipidology*, 7 6, 573-609.
 2. Ismail, Sophia & Tsoli, Stergiani & Chowdhury, *Rajiv*. (2017). Therapy-related strategies to improve adherence to diabetic medications. *Medicographia*. 39. 289-297.

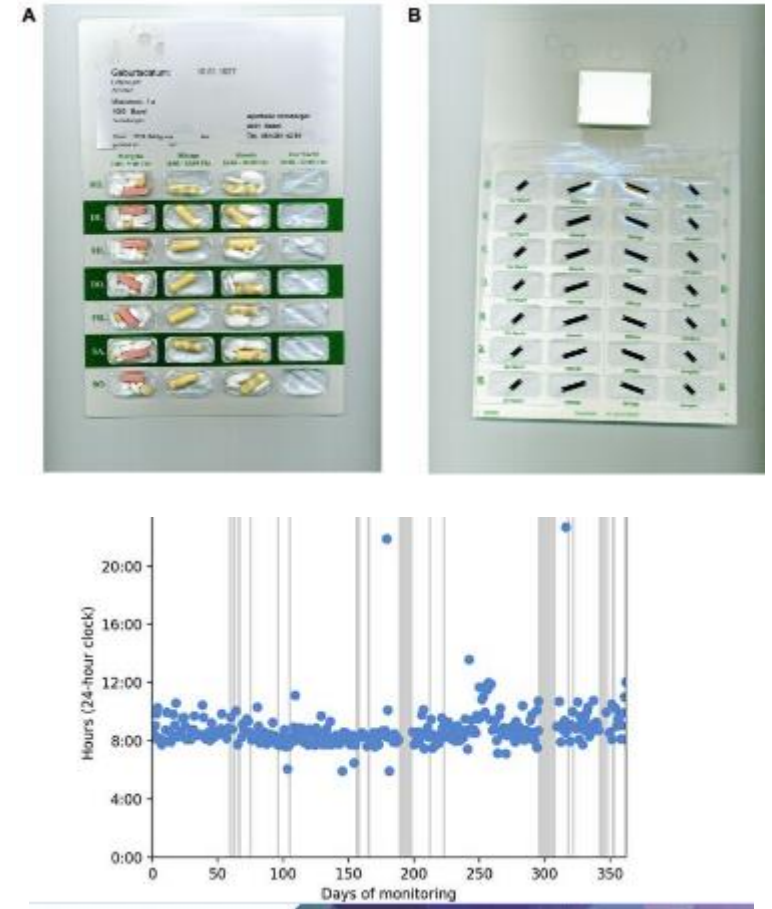
Patient engagement essential even for pharmacy care and for most other methods to work ! (2/2)



1. Cohen, J.D., Aspary, K., Brown, A.S., Foody, J.A., Furman, R., Jacobson, T.A., Karalis, D.G., Kris-Etherton, P.M., Laforge, R., O'Toole, M.F., Scott, R.D., Underberg, J.A., Valuck, T., Willard, K., Ziajka, P.E., & Ito, M.K. (2013). Use of health information technology (HIT) to improve statin adherence and low-density lipoprotein cholesterol goal attainment in high-risk patients: proceedings from a workshop. *Journal of clinical lipidology*, 7 6, 573-609.
 2. Ismail, Sophia & Tsoli, Stergiani & Chowdhury, *Rajiv*. (2017). Therapy-related strategies to improve adherence to diabetic medications. *Medicographia*. 39. 289-297.

Electronic monitoring systems show 97% accuracy

- Multicompartmental pillbox will transmit a signal to a receiver and into a computer shared with physician and emailed/texted to patient showing date and time
- Smart electronic packaging/device monitoring is 97% accurate, ahead of pill counts (60%), and patient self-reporting and electronic patient diaries (27%)
- Does not guarantee pill is swallowed



1. Isabelle Arnet*, Philipp N. Walter and Kurt E. Hersberger. Polymedication Electronic Monitoring System (POEMS) – a new technology for measuring adherence (2013). *Frontiers in Pharmacology*. 4(26):1-6. 2. Helen L. Figge. Electronic Tools to Measure and Enhance Medication Adherence. *US Pharm* 2010;36(4)(Compliance & Adherence suppl):6-10. 3. Vrijens B. Digital Medication Adherence in Clinical Trials. *Clinical and Medical Research*, 2021;13(1):58-89.

Adherence measurement using ingestible sensor

- The sensor emits a signal when it encounters the acidic environment of the stomach, detectable by an externally worn patch and linked software app.
- Longitudinal adherence data in the form of daily progress charts for sensed dosing events as compared with scheduled dosing are visible to patients
- Self reported adherence 90 %
- Sensor reported adherence 57 % despite motivated and select patients !
- We really need to educate and convince our patients !

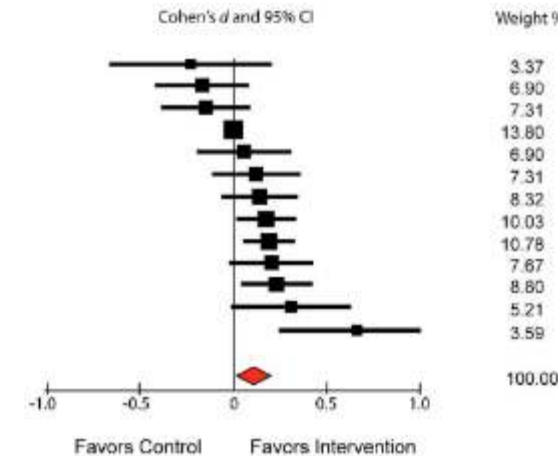


Thompson D, Mackay T, Matthews M, Edwards J, Peters NS, Connolly SB. Direct Adherence Measurement Using an Ingestible Sensor Compared With Self-Reporting in High-Risk Cardiovascular Disease Patients Who Knew They Were Being Measured: A Prospective Intervention. *JMIR Mhealth Uhealth*. 2017 Jun 12;5(6):e76.

You need patient motivation for even most sophisticated methods

- New nucleic acid-based therapies with once yearly injections, new medications with less side effects or FDC and new Technologies are helpful
- Shared decision making with the patient is the key!
- Nothing about me without me!
– Valerie Billingham

Study name	Cohen's d	SE	Lower limit	Upper limit	Z-Value	p-Value
Bieber (2006)	-0.23	0.22	-0.67	0.20	-1.05	0.29
Williams (2001)	-0.17	0.13	-0.42	0.08	-1.35	0.18
White (2011)	-0.15	0.12	-0.39	0.09	-1.25	0.21
Sequist (2010)	0.00	0.02	-0.05	0.04	-0.09	0.93
Kinmonth (1998)	0.06	0.13	-0.19	0.30	0.43	0.66
Cooper (2001)	0.12	0.12	-0.12	0.36	1.00	0.32
Girgis (2009)	0.14	0.10	-0.07	0.34	1.33	0.18
Cleland (2007)	0.17	0.08	0.02	0.33	2.18	0.03
Chassany (2006)	0.19	0.07	0.05	0.33	2.71	0.01
Christian (2008)	0.20	0.11	-0.02	0.43	1.77	0.08
Cals (2009)	0.23	0.10	0.04	0.42	2.37	0.02
Aiarzaguena (2007)	0.31	0.18	-0.01	0.62	1.90	0.06
Bolognesi (2006)	0.66	0.21	0.24	1.08	3.11	0.00
Combined	0.11	0.05	0.02	0.20	2.30	0.02



Kelley JM, Kraft-Todd G, Schapira L, Kossowsky J, Riess H. The influence of the patient-clinician relationship on healthcare outcomes: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2014 Apr 9;9(4):e94207.



Which method to measure adherence would you prefer to use in your clinical practice?



Self report



Lab markers



Pharmacy refill rates



Pill count



Electronic monitors

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ACTING ON THE UNSEEN: HOW DO WE HELP PATIENTS TO REMAIN
ADHERENT WHEN THEY ARE ASYMPTOMATIC?

Influencing Adherence to Hypertension Medications when Patients “Feel Fine”

Dr. Sheri Pruitt, PhD

Clinical Psychologist and Behavioral Science Consultant
California, US

Medications for hypertension are highly effective

- 1** High adherence to antihypertensive medication is associated with higher odds of blood pressure control¹

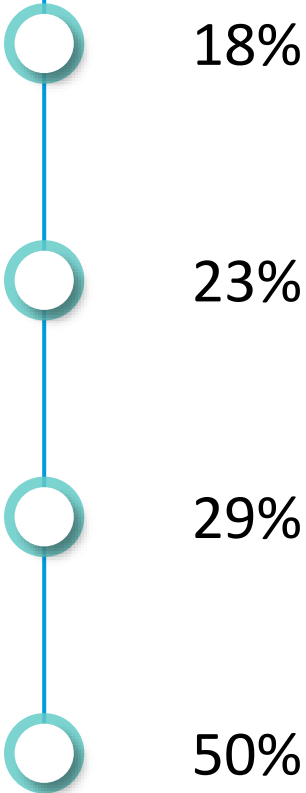
- 2** Non-adherence to medications increases a patient's risk of death from 50% to 80%¹

- 3** Poor adherence to hypertension treatment is the most important cause of complications²

1.Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009 Jun 16;119(23):3028-35. 2.Ashoorkhani M, Majdzadeh R, Gholami J, Eftekhar H, Bozorgi A. Understanding Non-Adherence to Treatment in Hypertension: A Qualitative Study. *International Journal of Community Based Nursing and Midwifery*. 2018 Oct;6(4):314-323.

Hypertension is increasing

WHAT PERCENTAGE OF THE WORLD'S POPULATION WILL HAVE HYPERTENSION BY 2025?

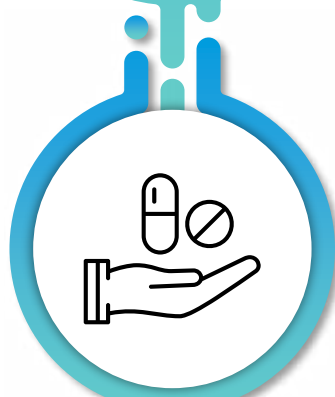


Hasan DM, Emeash AH, Mustafa SB, Abdelazim GE, El-din AA. Hypertension in Egypt: a systematic review. *Curr Hypertens Rev.* 2014;10(3):134-41.

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29% will have hypertension by 2025



Only 50% will take their medicines as prescribed



How can we do better with the hypertension medicines we have?

Serious complications from non-adherence to advice

- Heart attack or stroke
- Aneurysm
- Heart failure
- Weakened and narrowed blood vessels in kidneys
- Thickened, narrowed or torn blood vessels in the eyes
- Metabolic syndrome
- Trouble with memory or understanding
- Dementia



Why don't patients do everything they can to prevent these complications!?

Because there is a very long list of recommendations

○ **And**, because patients

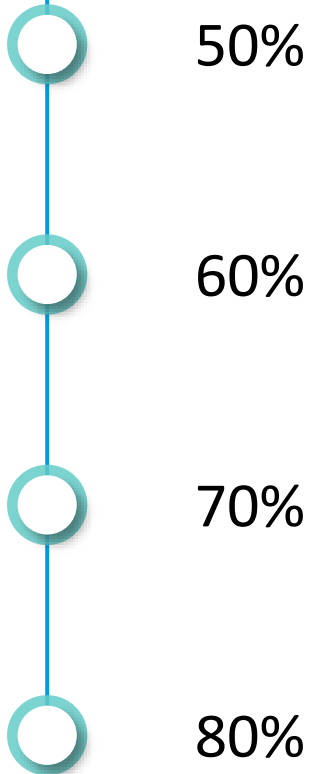
- “Feel fine”
- May not know about complications
- Think of complications as far off in the future
- Can’t tell whether the medicines are working
- “Normalize” nonadherence
- Feel overwhelmed with so many self-management tasks

○ **Patients feel like a failure before they even start!**

- 1 Eat a well-balanced diet, low salt diet
- 2 Limit alcohol
- 3 Get regular physical activity
- 4 Manage stress
- 5 Maintain a healthy weight
- 6 Quit smoking
- 7 Take medications as prescribed
- 8 Limit caffeine
- 9 Work with your doctor

Non-adherence goes up with complexity of regimen

WHEN REGIMENS ARE COMPLEX AND/OR REQUIRE LIFESTYLE CHANGES AND THE MODIFICATION OF DAILY HABITS, NON-ADHERENCE CAN BE AS HIGH AS _____%?



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What can providers do to improve adherence to recommendations for hypertension control?

Tailor advice and leverage patient's emotions

TAILOR: START SMALL, SELECT ONE THING, BE SURE IT IS A BEHAVIOR THE PATIENT CAN ACHIEVE

Is the patient confident he can take one pill, every day?

Is the patient confident he can make significant dietary changes?

USE EMOTION/VALUES TO ENHANCE INTRINSIC MOTIVATION

Forget persuading with logic, demands, threats, orders, shaming, judging, criticizing, blaming, warning, telling what you “should” do, disagreeing . . .
These approaches don't work

Tap into the patient's emotions, hopes, values, and desires to increase adherence to your advice

How to use patient's emotions/values to enhance intrinsic motivation to adhere to advice

Ask open-ended questions



○ If you were to take this medicine, how might things be better for your family?

○ What long-term benefits for you and your family do you see from taking this medicine?

○ If you were taking this medicine, how might it impact your future and the things you could do in your life?

○ How important is it for you to live a long, healthy life and see your children grow up?



Providers can absolutely influence adherence

Effective two-way communication is critical



Meet patients “where they are” in terms of what they can achieve



Don't tell patients what to do



Use patient's emotions/values to create intrinsic motivation to be healthy and follow your advice