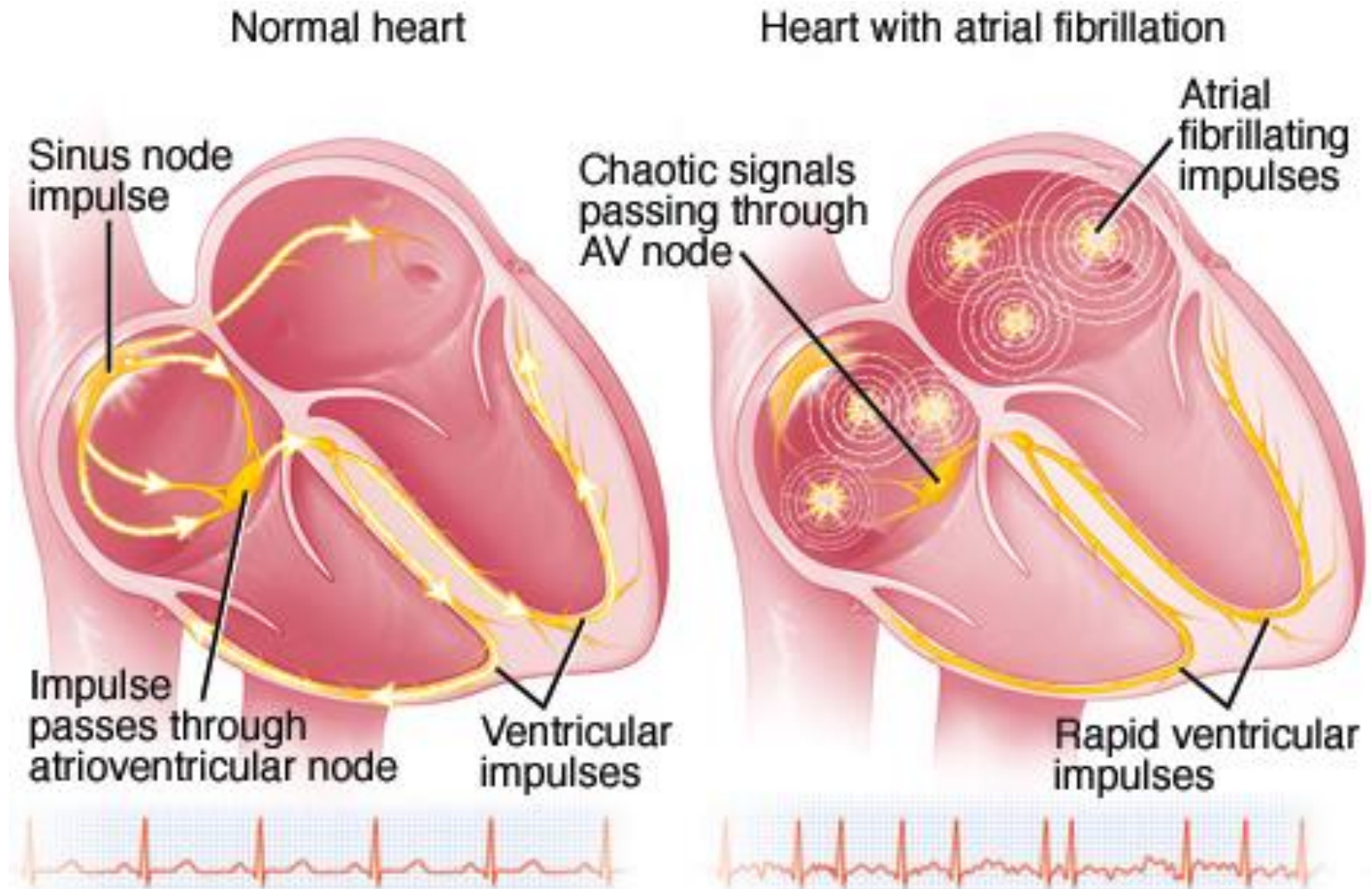


Sentinel IMPACT-AFib: Transforming Pragmatic Clinical Trials Using a Nationwide Distributed Claims Database

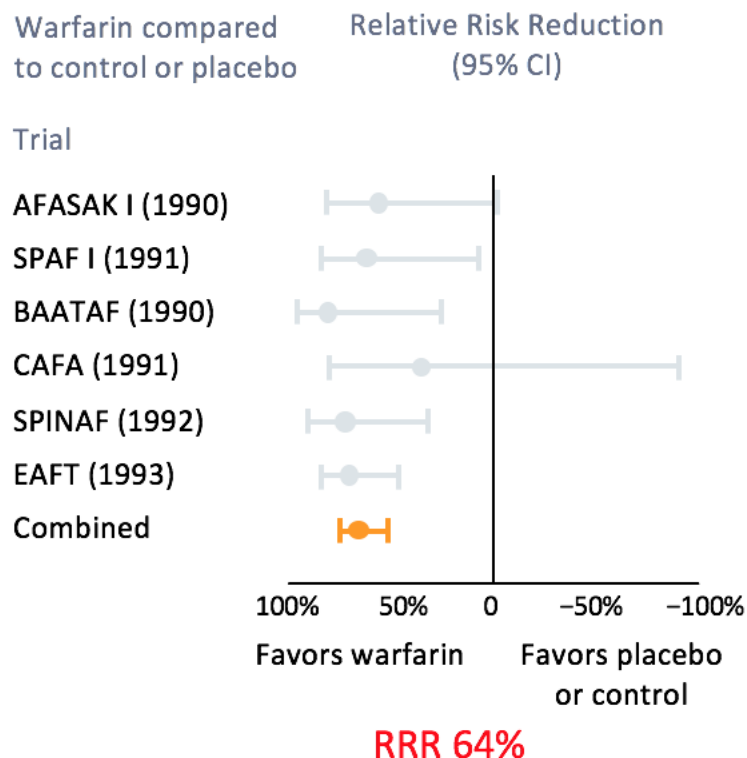
April 20, 2017

Sean Pokorney, MD, MBA
Duke Clinical Research Institute
Duke University School of Medicine

What is Atrial Fibrillation?

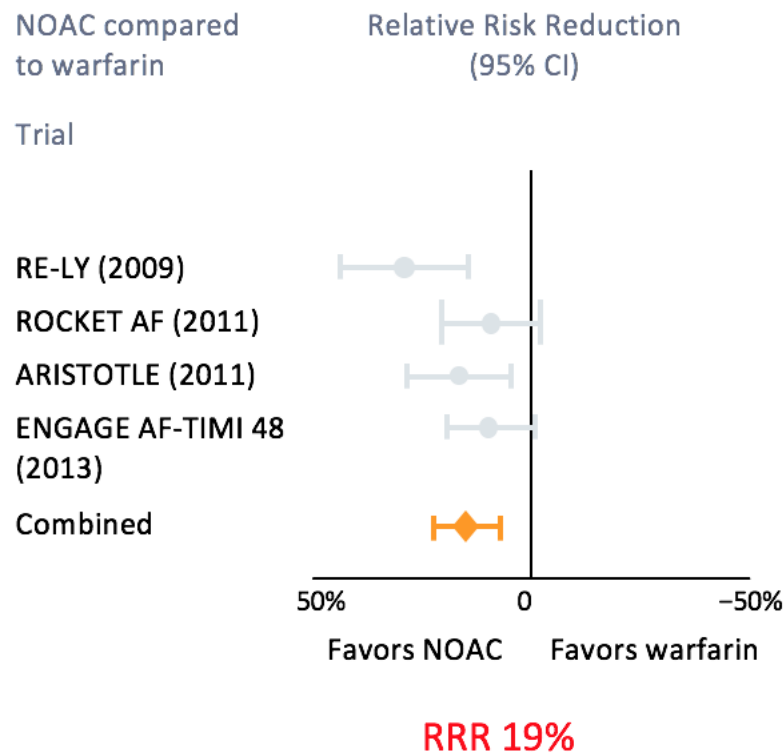


Effective Medications to Prevent Stroke



Warfarin vs. Placebo or Control
(6 trials, total n=2,900)

Hart R, et al. Ann Intern Med. 2007;146:857-867.



NOAC vs. Warfarin
(4 trials, total n=71,683)

Ruff C, et al. Lancet. 2014;383:955-962.

Underuse of Anticoagulation for AF

Criteria	Patients
Total number of patients (Aetna, Humana, Harvard Pilgrim)	16.2 million
Patients with AF	231,696 (1.4% of all patients)
AF pts with $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$	201,882 (87% of AF patients)
Patients with at least one oral anticoagulation fill	105,256 (52% of AF patients with $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$)
Proportion of days covered by anticoagulation in AF patients	32%

Public Health Impact: Low Anticoagulation Use

- > 5 million people in the US have AF
- Of those with additional risk factors for stroke, more than half are not treated with oral anticoagulants
- Of these, 5% stroke per year
- Of these, 70% are preventable
- Hundreds of thousands of preventable strokes each year world wide

IMPACT-AF Cluster Randomized Trial

Argentina, Brazil, China, India, Romania



Argentina	Cecilia Bahit	INECO	Rosario
Brazil	Renato Lopes	Federal University	Sao Paulo
India	Denis Xavier	St. John's	Bangalore
China	Huo Yong	Peking University	Beijing
Romania	Dragos Vinereanu	Carol Davila University	Bucharest

Initiatives for Clinical Trials with Distributed Database



MINI-SENTINEL and CLINICAL TRIALS TRANSFORMATION INITIATIVE

**DEVELOPING APPROACHES TO CONDUCTING RANDOMIZED TRIALS USING THE
MINI-SENTINEL DISTRIBUTED DATABASE**

February 28, 2014

Rationale for IMPACT-AFib trial

- OAC underuse is a public health priority
- Also a priority of health plans
- Interventions (mailings!) are consistent with routine health plan interventions
- Eligible population and major outcomes measurable using Sentinel Distributed Database

FDA-Catalyst: IMPACT-AFib Randomized Trial

Implementation of a randomized controlled trial to improve treatment with oral AntiCoagulanTs in patients with Atrial Fibrillation

- Randomized controlled trial of direct mail to health plan members with AFib and to their providers to encourage consideration of oral anticoagulation
- Proof of concept randomized trial using Sentinel Initiative infrastructure

IMPACT-Afib Workgroup



Duke Clinical Research Institute



Harvard Pilgrim
HealthCare



Patient representative

HealthCore® Anthem®



U.S. FOOD & DRUG
ADMINISTRATION

HUMANA®



OPTUM™



CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE

IMPACT-AFib

Conceptual Trial Overview

Patients

- Atrial fibrillation (AF) (two claims)
- CHADS-VASc ≥ 2
- No admission for bleeding in prior 6 months
- Not prescribed anticoagulant for prior 12 months
- Age ≥ 30 years

All Patients Meeting Inclusion and Exclusion Criteria

- Aim to increase the use of oral anticoagulation (OAC) among patients with AF and risk of stroke
- Combined patient and provider level intervention

Randomized Patients
~40,000 patients

Randomized Control
Patients

Patient- + provider-
level intervention

Primary comparison: difference in the proportion of AF patients started on OAC over the course of the 12-month trial

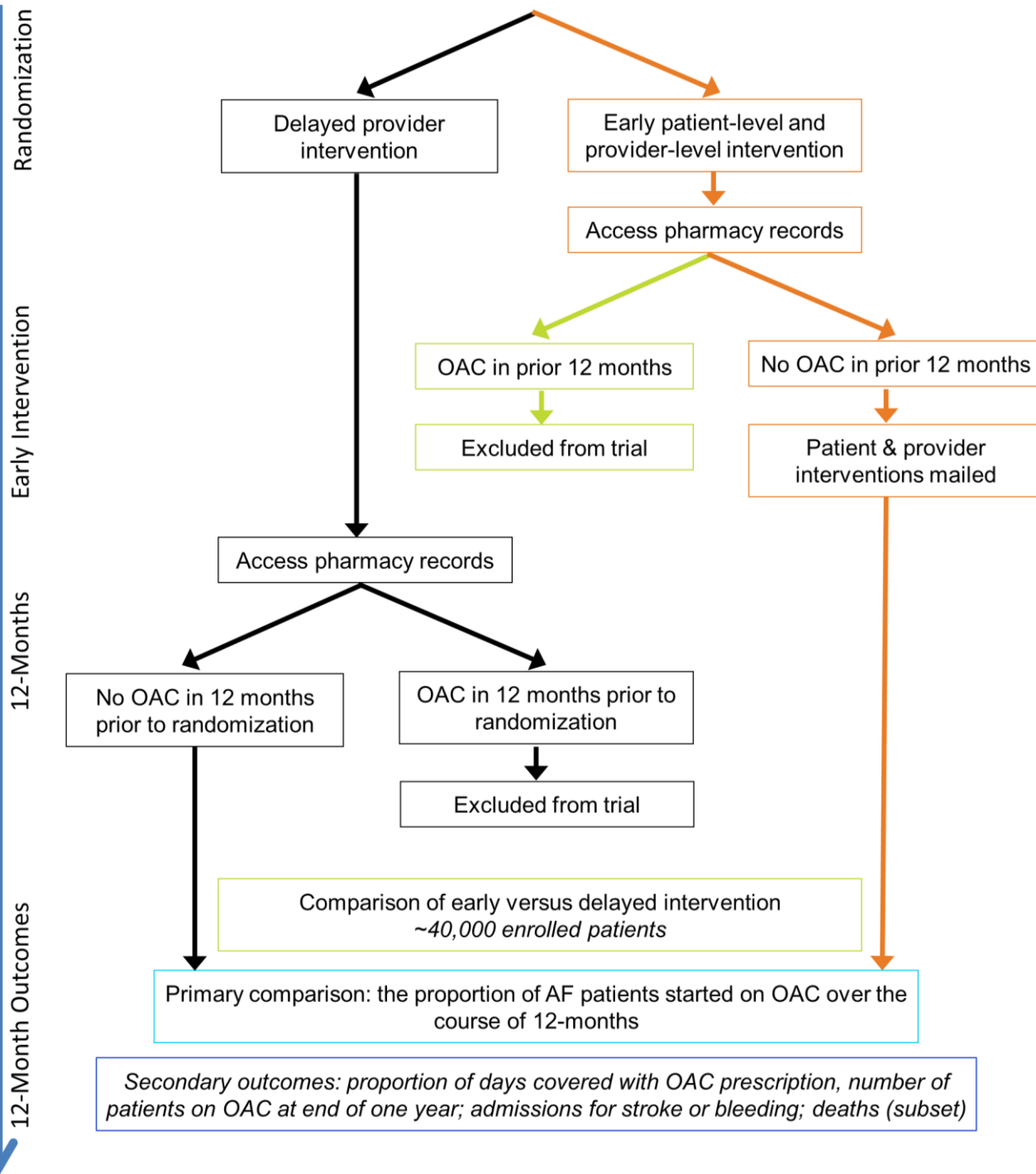
Secondary outcomes: proportion of days covered with OAC prescription, number of patients on OAC at end of one year; admissions for stroke or bleeding; deaths (subset)

Inclusion and Exclusion Criteria

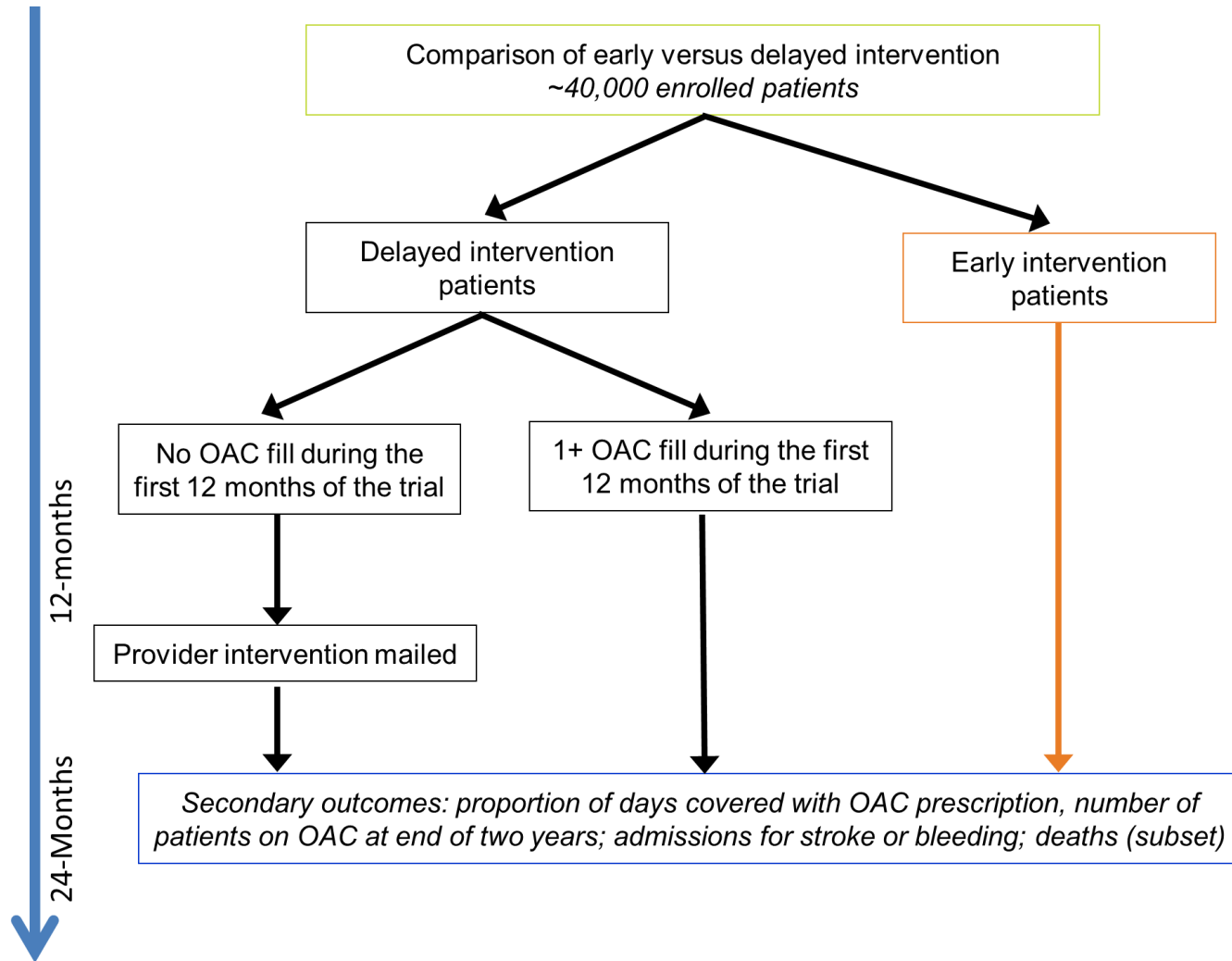
Patients

- Atrial fibrillation (AF) (two claims)
- CHADS-VASc ≥ 2
- No admission for bleeding in prior 6 months
- Not prescribed anticoagulant for prior 12 months
- Age ≥ 30 years

IMPACT-AFib



Second 12 Months of the Study



Intervention Materials for Patients

- Letter from health plan CMO, describes call to action
- Patient brochure – additional information on AF and OACs
- Patient pocket card - tool designed to facilitate a conversation between patient and provider

IMPACT AFib address
IMPACT AFib address

[Date]
[Member Name]
[Member Address]
[Member City, St, zip]

Dear [Member Name],

You can lower your risk of stroke.
Bring this letter and pocket card to your next doctor's appointment.

Talk to your doctor about the use of anticoagulant medications to prevent stroke.

According to our records, you may have been diagnosed with atrial fibrillation. We know that managing your health can be a challenge, and hope this information about how to lower your risk for stroke will help.

People who have the heartbeat irregularity known as "atrial fibrillation" are at an increased risk of having a stroke.

Please visit www.IMPACT-AFib.org, to learn more about atrial fibrillation, stroke risk, and anticoagulant medications. More information about the IMPACT-AFib initiative is available by calling [XXX-XXX-XXXX] or emailing [name@duke/healthplan.ext]

If you have questions about your benefits, call the number on the back of your health plan ID card.

Talk to your doctor about anticoagulant medications.

This packet contains information about the benefits of taking anticoagulant medications, also called blood thinners, to lower your risk of having a stroke. We recommend that you bring this information packet to your next doctor's appointment. We sent similar information to your doctor.

Anticoagulant medications may not be right for all patients, but they might be right for you. Even if you have talked about this with your doctor in the past, we encourage you to have another conversation about these medications. New anticoagulant medications are safe and effective options for many patients.

Should I be taking an anticoagulant medication?

Protecting your health information

We take protecting your health information seriously. None of your health information has been shared with other health organizations. Only you and your doctor were sent this information.

Sincerely,

Chief Medical Officer
Enclosures

If you have any questions, please contact [name] at [phone #] or [email]

Facts about atrial fibrillation, anticoagulant medication, and stroke

- Atrial fibrillation is an abnormal heartbeat in the top chambers of the heart that causes the chambers not to contract (squeeze) normally. This allows blood clots to form in the non-beating chambers.
- Atrial fibrillation increases the risk of a stroke because a blood clot may form in the heart, then travel to the brain causing a stroke.
- Anticoagulants, also known as blood thinners, are a type of medication that reduces the body's ability to form blood clots and decreases the chance of a clot forming in the top chambers of the heart.
- Aspirin is NOT effective in decreasing the risk of stroke.
- Most people with atrial fibrillation should take an anticoagulant medication to reduce their risk of a stroke.

This packet and the packet sent to your doctor are funded by the IMPACT-AFib Initiative. This U.S. Food and Drug Administration-sponsored research study is being conducted by [Health Plan], in collaboration with researchers at Harvard Pilgrim Health Care Institute and the Duke Clinical Research Institute. The goal of this initiative is to improve the use of oral anticoagulant medications for stroke prevention in patients with atrial fibrillation.

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Patient Information

You may have atrial fibrillation and may be at risk of a stroke.

Taking an anticoagulant medication may prevent a stroke.

Atrial fibrillation (AFib) is a heartbeat irregularity. If you have AFib your blood can pool, which increases the risk of a blood clot forming in your heart. The blood clot can travel to your brain, causing a stroke.

Anticoagulant medications, also called blood thinners, can prevent most strokes in patients with AFib. If you are not taking an anticoagulant medication, you may suffer a stroke that could have been prevented.

Please review this information and talk with your doctor to find out if you should be on an anticoagulant medication to prevent a stroke.



DEPARTMENT OF POPULATION MEDICINE
HARVARD
HARVARD PILGRIM
HEALTH CARE SYSTEM



How do I know if I'm at a high risk for stroke?

If you have AFib, you are at a higher risk of stroke.

You are at additional risk if you:

- Have high blood pressure
- Have high blood sugar
- Have weak heart function
- Have had a stroke or mini-stroke
- Have had a heart attack or a blocked vessel in your leg
- Are over 64 years old
- Are a woman

I have AFib only sometimes. Am I still at risk for a stroke?

Yes, the risk is similar whether your AFib is all the time, often, or only occasionally.

What is an anticoagulant?

Anticoagulants are medications that:

- Prevent blood clots
- Keep existing clots from moving

Examples include: Coumadin, Eliquis, Pradaxa, Savaysa, warfarin, and Xarelto.*

**The information in this mailing is NOT sponsored by any drug company.*

For more information, please visit impact-afib.org

If my doctor prescribes an anticoagulant, how should I take it?

- Take your medication exactly as directed by your doctor
- Take it at the same time each day
- If you forget to take your medication one day, take a dose as soon as possible on the same day
- Do not take a double dose the following day to "catch up"

Tell your doctor if you are pregnant or plan to become pregnant, are breastfeeding or plan to breastfeed, if you have liver or kidney problems, or are planning to have surgery.

Will anticoagulant medications prevent strokes?

- Anticoagulant medications reduce the risk of stroke by 70% in patients with atrial fibrillation.

What about aspirin?

- Aspirin is **not** an effective medication for decreasing the risk of stroke caused by atrial fibrillation.



How can I keep myself safe from bleeding and falls?

(As with other medications, there is a risk of experiencing side effects while taking anticoagulants. The main side effect is that you can bleed too easily.)

- Use a soft bristle toothbrush and waxed dental floss
- Use an electric razor to shave
- Be careful with sharp objects: toothpicks, knives, tools, scissors, etc.
- Wear shoes or non-skid slippers at all times
- Avoid nonsteroidal anti-inflammatory drugs like ibuprofen, naproxen, etc.
- Be careful when trimming toenails or callouses
- Avoid activities that increase risk of falls or involve hard contact, such as contact sports

Is it OK to take an anticoagulant medication if I have had bleeding? What if I fall?

- If you are at high risk for bleeding, the use of an anticoagulant medication depends on whether the benefit of preventing a stroke is more important than the risk of bleeding. Talk with your doctor about your risk.
- The benefits of preventing stroke outweigh the risk of bleeding for many people who might fall.

If I have bleeding, is there something to reverse the effect of anticoagulant medications? An antidote?

- Yes, there are antidotes for warfarin and Pradaxa
- Reversal drugs are in development for other anticoagulant medications
- There is no antidote for aspirin

Will an anticoagulant medicine interact with other medicines or foods?

- Warfarin interacts with foods that are high in vitamin K
 - You should ask your doctor or pharmacist for a list of food interactions
- Xarelto should be taken with food to help your body absorb the medicine

Talk with your doctor or pharmacist if you have questions about any medications or foods that might affect your anticoagulant medication, including nonprescription medicines, vitamins, and herbal supplements.

Am I at risk for stroke?

- The CHA₂DS₂-VASc calculates stroke risk for patients with atrial fibrillation.
- Complete the following CHA₂DS₂-VASc calculator to determine your personal risk.
- If you have AFib and a CHA₂DS₂-VASc score of 2 or greater, you have an increased risk of stroke.



CHA ₂ DS ₂ -VASc RISK SCORE	If yes, add points
Do you have congestive heart failure?	+1
Do you have high blood pressure or are you taking blood pressure medication(s)?	+1
Are you between 65–74 years of age?	+1
Are you 75 years old or older?	+2
Do you have diabetes?	+1
Have you ever had a stroke or TIA (mini-stroke)	+2
Have you ever had vascular disease (bypass surgery, heart attack, peripheral artery disease, or aortic plaque)?	+1
Are you female?	+1
MY TOTAL	



IMPACT-AFib

Dear Doctor,

As you know, patients who have atrial fibrillation and a CHA₂DS₂-VASc score of 2 or more are at risk of a stroke and would likely benefit from taking an anticoagulant medication.

The CHA₂DS₂-VASc calculator shows a patient's risk of a stroke. The score helps determine whether a patient would benefit from an anticoagulant.

CHA₂DS₂-VASc CALCULATOR

	Risk factor	If patient has risk factor, add points
C	Congestive Heart Failure	+1
H	High Blood Pressure (hypertension, including normal blood pressure on blood pressure medications)	+1
A₂	Age 75 years old or older	+2
D	Diabetes	+1
S₂	Stroke or TIA (mini-stroke)	+2
V	Vascular Disease (prior bypass surgery, heart attack peripheral artery disease, or aortic plaque)	+1
A	Age 65-74 years	+1
Sc	Sex Category: Female sex	+1
	TOTAL	

Patients with a score of 2 or greater are at high risk for stroke. Strokes may be prevented with an anticoagulant medication.

Is IMPACT-AFib new to you? For more information, please visit www.Impact-AFib.org.



IMPACT-AFib

Dear Patient,

Talk with your doctor to find out if taking an anticoagulant medication is right for you. Anticoagulant medications prevent blood clots and are sometimes called blood thinners.

Not sure where to start? Here is a way to start the conversation with your doctor:
I received this letter, information sheet, and card in the mail from my health plan. My health plan suggests that I talk with my physician about taking an anticoagulant to help prevent a stroke.

QUESTIONS TO ASK YOUR DOCTOR:

1. Do I have atrial fibrillation?
2. What are my risk factors for stroke?
3. Based on my CHA₂DS₂-VASc score from the other side of this card, should I be taking an anticoagulant medication?
 - If no, why not?
 - If yes, what kind of anticoagulant would work best for me?
4. Is aspirin good for me to take? The information I received said it was not effective in preventing stroke caused by AFib.
5. Should I be concerned with bleeding if I take an anticoagulant?

Most anticoagulant medications are covered by your health plan. Check with your health plan's information or call the phone number on your health plan card to determine which of the following drugs are covered: Coumadin, Eliquis, Pradaxa, Savaysa, warfarin, and Xarelto.*

For additional information, please visit www.Impact-AFib.org.

*This mailing is NOT sponsored by any drug company.



Intervention Materials for Providers

- Provider letter - sent from health plan CMO, describes call to action
- Response mailer - way for providers to share feedback
- Provider enclosure – myths and facts on use of OACs

Dear Provider:

As part of our effort to improve the use of oral anticoagulant medications for stroke prevention in patients with atrial fibrillation (AFib), we would like to introduce you to the IMPACT-AFib initiative. The objective of the IMPACT-AFib initiative is to increase awareness and education among patients and you. This FDA-sponsored initiative is being conducted by (HEALTH PLAN) in collaboration with researchers at Harvard and Duke.

Educational materials were sent to patient(s) who appear to have atrial fibrillation, have high stroke risk (CHA₂DS₂-VASC score ≥ 2), and have no record available to us of having filled a prescription for an anticoagulant in the past year. Please see the next page for a list of patients who received these materials.

Facts about atrial fibrillation

- Patients with AFib have a five times higher stroke risk relative to patients without AFib (*Circulation* 2011; 123(10):269–367)
- More than two-thirds of strokes caused by AFib are preventable with anticoagulation (*Annals of internal medicine* 146.12 (2007): 857–867)
- 50% of patients with AFib and high stroke risk have not filled an anticoagulant prescription (*Circulation* 2014; 129 (15), 1568–1576)

Common misperceptions about stroke prevention

Aspirin is good enough

- Aspirin reduces stroke by $< 20\%$, if at all, compared with 70% reduction with anticoagulation; therefore, aspirin is not sufficiently effective for stroke prevention¹

Patients with AFib are at greater risk of bleeding than stroke

- 30% of elderly patients fall in a year, but a patient would need to fall nearly every day before the risk of intracranial bleeding outweighs the benefits of anticoagulants.²
- The risk of recurrent GI bleeding averages 1.2% per year, but would have to exceed 10% before the risk of GI bleeding outweighs the benefit of anticoagulants.³

There are appropriate reasons for patients to not take an anticoagulant, including pregnancy and history of intracranial hemorrhage. A response mailer is enclosed for you to share these reasons, should they exist for your patient(s).

¹ European Heart Journal 2015; 36: 653-656 ² Arch Intern Med 1999;159:677-685 ³ Arch Intern Med 2002;162:541-550

What should you do?

Please review and discuss anticoagulation and stroke risk with your patient(s) at their next visit.

For Health Plan pharmacy coverage policy, go to www.HealthPlan.com. You can visit www.Impact-AFib.org or call xxx-xxx-xxxx, or email [name@duke/healthplan.ext] for more information about this initiative.

If you have questions or concerns, please contact us at MD@HealthPlan.com or xxx-xxx-xxxx.

Enclosed is an information card and the patient information.

Sincerely,

Chief Medical Officer
Health Plan

[illegible]

This packet and the packet sent to your patient(s) are funded by the IMPACT-AFib initiative. This U.S. Food and Drug Administration-sponsored research study is being conducted by (Health Plan), in collaboration with researchers at Harvard Pilgrim Health Care Institute and the Duke Clinical Research Institute. The goal of this initiative is to improve the use of oral anticoagulant medications for stroke prevention in patients with atrial fibrillation.

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If we have incorrectly identified a patient as being able to benefit from taking an oral anticoagulant, we would like to hear from you.

Please complete the information below, then seal and return this mailer.

IMPACT-AFib

fold here

IMPACT-AFib

Patient name: _____

Date of Birth: ____ / ____ / 19____
Month Day Year

Should not be prescribed an oral anticoagulant because— *(please check all that apply)*

- ☐ He/she is not my patient and/or I am not the prescribing physician
- ☐ Patient does not have atrial fibrillation
- ☐ Patient already takes an anticoagulant
- ☐ An anticoagulant has already been prescribed
- ☐ Very high risk of major/life-threatening bleeding
- ☐ Unable to tolerate warfarin
- ☐ Unable to afford a non-vitamin K oral anticoagulant
- ☐ Patient decision after thorough review of risks, benefits, concerns
- ☐ Other (please explain): _____

IMPACT-AFib

Patients with atrial fibrillation (AFib) are at five times higher risk of stroke (*Circulation* 2011;123(10):e269–367)

- Two-thirds of strokes in patients with atrial fibrillation are preventable with anticoagulation, as recommended in clinical practice guidelines (*Annals of internal medicine* 146.12 (2007): 857–867)
- Despite this guideline, at least 50% of patients with a CHA₂DS₂-VASc score of 2 or higher are not being prescribed an oral anticoagulant (*Circulation* 2014; 129 (15), 1568–1576)

You can change these statistics by—

- Educating all of your patients with AFib about anticoagulant use
- Stopping the use of aspirin as an anticoagulant

For more information visit
www.IMPACT-AFib.org

IMPACT-AFib

Patients with atrial fibrillation are having PREVENTABLE strokes because they are not taking oral anticoagulants.

Myth vs. Reality

Myth: Aspirin prevents stroke and is safe

Reality: Aspirin is neither safe nor effective (*Eur Heart J* 2015;36:653-6)

Myth: It is risky to resume oral anticoagulation therapy in the months after bleeding

Reality: Benefits generally outweigh risks (*Arch Intern Med* 2002;162:541-550)

Myth: It is risky to prescribe oral anticoagulants to patients who are at risk of falling

Reality: "... persons taking warfarin must fall about 295 times in 1 year for warfarin to not be the optimal therapy." (*Arch Intern Med* 1999;159:677-685)

Myth: Patients who don't tolerate warfarin won't tolerate any oral anticoagulant

Reality: Most patients tolerate novel oral anticoagulants (*N Engl J Med* 2011;364:806-17)

Myth: Patients with paroxysmal AFib are low risk of stroke

Reality: Risk is about the same for paroxysmal or permanent AFib, indicating need for anticoagulation (*Circulation* 2014;130: e199-e267)

Myth: There is no antidote for novel oral anticoagulants

Reality: An injectable reversal agent (Praxbind) is available for the novel oral anticoagulant Pradaxa (dabigatran). (*N Engl J Med.* 2015;373:511-20)

Challenges along the way

- Unit of randomization
- Medicare Advantage member enrollment
- Similar outreach initiatives at health plans
- Turnover of population and timing of mailing
- Waiver of consent
- Need for Independent Advisory Committee
- Distributed data for analysis

Thank you!

Back-up Slides



Leveraging Distributed Database

Medical Product Safety

Surveillance

FDA



Sentinel
Coordinating
Center

Coordinating
Center(s)



Sponsor(s)

Medical Product Safety

Coordinating
Center(s)



Sponsor(s)

Clinical Research

DISTRIBUTED NETWORK GOVERNANCE

Payers

- Public
- Private

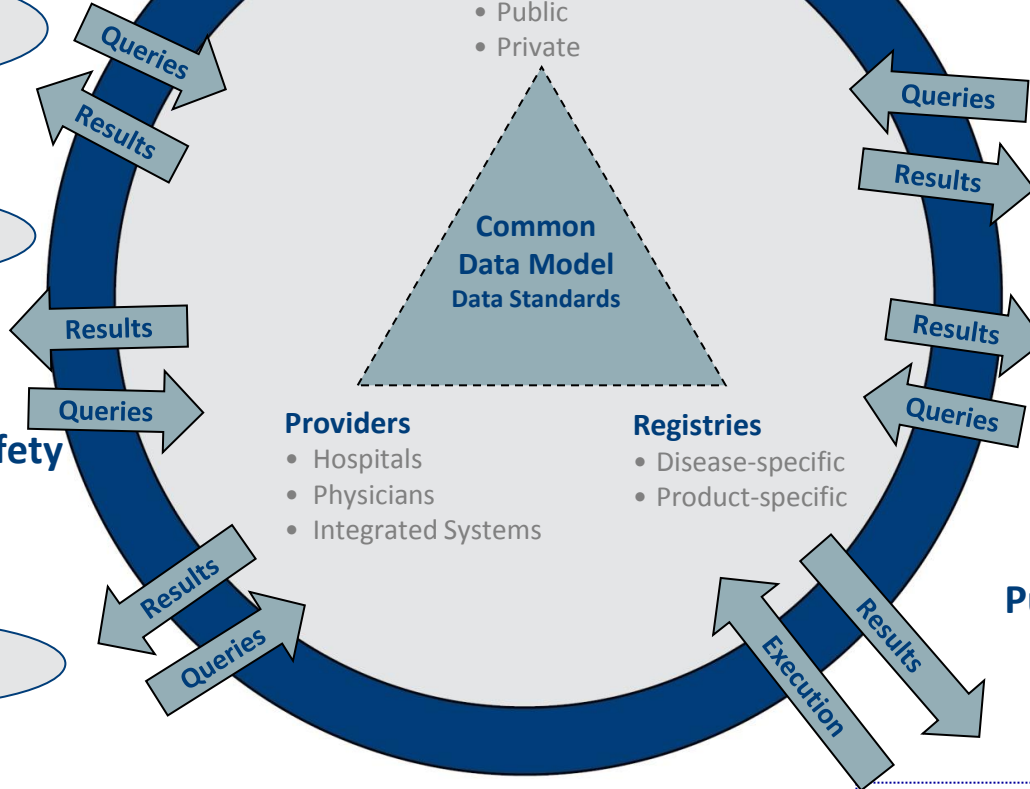
Common
Data Model
Data Standards

Providers

- Hospitals
- Physicians
- Integrated Systems

Registries

- Disease-specific
- Product-specific



Quality of Care

Sponsor(s)



Coordinating
Center(s)

Coordinating
Center(s)



Sponsor(s)

Public Health Surveillance

Randomized Clinical Trials

Sentinel Initiative

- Sentinel Distributed Database
 - Routinely collected health data (health plan enrollment, claims, pharmacy dispensing, etc.)
- Sentinel System
 - Uses Sentinel Distributed Database
 - Operates under FDA's public health authority
- FDA-Catalyst
 - Directly contacts health plan members/providers or changes care (request more information, randomize care, etc.). May also use the Sentinel Distributed Database.
 - Common Rule applies – IRB oversight

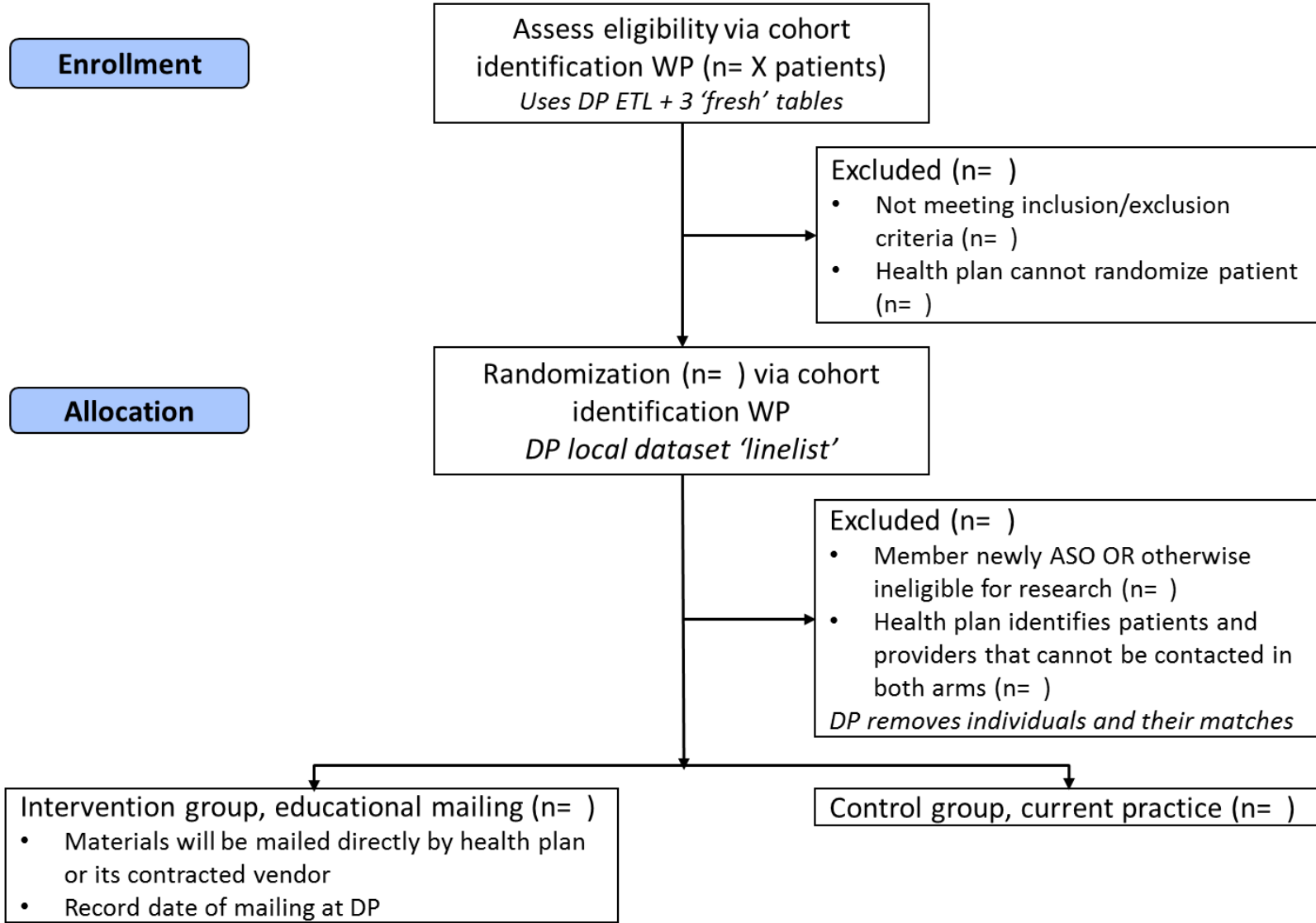
Data Partners' Trial Experience

- Nearly all had experience in randomized trials
- Experience contacting patients and providers via various methods
- ~Half had internal research departments

Data Partners' Trial Interest

- 3 primary factors:
 - Topic must align with organizational or provider priorities
 - Could not compete for resources
 - Adequate financial support
- 7 interested in future trials

Flow Diagram



Inclusion Criteria

- Adult ≥ 30 years old
- Medical & pharmacy coverage for ≥ 365 days
- ≥ 2 atrial fibrillation diagnosis codes with 1 in the last year
- No OAC fill within the previous 12 months
- CHA₂DS₂-VASc score ≥ 2

Exclusion Criteria

- Any OAC dispensing within the last year (or ≥ 4 INRs)
- Conditions other than AF that require anticoagulation
 - Mechanical prosthetic valve, DVT, pulmonary embolism
- Any history of intracranial hemorrhage
- Bleeding related hospitalization in the last 6 months
- Current pregnancy
- P2Y12 inhibitor treatment, e.g., clopidogrel within 90 days

Sample size estimate using Sentinel tools

- Run March 2016 at 5 Data Partners
- Overview:
 - Identify patients with AF in 2013 and no prior OAC use
 - Estimate CHA₂DS₂-VASc scores
 - Assess subsequent treatment with OAC in 1 year follow-up
 - Assess rates of stroke and bleeding among those treated and not
- 38,759 patients identified