



CLUSTER RANDOMIZED TRIALS IN HEALTH CARE DELIVERY SYSTEMS: lessons from STIC2IT

Nitesh K. Choudhry, MD, PhD

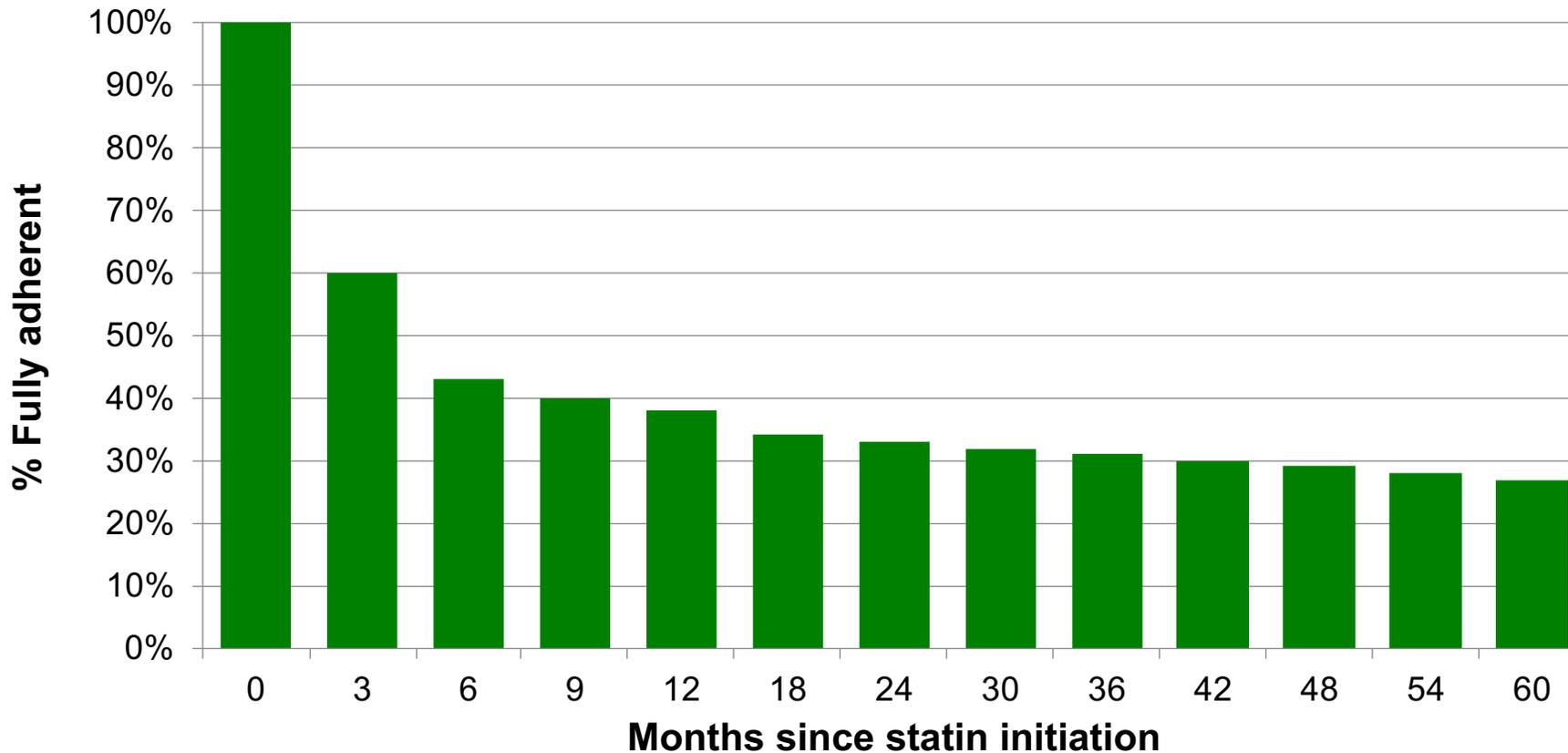
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Over the long-term, only half of patients adhere to the evidence-based drugs prescribed to them



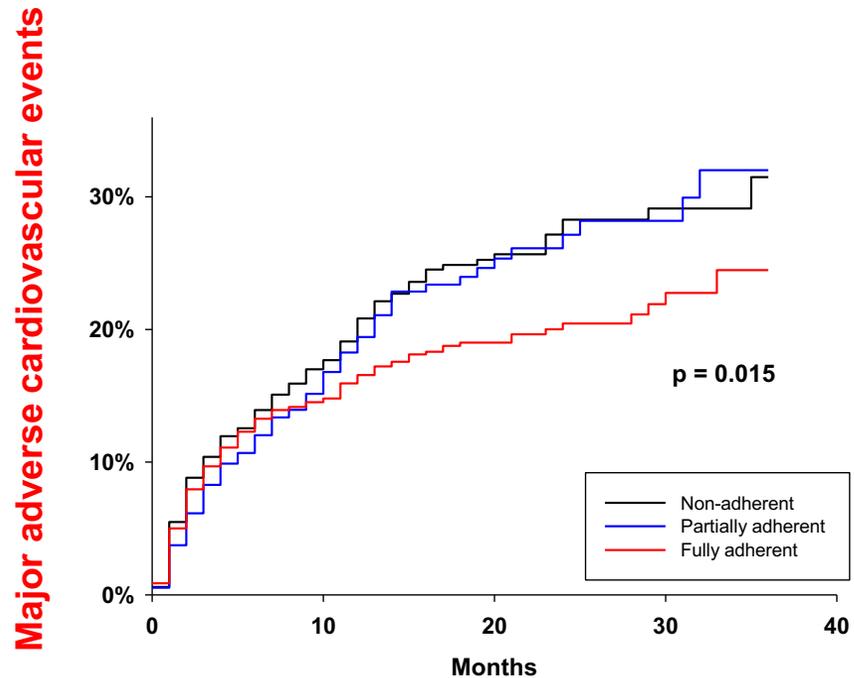
SOURCES: Benner et al. JAMA 2002; 288: 455; Jackevicius et al. JAMA 2002; 288: 462; Akincigil et al. JGIM 2008; 23: 115; Choudhry et al. Circulation 2008;117;1261-1268



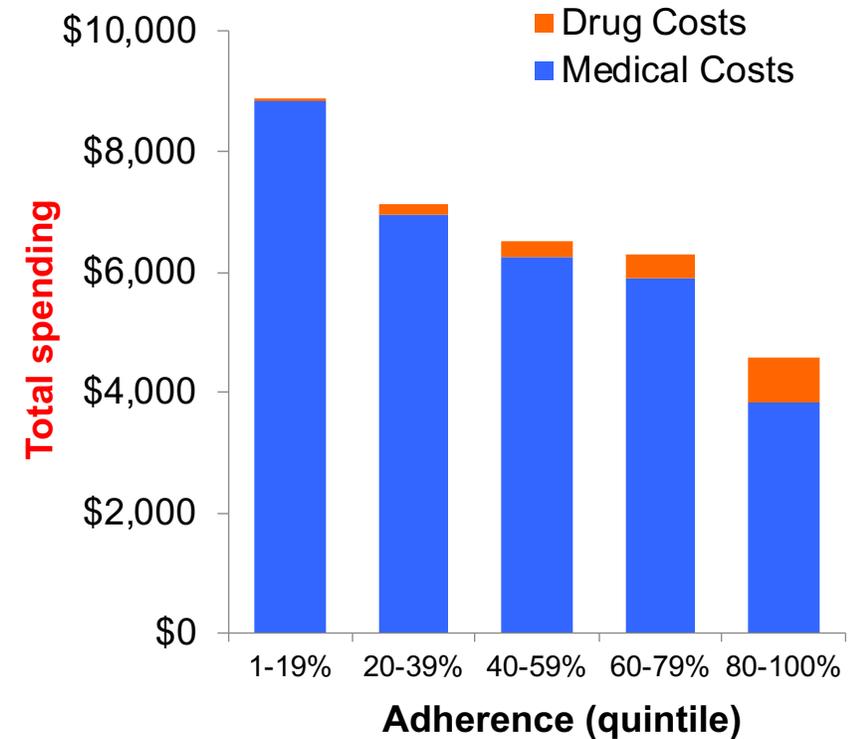
“Drugs don’t work in people who don’t take them”

-- C. Everett Koop

Worse health outcomes



Higher spending



SOURCE: Choudhry et al. Am Heart J 2014; 167: 51-58; Sokol et al. Med Care 2005; 43: 520



Non-adherence is a public health problem

- At a national level in the US non-adherence accounts for:
 - 125,000 deaths per year in U.S
 - 11% of hospitalizations
 - \$100 billion to \$300 billion in annual spending
- Non-adherence also threatens the billions of dollars that have been invested in:
 - Identifying new medications
 - Rigorous evaluation
 - Improving drug prescribing

Many interventions to improve adherence have been tested

FINANCIAL INCENTIVES

REMINDER DEVICES

TEXT MESSAGES

SMARTPHONE APPLICATIONS

MEDICATION SYNCHRONIZATION

THE NEW ENGLAND JOURNAL OF MEDICINE

SPECIAL ARTICLE

Full Coverage for Preventive Medications after Myocardial Infarction

Nitesh K. Choudhry, M.D., Ph.D., Jerry Avorn, M.D., Robert J. Glynn, Sc.D., Ph.D., Elliott M. Aronson, M.D., Sebastian Schneeweis, M.D., Sc.D., Michele Toscano, M.S., Lonny Reisman, M.D., Jaquim Fernandes, M.S., Claire Spertell, Ph.D., Joy L. Lee, M.Sc., Tania Golig, M.S., Tanya Brennan, M.D., J. M. P.H., and William H. Shrank, M.D., M.S.H.S., for the Post-Myocardial Infarction Free-Rate Event and Economic Evaluation (M-FREE) Trial

ABSTRACT

BACKGROUND: Adherence to medications that are prescribed after myocardial infarction is poor. Limiting out-of-pocket costs may increase adherence and improve outcomes.

DESIGN, SETTING, AND PARTICIPANTS: This 4-arm, block-randomized clinical trial involved 53 480 members of CVS Caremark, a pharmacy benefit manager, across the United States. Eligible participants were aged 18 to 64 years and had 1 to 3 oral medications for long-term use. Participants had to be subsequently adherent to all of their prescribed therapies (with a medication possession rate of 70% to 80%) during the 12-month study period.

OBJECTIVE: To compare the effect of 3 low-cost reminder devices on medication adherence.

DESIGN, SETTING, AND PARTICIPANTS: This 4-arm, block-randomized clinical trial involved 53 480 members of CVS Caremark, a pharmacy benefit manager, across the United States. Eligible participants were aged 18 to 64 years and had 1 to 3 oral medications for long-term use. Participants had to be subsequently adherent to all of their prescribed therapies (with a medication possession rate of 70% to 80%) during the 12-month study period.

RESULTS: Of 53 480 participants, more than 50% were aged 45 to 59 years and 50% were female. In the primary analysis, 15.7% of patients in the chronic disease stream assigned to the standard plan, and 15% assigned to the digital timer cap, 9% assigned to the both stop watch, and 8% assigned to the control arm were optimally adherent to their prescribed treatments during follow-up. There was no statistically significant difference in the odds of optimal adherence between the control and any of the devices (standard follow-up odds ratio [OR], 1.03 [95% CI, 0.95-1.13]; digital timer cap, OR, 1.00 [95% CI, 0.92-1.09]; and both stop watch, OR, 0.98 [95% CI, 0.90-1.07]). In direct comparisons, the odds of optimal adherence were higher with standard follow-up than with the both stop watch (OR, 1.02 [95% CI, 1.00-1.03]). Secondary analyses yielded similar results.

CONCLUSIONS AND RELEVANCE: Low-cost reminder devices did not improve adherence among consistent users who were taking up to 3 medications to treat common chronic conditions. The devices may have been most useful for patients who were nonusers or users of 1 or 2 medications.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT02500506

JAMA Intern Med. doi:10.1001/jamaintern.2018.0287
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JAMA Internal Medicine | Original Investigation

Effect of Reminder Devices on Medication Adherence: The REMIND Randomized Clinical Trial

Nitesh K. Choudhry, MD, PhD, Alan A. Kravitz, MS, Fama M. Drake, MD, MPH, Christiane Gruber, MPH, Joseph J. Tang, MD, Robert J. Glynn, Sc.D., Tanya Brennan, MD, MS, MPH, Scott D. Martin, PhD, William H. Shrank, MD, MSc, Jessica M. Franks, PhD

ABSTRACT

OBJECTIVE: To compare the effect of 3 low-cost reminder devices on medication adherence.

DESIGN, SETTING, AND PARTICIPANTS: This 4-arm, block-randomized clinical trial involved 53 480 members of CVS Caremark, a pharmacy benefit manager, across the United States. Eligible participants were aged 18 to 64 years and had 1 to 3 oral medications for long-term use. Participants had to be subsequently adherent to all of their prescribed therapies (with a medication possession rate of 70% to 80%) during the 12-month study period.

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JMIR MHEALTH AND U-HEALTH

Original Paper

The Impact of Text Messaging on Medication Adherence and Exercise Among Postmyocardial Infarction Patients: Randomized Controlled Pilot Trial

Avinash Pandey¹, Alicia Kravitz², MS, Total Patel³, PhumD, Nitesh Choudhry^{1,2}, MD, PhD

ABSTRACT

Background: Adherence to evidence-based therapies such as medication and exercise remains poor among patients after a myocardial infarction (MI). Text message reminders have been shown to improve rates of adherence to medication and exercise, but the existing studies have been of short duration.

Objective: The single-center randomized controlled pilot trial was conducted to evaluate the impact of text message reminders over 12 months on adherence to evidence-based medications and exercise among patients receiving acute rehabilitation after hospitalization for MI.

Methods: In the medication adherence trial, 34 patients were randomized to receive usual care alone or usual care plus daily text message reminders delivered at the time of day at which medications were to be taken. In the exercise adherence trial, 50 patients were randomized to receive usual care alone or usual care plus a daily text message reminding them to exercise as directed.

Results: The text message reminders led to a mean 14.2 percentage point improvement in self-reported medication adherence over usual care (P=.001, 95% CI, 7.2-21.2). In the exercise trial, text message reminders resulted in an additional 0.2 km (P=.001, 95% CI, 0.14-0.4) or 16.4 minutes (P=.001, 95% CI, 2.4-6.0) of exercise per month over usual care and a nonsignificant increase of 1.2 metabolic equivalents (METs; P=.06) in exercise capacity as assessed by a BRUCE protocol of 12 months.

Conclusions: Text message reminders significantly improved adherence to medication and exercise among post-MI patients receiving care in an intensive cardiac rehabilitation program. This technology represents a simple and scalable method to ensure consistent use of evidence-based cardiovascular therapies.

TRIAL REGISTRATION: ClinicalTrials.gov NCT02832872 (<http://clinicaltrials.gov/ct2/show/NCT02832872>) (Archived by WebCite at <http://www.webcitation.org/full/8m505>)

JMIR Mhealth Uhealth 2017 | vol. 9 | iss. 10 | e10111 | <http://dx.doi.org/10.19196/jm.9.10.10111>

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JAMA Internal Medicine | Original Investigation

Association of a Smartphone Application With Medication Adherence and Blood Pressure Control: The MedSAFE-BP Randomized Clinical Trial

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ABSTRACT

OBJECTIVE: Medication nonadherence accounts for up to half of medication nonadherence and blood pressure control.

DESIGN, SETTING, AND PARTICIPANTS: This was a 2-arm, randomized clinical trial of Medication Adherence Improvement Support App for Engagement—Blood Pressure (MedSAFE-BP). Participants were recruited through online platforms and were mailed a home blood pressure cuff to confirm eligibility and to provide follow-up measurements. Of 1577 participants who were screened, 402 completed consent, and 346 were randomly assigned to either smartphone application, taking 1 to 3 antihypertensive medications, and were randomized to a 12-week intervention or control.

INTERVENTIONS: Intervention-arm participants were instructed to download and use the MedSAFE app, which includes reminder/alerts, adherence reports, and optional peer support.

MAIN RESULTS AND MEASURES: Co-primary outcomes were change from baseline to 12 weeks in self-reported medication adherence, measured by the Morisky medication adherence scale (MMAS) (range, 0-8), and blood pressure (including lower adherence and change in systolic blood pressure).

RESULTS: Participants (n = 402) in the intervention group and 202 controls had a mean age of 52.0 years and mean body mass index, calculated as weight in kilograms divided by height in meters squared, of 33.2 and 30.6, respectively, and 161 (39%) were female. After 12 weeks, the mean MMAS score on the MMAS-8 improved by 14.1 (3.1) among intervention participants and remained unchanged among controls (between-group difference, 0.4, 95% CI, 0.0-0.9, P=.05). The mean 12-week systolic blood pressure at baseline was 154.6 (16.0) mm Hg and 153.0 (16.0) mm Hg, among intervention and control participants, respectively. After 12 weeks, the mean 12-week systolic blood pressure decreased by 15.6 (3.6) among the intervention participants and 10.1 (5.4) among controls (between-group difference, -5.5, 95% CI, -7.4 to -3.7, P=.001).

CONCLUSIONS AND RELEVANCE: Among individuals with poorly controlled hypertension, patients who used a smartphone application had a small improvement in self-reported medication adherence but not in blood pressure or systolic blood pressure compared with controls.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT02707543

JAMA Intern Med. doi:10.1001/jamaintern.2018.0447
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PHARMACEUTICALS & MEDICAL TECHNOLOGY

By Alan A. Kravitz, Robert J. Glynn, Sebastian Schneeweis, Joshua J. Eggen, J. Samantha Daugherty, Gregory Bell, and Nitesh K. Choudhry

Medication Synchronization Programs Improve Adherence To Cardiovascular Medications And Health Care Use

ABSTRACT

OBJECTIVE: Medication synchronization programs based in pharmacies simplify the refill process by enabling patients to pick up all of their medications on a single visit. This can be especially important for improving medication adherence in patients with complex chronic diseases. We evaluated the impact of two synchronization programs on adherence, cardiovascular events, and resource use among Medicare beneficiaries treated between 2011 and 2014 for two or more chronic conditions—at least one of which was hypertension, hyperlipidemia, or diabetes. Among nearly 23,000 patients matched by propensity score, the mean proportion of days covered (a measure of medication adherence) for the control group of patients without a synchronization program was 0.84 compared to 0.87 for synchronized patients—a gain of 3 percentage points. Adherence improvement in synchronized versus control patients was three times greater in patients with low baseline adherence, compared to those with higher baseline adherence. Rates of hospitalization and emergency department visits and rates of outpatient visits were 9 percent and 3 percent lower in the synchronized group compared to the control group, respectively, while cardiovascular event rates were similar. Synchronization programs were associated with improved adherence for patients with cardiovascular disease, especially those with low baseline adherence.

CONCLUSIONS AND RELEVANCE: Simple chronic disease regimen optimization—an effort that can translate into meaningful differences in clinical outcomes, if programs offered by pharmacies to synchronize the timing of prescriptions aim to simplify the refill process by enabling patients to pick up all of their medications during a single visit. Standard components of medication synchronization programs, such as refill reminders and regular pharmacist appointments, are designed to maintain synchronization and reinforce adherence behavior over time. In 2014 an estimated 35.0 million patients were enrolled in medication synchronization programs in the United States, but only 1.5 million patients were enrolled in medication synchronization programs in the United States.

JAMA Intern Med. doi:10.1001/jamaintern.2018.0447
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SOURCES: Choudhry et al. NEJM 2011; 365: 2088-97; ; Choudhry et al. JAMA Internal Medicine 2017; 177: 624-31; Pandey et al. JMIR Mhealth and Uhealth 2017; Morawski et al JAMA Internal Medicine 2018; 178: 802-0; Krumme et al. Health Affairs 2018; 37: 125-33



Existing adherence improvement interventions have substantial limitations

- **Most interventions have only been modestly effective**
 - Do not adequately address each individual's unique adherence barriers
 - Imprecisely targeted to patients who do not need adherence assistance

- **Even effective interventions are difficult to sustain**
 - Often require new infrastructure and/or are expensive

OBJECTIVE

STIC2IT: Study of a Tele-pharmacy Intervention for Chronic diseases to(2) Improve Treatment adherence

- To evaluate the effect of a medication adherence intervention for diabetes, hypertension, and hyperlipidemia that was:

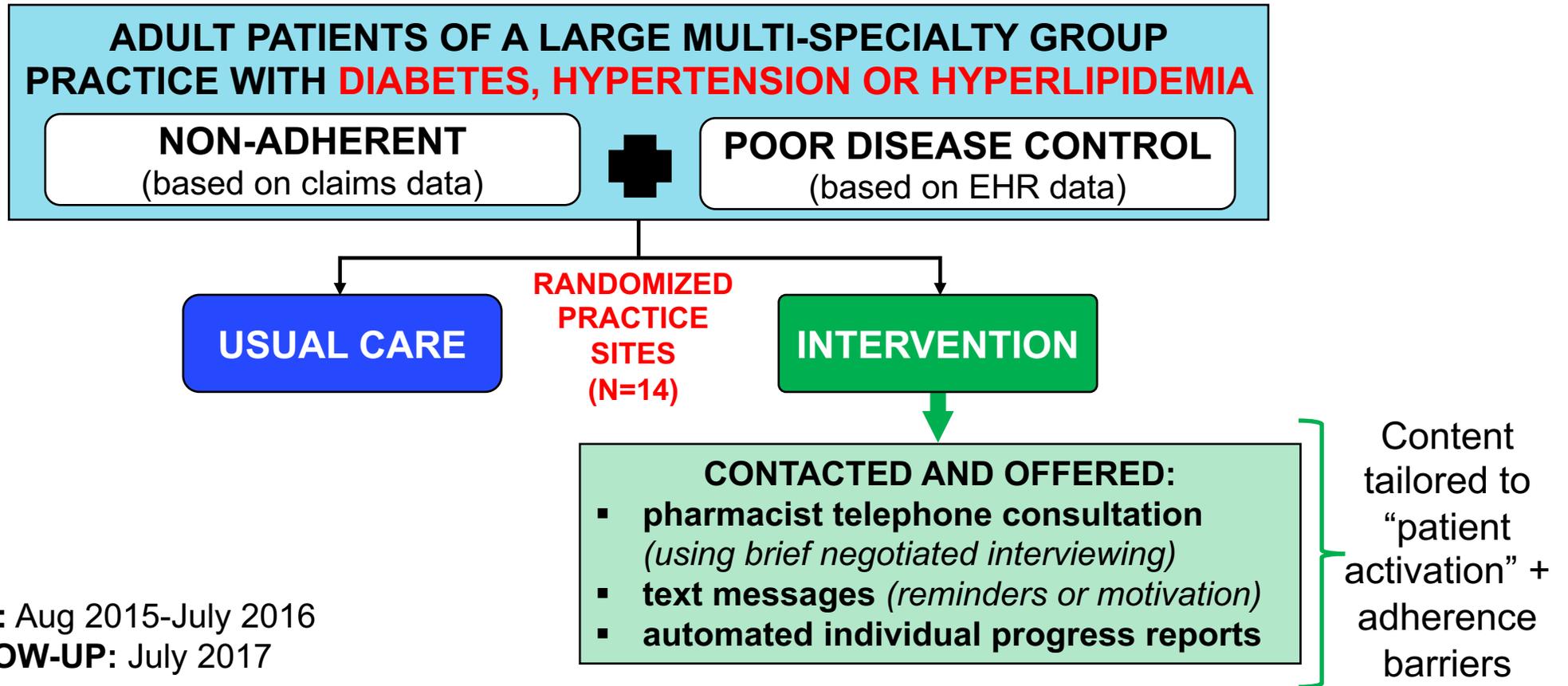


SOURCE: Choudhry et al. American Heart Journal 2016; 180: 90-97; Choudhry et al. JAMA Internal Medicine 2018; 178: 1174-1181



DESIGN

Open-label, pragmatic cluster-randomized trial



- **ENROLLMENT:** Aug 2015-July 2016
- **END OF FOLLOW-UP:** July 2017

METHODS

Randomization

- **CLUSTER:** Randomized clinics (practice sites) rather than individual providers or patients to reduce contamination
 - Individual providers (both physicians and pharmacists) care for multiple patients
 - Individual patients are cared for by multiple providers in a given practice site

- **BLOCK:** Practice sites differ from each other in important ways and simple cluster randomization may result in imbalanced groups
 - Practices categorized into “blocks” based on size and whether they had a previous clinical pharmacy program
 - Randomization performed within the blocks



METHODS

Recruitment

Identified potentially eligible patients in intervention practices

Randomly selected 85 every 2 weeks (to achieve timely outreach within resource constraints)

Contacted patients' PCP via EHR to request permission to enroll their patients → if no response, patients were opted into the study

Patients sent a letter (hand addressed, included small gift, signed by their PCP) informing them about the study

Follow-up letter

Telephone call by a RA and invited to participate, schedule a pharmacist call + administer baseline questionnaires [3 attempts]



METHODS

Outcomes assessed using routinely-collected data

- Outcomes assessed during the 12 months after randomization

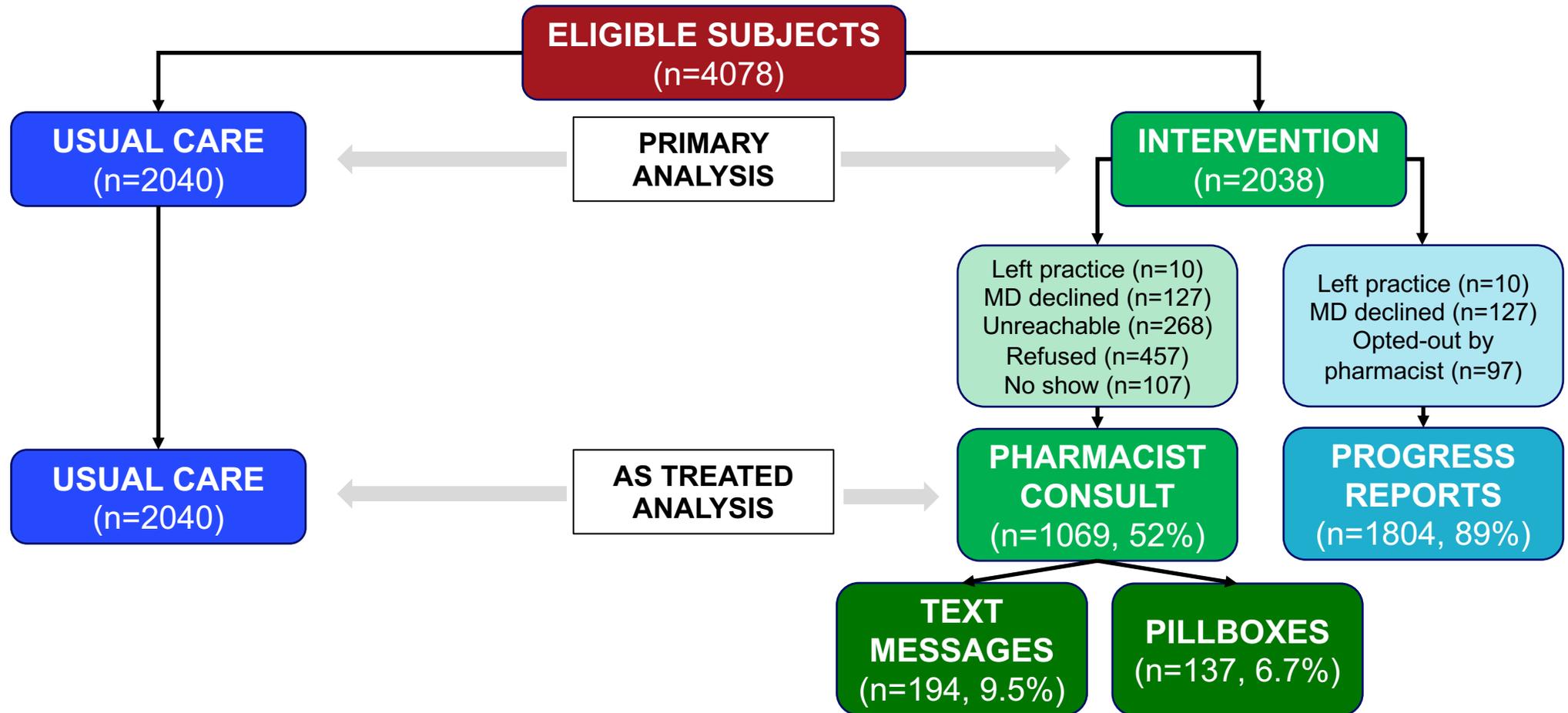
	Outcome	Data Source	Definition
1°	Medication adherence	Prescription health insurance data	Average adherence (“proportion of days covered”) for eligible medications at the time of randomization
2°	Disease control	Electronic health record data	Proportion of patients meeting guideline targets for: (a) all eligible conditions and (b) at least 1 eligible condition

Statistical considerations

- **Primary analyses conducted on an intention-to-treat basis**
 - Assumed that ~50% of patients would agree to a pharmacist consultation
 - Accounted for clustering at the practice level with a design effect of 1.10
 - Powered for a 2.5% mean improvement in adherence (assuming a SD of 25%) and 20% between-group difference in the relative risk of our secondary clinical outcome (assuming a baseline risk of 23%)
- **Clinical outcomes were evaluated using routinely collected data**
 - Used values that were closest to the end of each patient's 12-month follow-up period
 - Used multiple imputation (with 20 imputations to achieve in-range values and 99% relative efficiency)

RESULTS

Enrollment



Clinical pharmacist telephone consultations lasted a mean of 24.9 minutes; 1050 (98.2%) patients completed at least 2 calls and 175 (16.4%) patients received 3 or more calls
8 intervention and 11 control patients lost insurance eligibility within 2 weeks of randomization



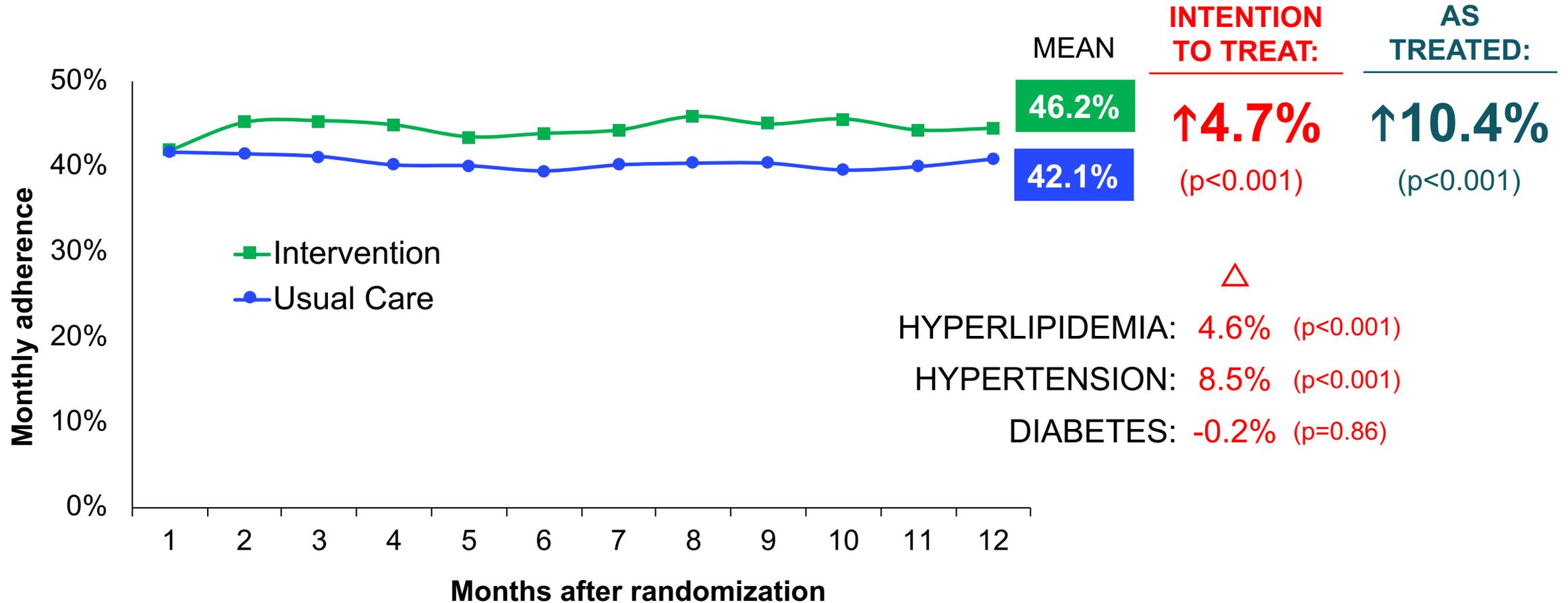
RESULTS

Baseline characteristics

CHARACTERISTIC	USUAL CARE (N=2040)	INTERVENTION (N=2038)
Age, mean years*	60.4	59.2
Male sex	54.7%	55.0%
White race*	53.6%	60.6%
Qualifying conditions		
Hyperlipidemia	72.0%	73.7%
Hypertension	25.9%	23.8%
Diabetes	12.1%	11.9%
Charlson comorbidity score, mean	0.90	0.74
Baseline disease control		
LDL cholesterol, mean mg/dL,	204.8	207.8
Systolic blood pressure, mean mmHg	149.9	149.2
Hemoglobin A _{1c} , mean	9.8	9.5
Baseline adherence, mean	57.0%	57.2%

* Standardized mean difference for age and race/ethnicity were >0.1; there were no other significant differences

STIC2IT: PRIMARY OUTCOME
Adherence

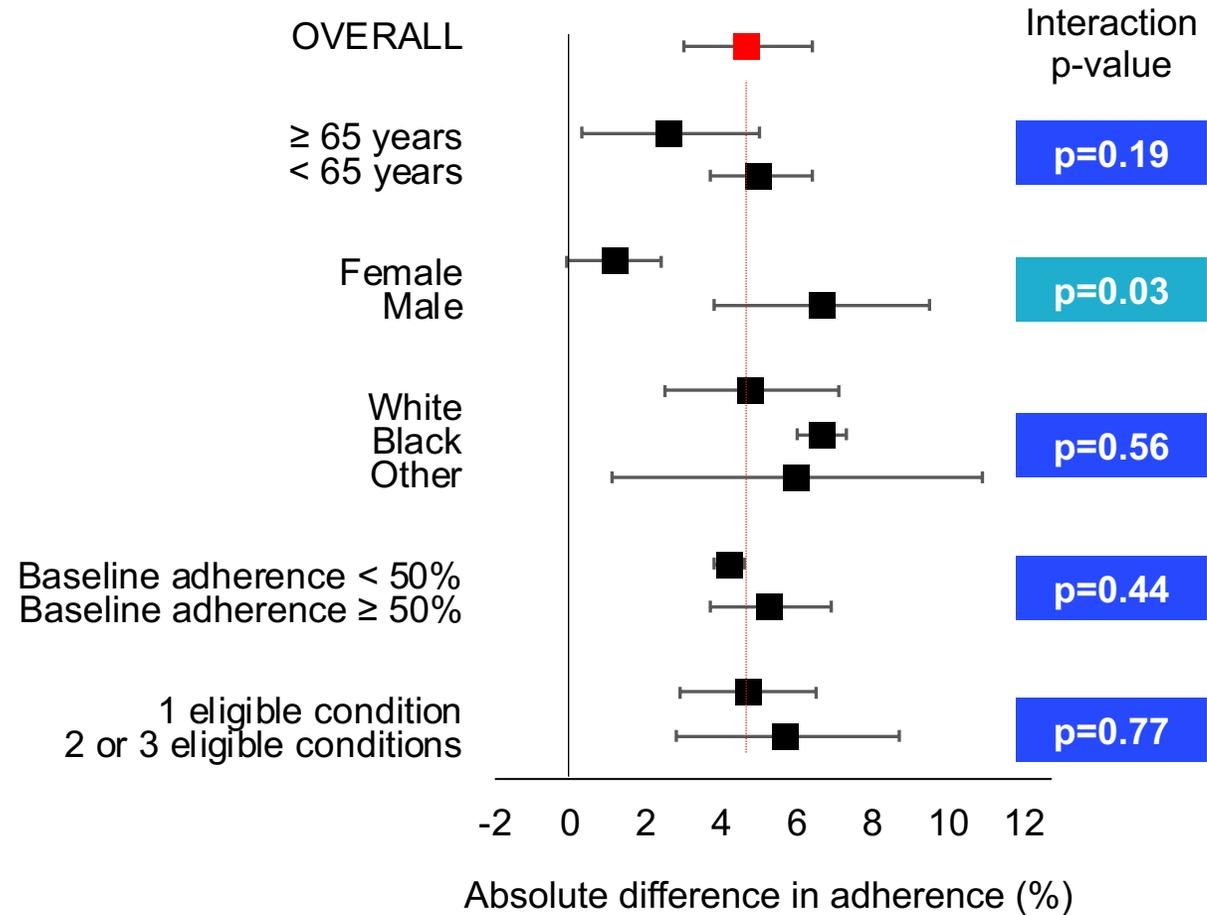


Median (IQR) time from randomization to pharmacist call (when it occurred): 22 (17 to 32) days



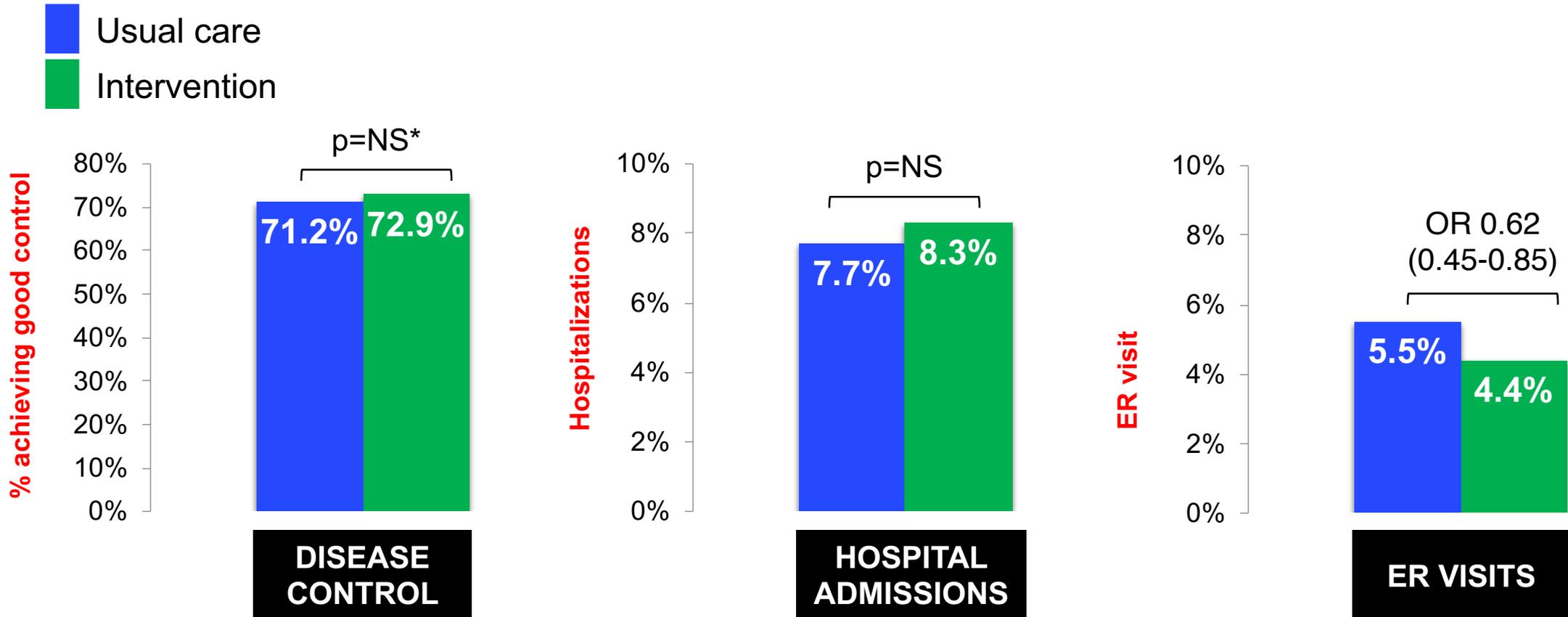
SUBGROUP ANALYSES

Adherence



STIC2IT: SECONDARY OUTCOMES (INTENTION TO TREAT)

Disease control and resource utilization

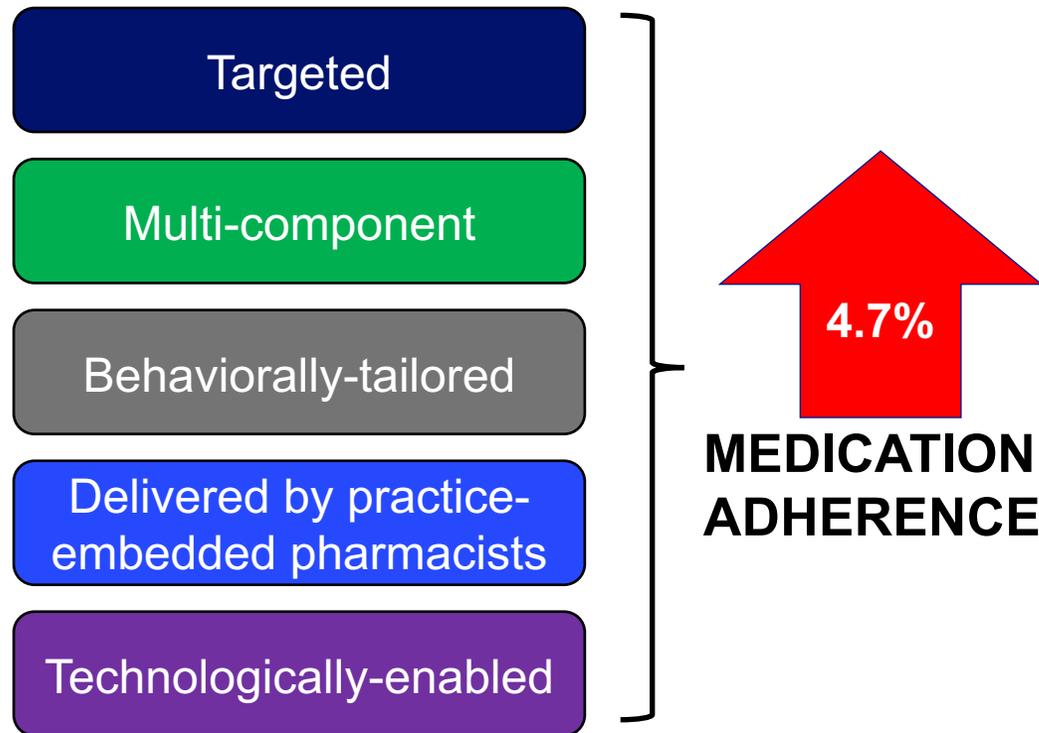


*As treated OR for good disease control (≥ 1 eligible condition): 1.24 (1.03-1.50)

SUMMARY

The STIC2IT intervention improved adherence

- An intervention for patients with diabetes, hypertension, and hyperlipidemia with poor medication adherence and suboptimal disease control:



- Effect size was similar to those achieved by more labor intensive interventions
- Used highly-pragmatic research methods to facilitate the generalizability of the results

SUMMARY AND IMPLICATIONS

Intervention did not improve secondary clinical outcomes

Routinely-collected data used inaccurate?

Adherence improvement too small?

Patients may have required therapeutic intensification?

FUTURE INTERVENTIONS MAY NEED TO:

- Be more intensive while still pragmatic
- Focus on a more impactable patient population
- Simultaneously address adherence and other barriers to optimal disease control

Multi-level engagement is critical

■ SYSTEM

- Many systems have multiple competing priorities
- Some do not want to randomize practices
- **STIC2IT**: High-level engagement (but still required many months of negotiation after the grant was awarded)

■ PHYSICIANS

- Patients are being cared for in real care environments
- Disconnecting PCPs could have implications for safety and patient willingness to participate
- **STIC2IT**: “opt-out” approach for PCP approval + pharmacist consultation notes saved in the HER

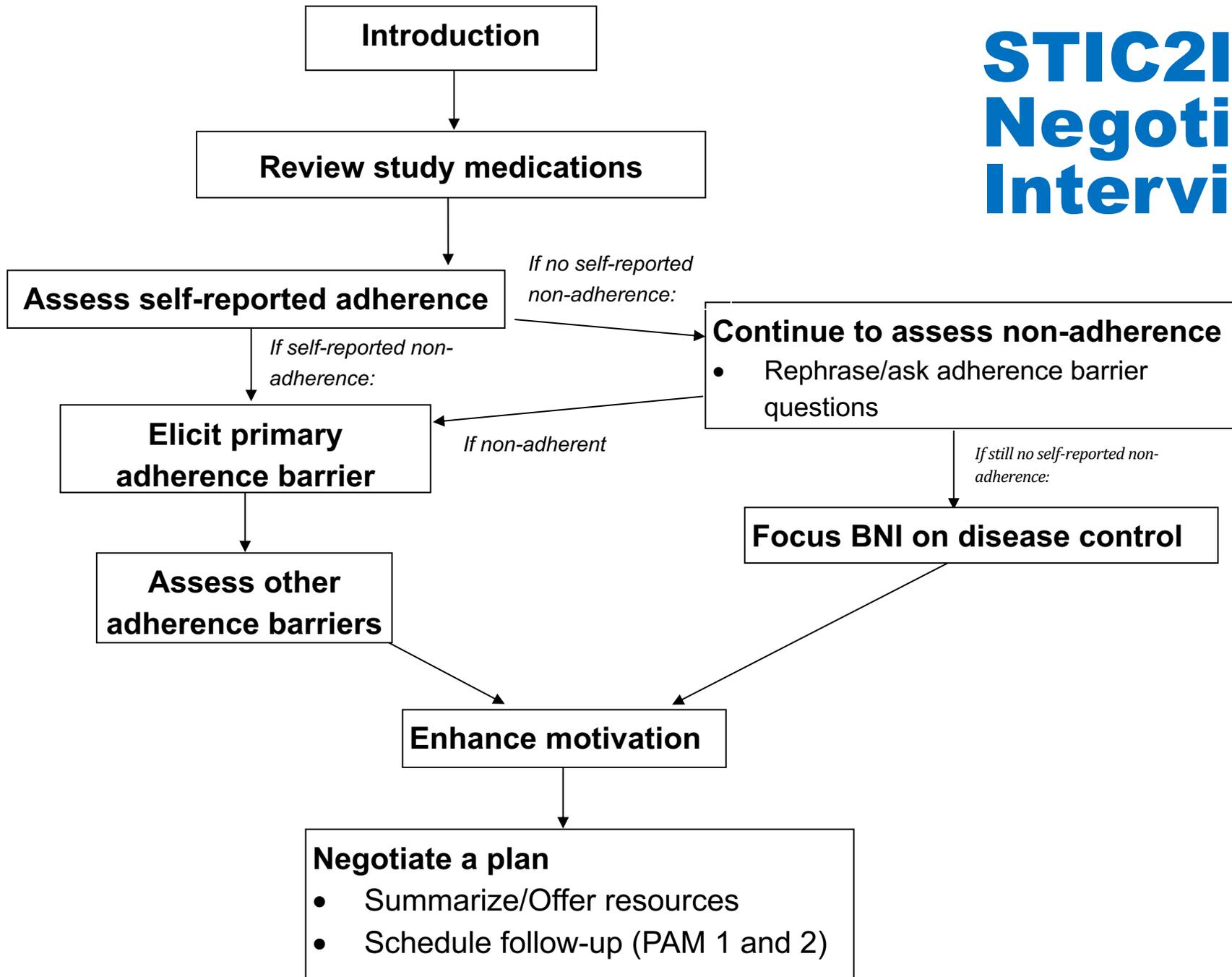
■ PATIENTS

- Amplified by cluster randomization and an ITT analytic approach (i.e. non-receipt of the intervention = little likelihood of benefit)
- **STIC2IT**: patient outreach all signed by patients’ PCPs

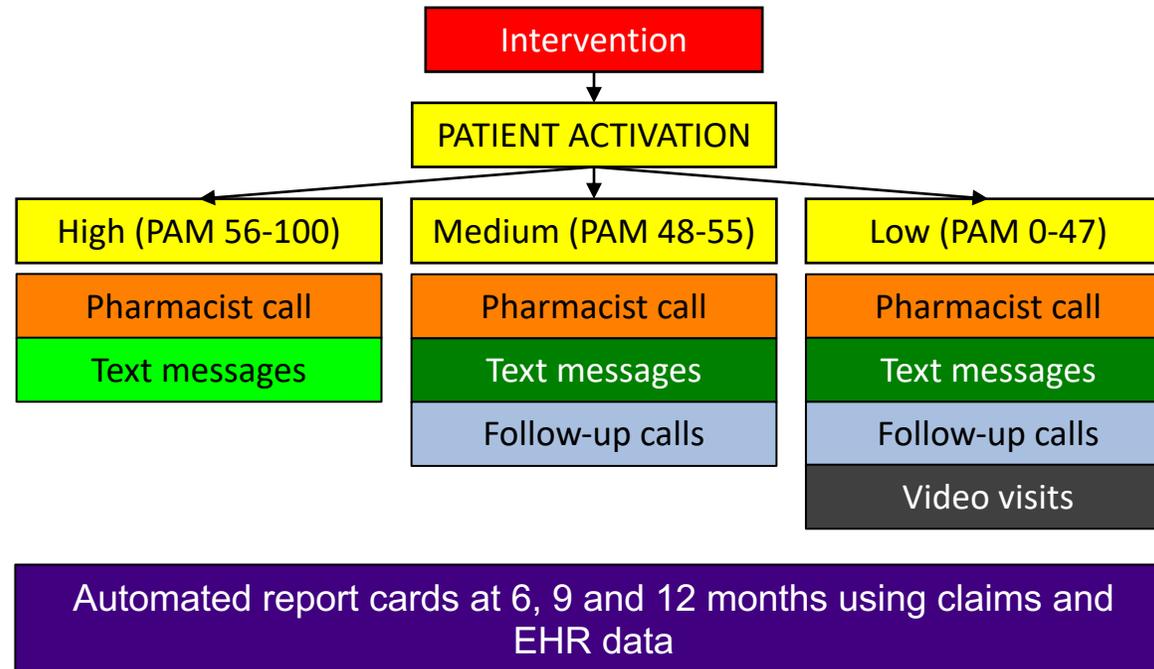
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STIC2IT: Brief Negotiated Interviewing



STIC2IT: Intervention Tailoring



PATIENT ACTIVATION MEASURE (PAM)

- Assesses individual's willingness, knowledge, skills and confidence for managing one's health



SOURCES: Hibbard et al. 2004 *HSR*; Hibbard et al. 2005 *Health Serv Res.*; Mosen et al. 2007 *J Am Care Manag*; Begum N et al. 2011 *Diabetes Res Clin Pract.* Lorig K et al. 2010 *Diabetes Care*; Hibbard et al. 2009 *Am J Manag Care*; Hibbard et al. 2013 *Health Aff* ; Kinney et al. 2015 *Patient Educ Couns*

