

# IMPACT-AFib: An 80,000 Person Randomized Trial Using the FDA Sentinel System Platform

*January 5, 2018 – NIH Collaboratory Grand Rounds*

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# Outline

- FDA's Sentinel System, FDA-Catalyst in brief
- The public health importance of atrial fibrillation
- IMPACT-AFib – trial design
- Current status and baseline data
- Lessons learned

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# Sentinel is a National Medical Product Monitoring System

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**ABOUT**

- Background
- Coordinating Center
- Privacy and Security
- The Sentinel System Story
- Reagan-Udall Foundation and IMEDS



**MEDICAL PRODUCT ASSESSMENTS**

- Active Risk Identification and Analysis System
- Ongoing ARIA Assessments
- Assessments of Drugs
- Assessments of Vaccines, Blood, & Biologics
- FDA-Catalyst

### Latest Postings

**SPOTLIGHT**

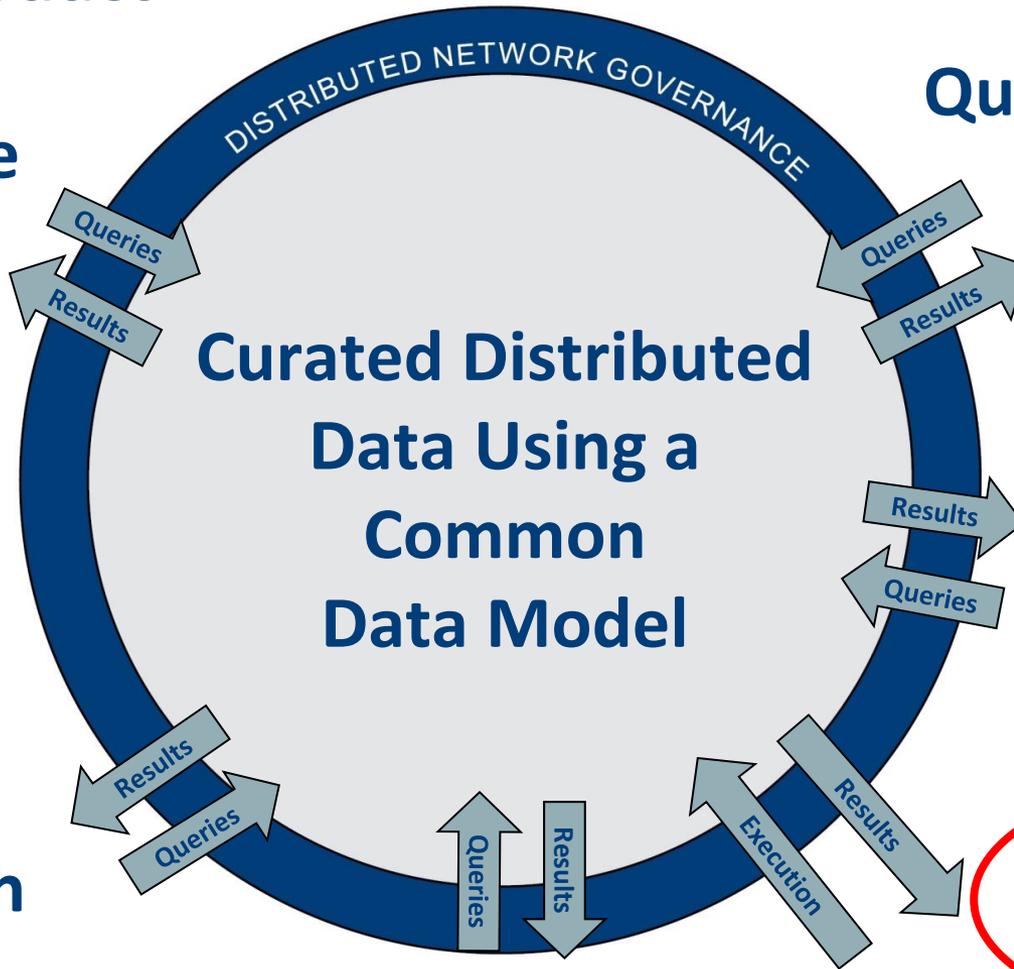
- **CDER Conversation: The FDA's Sentinel Initiative**  
*Mon, 11/27/2017*

**PUBLICATIONS AND PRESENTATIONS**

- **Development of Metrics to Assess Appropriate Prescribing of Opioids in the Mini-Sentinel Distributed Database (MSDD)**  
*Mon, 11/20/2017*



Medical Product  
Safety  
Surveillance



Quality of Care

Public Health Surveillance

Randomized Clinical Trials

Comparative Effectiveness

Clinical Research



**MINI-SENTINEL and CLINICAL TRIALS TRANSFORMATION INITIATIVE**  
**DEVELOPING APPROACHES TO CONDUCTING RANDOMIZED TRIALS USING THE**  
**MINI-SENTINEL DISTRIBUTED DATABASE**

**February 28, 2014**

# FDA-Catalyst: IMPACT-AFib randomized trial

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

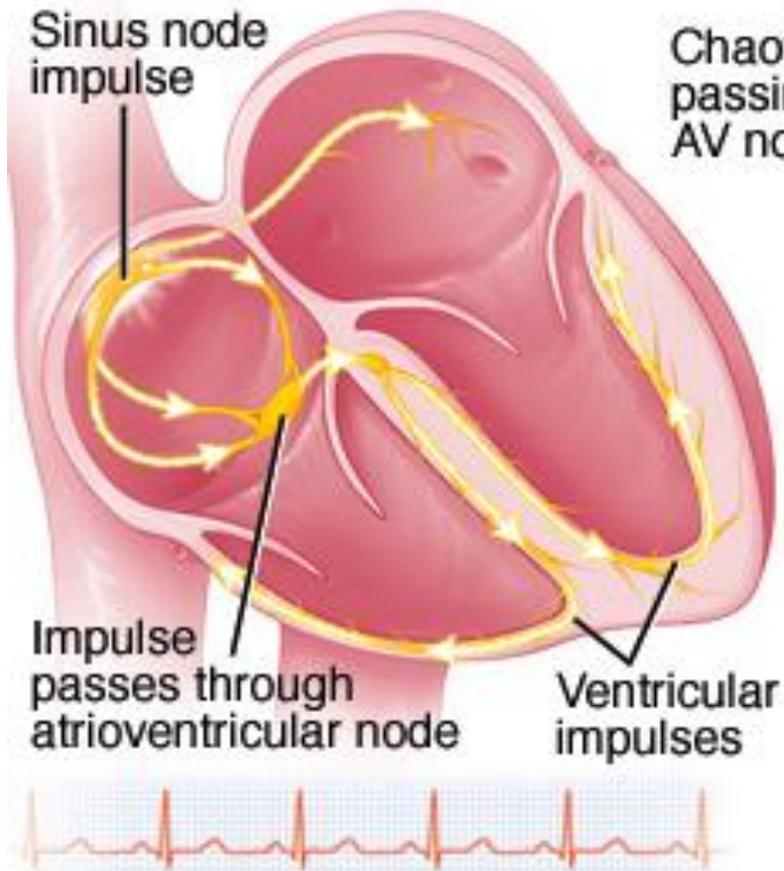
- Direct mailer to health plan members with AFib, high risk for stroke and no oral anticoagulant (OAC) treatment, and to their providers, to encourage consideration of OACs

# Outline

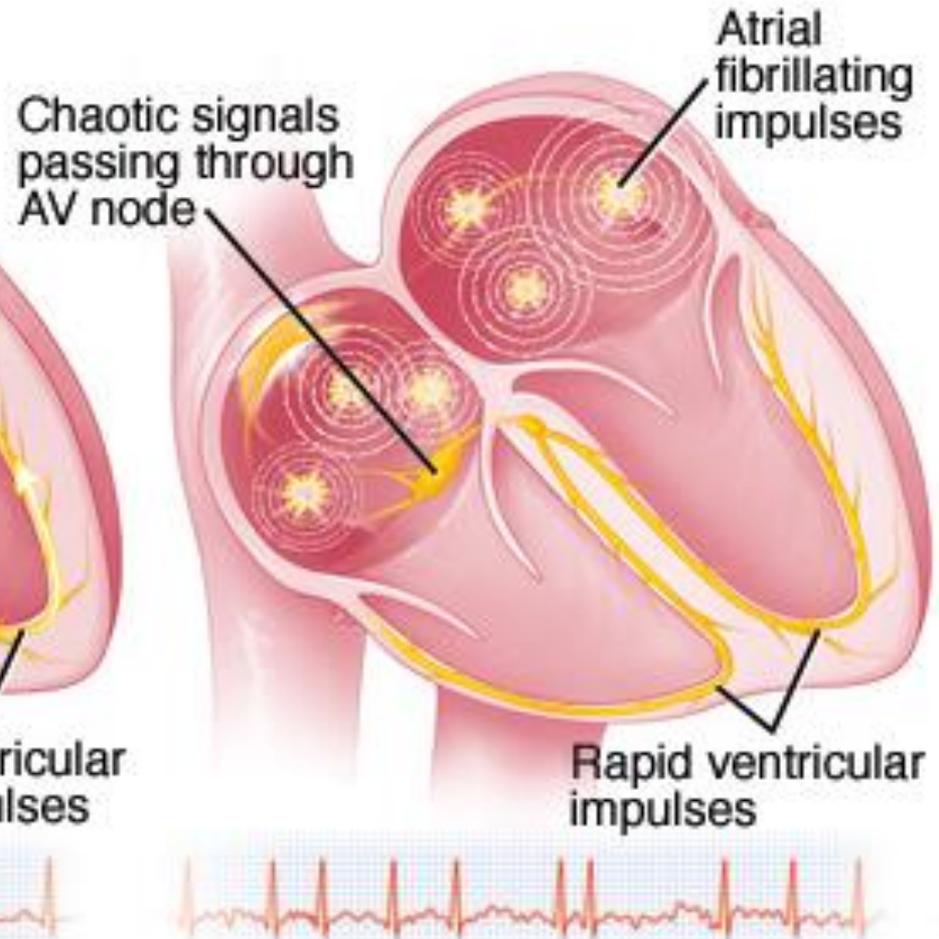
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# What is Atrial Fibrillation?

Normal heart



Heart with atrial fibrillation



# Atrial fibrillation, a common and important problem

- Over 5 million people in the United States have AFib
  - 2% of people younger than age 65
  - 9% of people aged  $\geq 65$  years
- 5 fold increase in risk of stroke
  - 15-20% of ischemic strokes are due to AFib
- Contributes to 130,000 deaths
- \$6 billion added annual cost (\$8,700 per person with AFib)

[www.cdc.gov/dhdsp/data\\_statistics/fact\\_sheets/fs\\_atrial\\_fibrillation.htm](http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm)

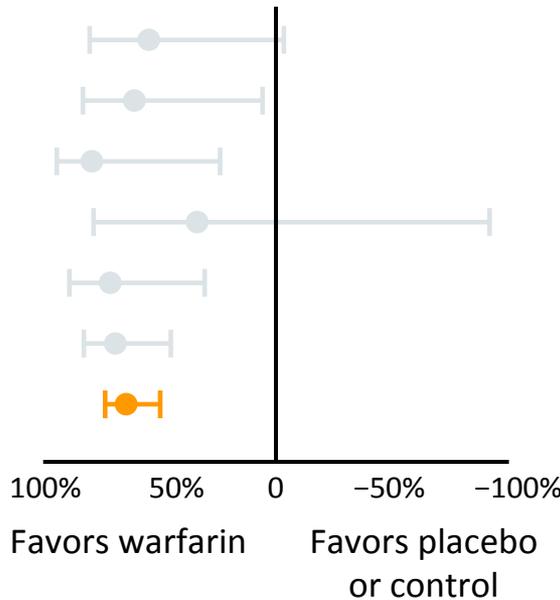
# Anticoagulation Prevents a Majority of Strokes

Warfarin compared to control or placebo

Relative Risk Reduction (95% CI)

Trial

- AFASAK I (1990)
- SPAF I (1991)
- BAATAF (1990)
- CAFA (1991)
- SPINAF (1992)
- EAFT (1993)
- Combined



**RRR 64%**

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

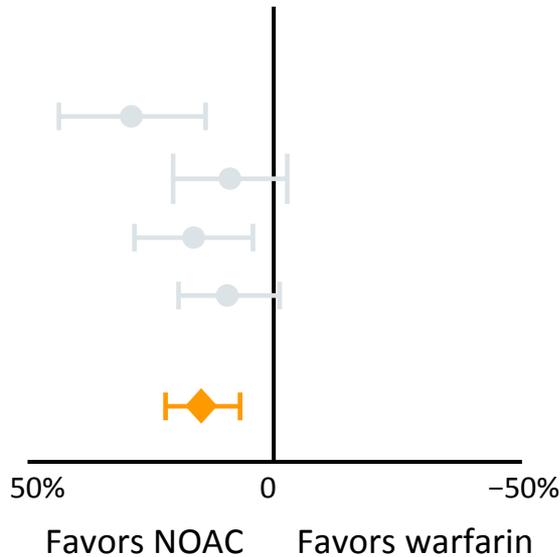
Hart R, et al. Ann Intern Med. 2007;146:857-867.

NOAC compared to warfarin

Relative Risk Reduction (95% CI)

Trial

- RE-LY (2009)
- ROCKET AF (2011)
- ARISTOTLE (2011)
- ENGAGE AF-TIMI 48 (2013)
- Combined



**RRR 19%**

Non-vitamin K antagonist Oral Anticoagulant (NOAC) vs. Warfarin

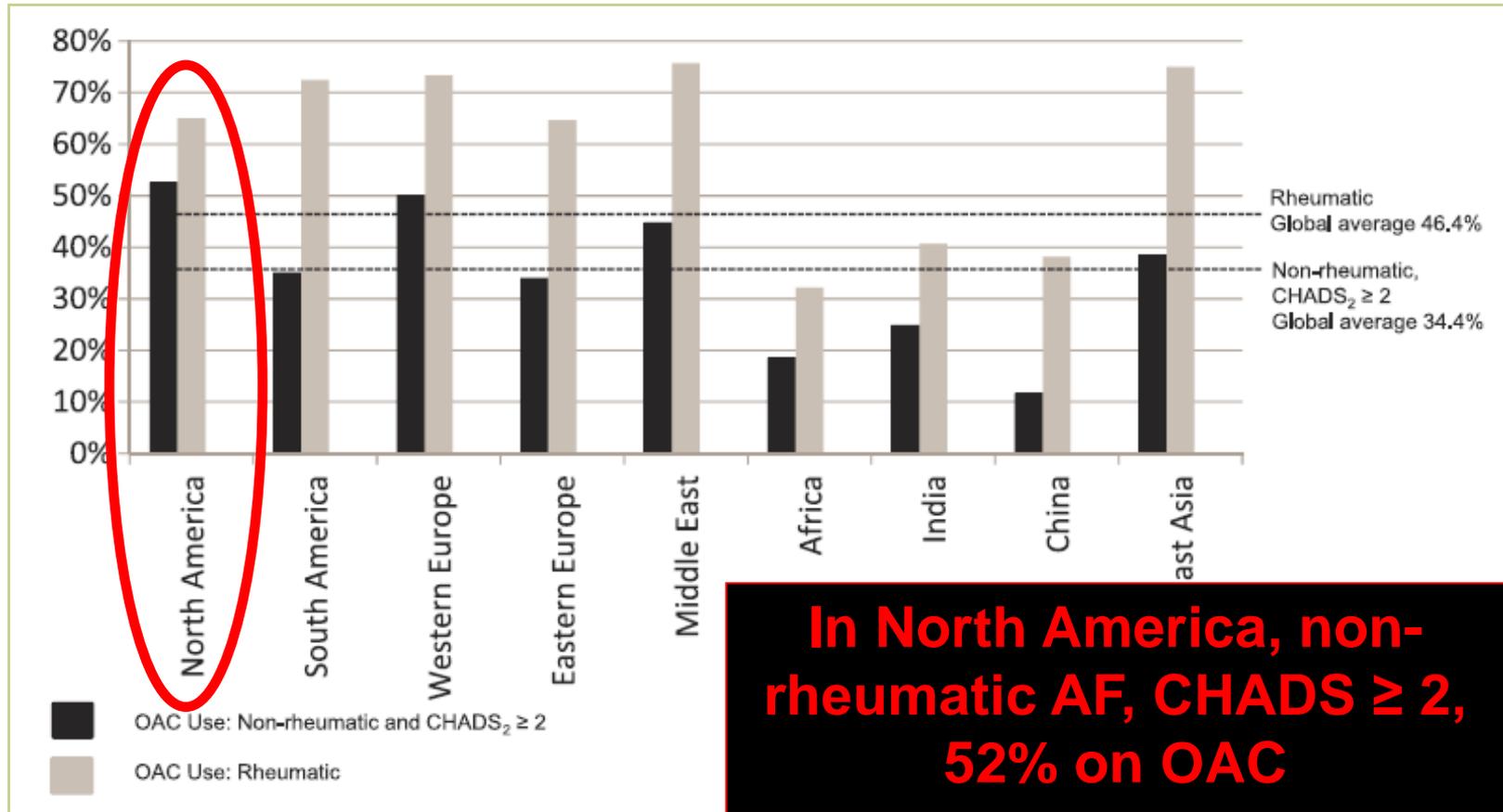
(4 trials, total n=71,683)

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

## CHA<sub>2</sub>DS<sub>2</sub>-VASC CALCULATOR

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

# Anticoagulation Use in RE-LY Registry



## Rates of Anticoagulation for Atrial Fibrillation – Preliminary Sentinel Data

Criteria	Patients
Potentially eligible members (Aetna, Humana, Harvard Pilgrim)	16.2 million
Patients with >1 AF diagnosis	231,696 (1.4% of all members)
AF pts with CHA <sub>2</sub> DS <sub>2</sub> -VASc ≥ 2	201,882 (87% of AF patients)
Patients with at least one oral anticoagulation fill	105,256 (52% of AF patients with CHA <sub>2</sub> DS <sub>2</sub> -VASc ≥ 2)
Proportion of days covered by anticoagulation in AF patients	32%

# Interventions (including patient education) can be effective at increasing the proportion of patients with Afib and risk for stroke who are treated with oral anticoagulation

A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial



*Dragos Vinereanu, Renato D Lopes, M Cecilia Bahit, Denis Xavier, Jie Jiang, Hussein R Al-Khalidi, Wensheng He, Ying Xian, Andrea O Ciobanu, Deepak Y Kamath, Kathleen A Fox, Meena P Rao, Sean D Pokorney, Otavio Berwanger, Carlos Tajer, Pedro G M de Barros e Silva, Mayme L Roettig, Yong Huo, Christopher B Granger, on behalf of the IMPACT-AF investigators\**

*The Lancet (published online August 28 2017)*

# 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 are identifiable and major outcomes measurable using Sentinel Distributed Database

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- FDA's Sentinel System, FDA-Catalyst in brief
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# IMPACT-Afib Workgroup



DEPARTMENT OF POPULATION MEDICINE



HARVARD  
MEDICAL SCHOOL



Harvard Pilgrim  
Health Care Institute



Patient representative



**U.S. FOOD & DRUG**  
ADMINISTRATION



CLINICAL  
TRIALS  
TRANSFORMATION  
INITIATIVE

**IMPACT-AFib**

# Inclusion Criteria

- $\geq 30$  years old
- Medical & pharmacy coverage for  $\geq 365$  days
- $\geq 2$  atrial fibrillation diagnosis codes with 1 in the last year
- No OAC fill within the previous 12 months
- $\text{CHA}_2\text{DS}_2\text{-VASc}$  score  $\geq 2$

# Exclusion Criteria

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

**Patients with AFib, CHADS-VASc  $\geq 2$**

**RANDOMIZE**

Randomization

Early Intervention

12-months

Usual Care and Delayed  
Provider intervention

Early Patient-level and  
Provider-level intervention

Access Pharmacy Records

OAC in prior 12 months

No OAC in prior 12 months

Excluded

Intervention Mailed

**Primary outcome:** Proportion of AFib 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 TIA
- Admissions for stroke
- Admissions for bleeding
- Deaths (subset)

# Intervention Materials

## PATIENTS

- Letter from health plan
- Patient brochure – information on AF and OACs
- Patient pocket card – designed to facilitate conversation between patient and provider

## PROVIDERS

- Letter from health plan
- Provider enclosure – myths and facts on OACs
- Response mailer – providers to share feedback

IMPACT AFib address  
IMPACT AFib address

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

Dear [Member Name],

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](http://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.



### 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]

# MEMBER LETTER

### 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.

*Disclaimer: Lorem ipsum dolor sit amet, est donec semper pharetra orci, mus ac nec ultricies id, dictum condimentum massa non dapibus. In viteae vestibulum purus facilisis, amet ornare nec quis nec.*



PROVIDER LETTER

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):e269-367)
• 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
Patients with AFib are at greater risk of bleeding than stroke
Aspirin reduces stroke by < 20%, if at all, compared with 70% reduction with anticoagulation; therefore, aspirin is not sufficiently effective for stroke prevention1
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

Table with 2 columns: Name, Date of Birth. Multiple empty rows for patient information.

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.

Disclaimer: Lorem ipsum dolor sit amet, est donec semper pharetra orci, mus ac nec ultricies id, dictum condimentum massa non dapibus. In vitae vestibulum purus facilisis, amet ornare nec quis nec.

## PROVIDER RESPONSE

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

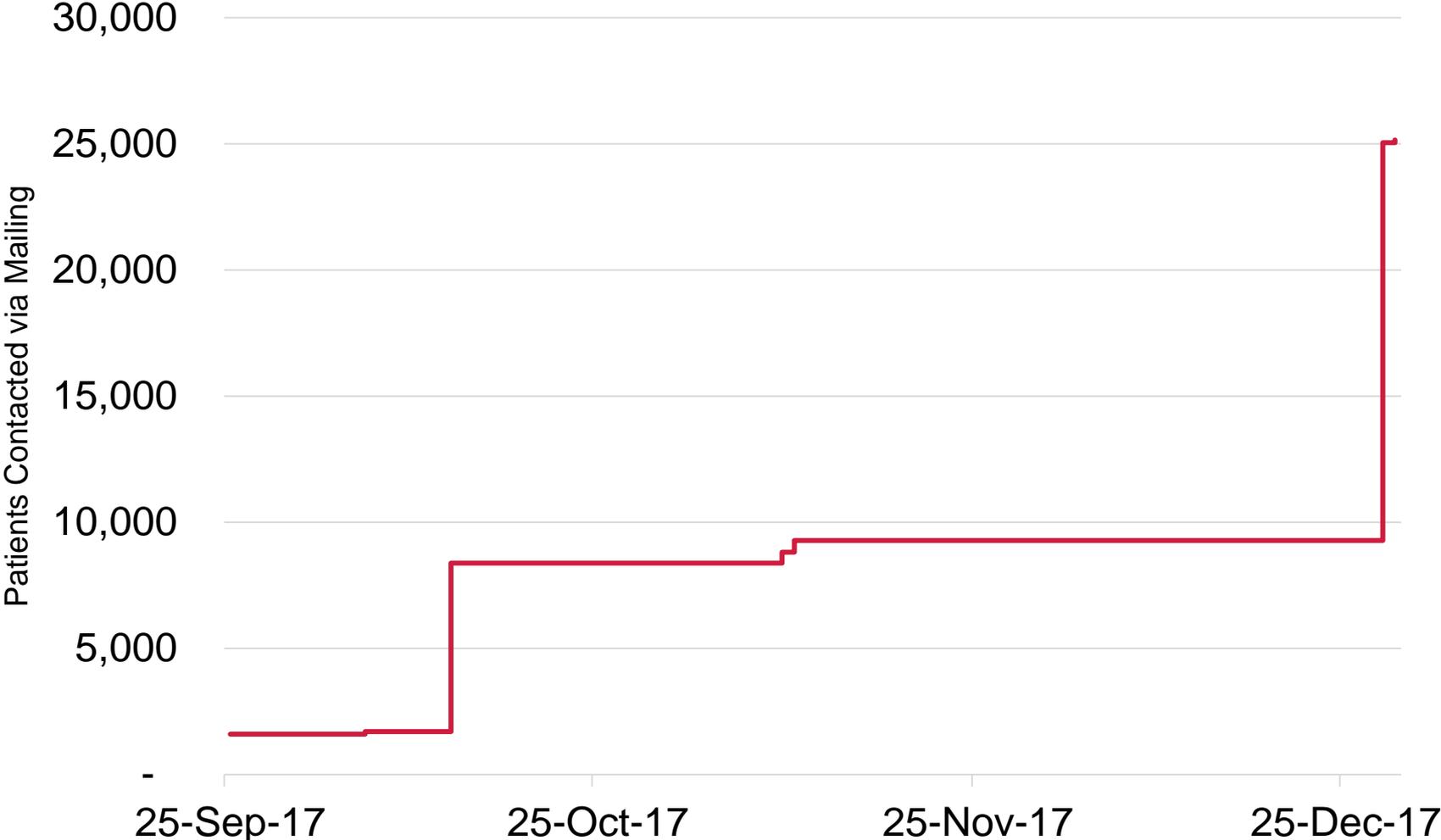
Should not be prescribed an oral anticoagulant because— *(please check all that apply)*

- 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): \_\_\_\_\_

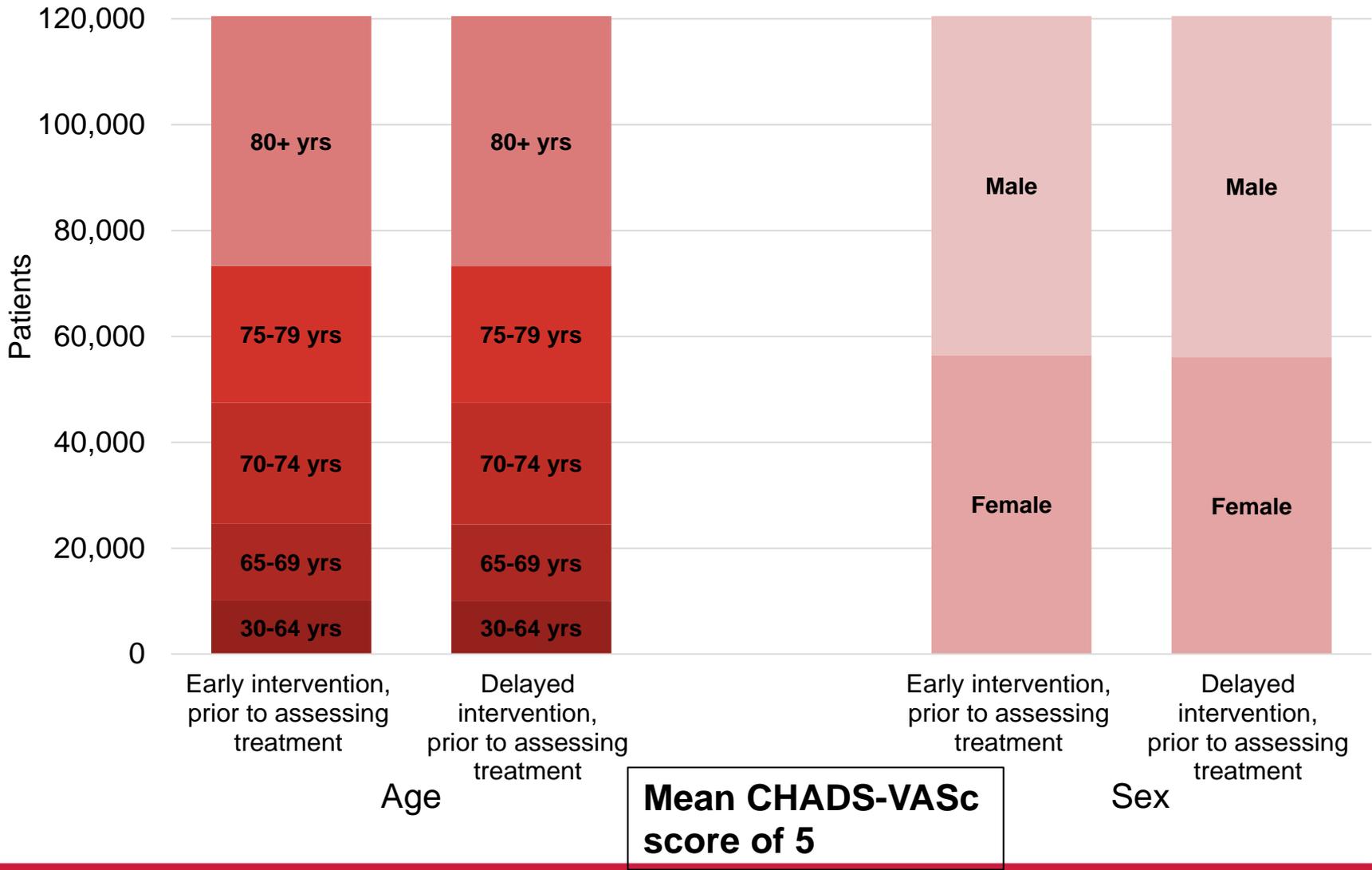
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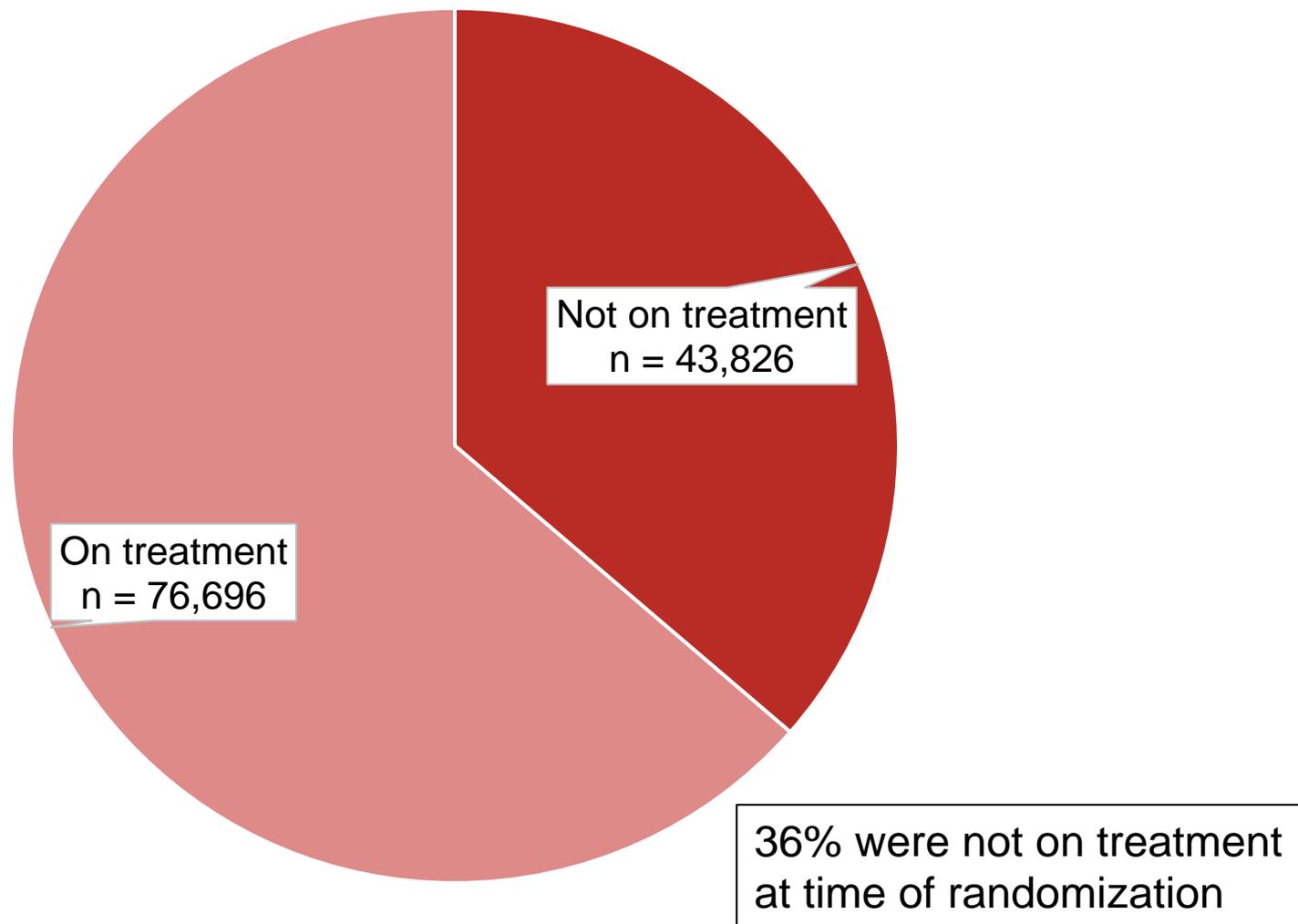
# Early Intervention Launch



# Age and Sex Distribution by Group



## Members in Early Intervention Arm



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# Good practices (lessons not to forget)

<b>Early project preparation</b>	<ul style="list-style-type: none"><li>• Involvement of health plans from the very beginning</li><li>• Need for buy in from clinical leadership</li><li>• Adequate funding / resources for all sites from the start</li></ul>
<b>Patient engagement</b>	<ul style="list-style-type: none"><li>• Patient advocate on project team - guidance on intervention design as well as cohort inclusion (e.g. patients <math>\geq 30</math>)</li><li>• Patient advocate on project as well as patient and provider focus groups not planned from the start but provided key information for intervention materials (e.g. response mailer)</li></ul>
<b>IRB approach</b>	<ul style="list-style-type: none"><li>• Single IRB facilitates process across multiple institutions</li><li>• Commercial IRB most efficient (meet more regularly, have more streamlined processes in place, have cross-jurisdictional expertise)</li><li>• Waiver of consent obtained</li></ul>
<b>Timing of trial start and mailings</b>	<ul style="list-style-type: none"><li>• Annual open enrollment and other key points in time had to be accommodated when planning for trial execution</li></ul>

# Lessons learned (1)

<b>Similar initiatives at health plans</b>	<ul style="list-style-type: none"><li>• At 2 health plans: non-research initiatives underway include written outreach to members with AF at high risk of stroke</li></ul>
<b>Trial design and protocol</b>	<ul style="list-style-type: none"><li>• Many iterations necessary to finalize protocol due to need for agreement by clinical management teams from all sites</li></ul>
<b>Intervention materials</b>	<ul style="list-style-type: none"><li>• Branding, logos, details of materials required substantial discussion, lengthy review processes at each health plan</li></ul>
<b>Medicare/Medicaid beneficiaries participants</b>	<ul style="list-style-type: none"><li>• Health plan concerns re inclusion of members with Medicare Advantage (complaint from such members could impact Star ratings); letter of support was obtained from the CMS</li></ul>

## Lessons learned (2)

<b>Code list review</b>	<ul style="list-style-type: none"><li>• Clinician reviewed thousands of codes (ICD-9, 10) for elements of CHADS-VASC score and other conditions</li></ul>
<b>Underestim. of sample size</b>	<ul style="list-style-type: none"><li>• Combination of changes in definitions and limitations of approach yielded underestimate</li><li>• Sample size and budget were based on underestimate</li></ul>
<b>“Facility” as provider</b>	<ul style="list-style-type: none"><li>• 20-40% of all providers identified by workplan were actually facilities</li></ul>
<b>Members whose AF dx codes likely rule outs</b>	<ul style="list-style-type: none"><li>• Evident after follow-up on initial calls received to project phone line</li><li>• Can Common Data Model help with this?</li></ul>
<b>Ethics issues</b>	<ul style="list-style-type: none"><li>• Questions raised about delaying contact of the usual care group</li></ul>

# Acknowledgements

- **Aetna:** Cheryl Walraven, Annemarie Kline, Daniel Knecht
- **Clinical Trials Transformation Initiative:** Jennifer Goldsack
- **Duke Clinical Research Institute:** Hussein Al-Khalidi, Wensheng He, Emily O'Brien, Jennifer Rymer, Sana Al-Khatib
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- **HealthCore:** Kevin Haynes, Lauren Parlett
- **Humana:** Vinit Nair, Thomas Harkins, Yunping Zhou
- **Optum:** Nancy Lin
- **Patient Representative:** Debbe McCall
- **U.S Food & Drug Administration:** Jacqueline Corrigan-Curay, Dianne Paraoan, David Martin, Melissa Robb, Patrick Archdeacon

**Thank you!**



**IMPACT-AFib**

# EXTRA SLIDES

		All Randomized with AFib		Delayed intervention, prior to assessing treatment		Early intervention, prior to assessing treatment		Early intervention, not on treatment	
<b>Totals</b>		241,044		120,522		120,522		43,826	
		No.	%	No.	%	No.	%	No.	%
<b>Age</b>	<b>30-64</b>	20,175	8.4	10,085	8.4	10,090	8.4	3,525	8.0
	<b>65-69</b>	28,936	12	14,424	12	14,512	12	5,286	12.1
	<b>70-74</b>	45,838	19	22,948	19	22,890	19	8,057	18.4
	<b>75-79</b>	51,636	21.4	25,817	21.4	25,819	21.4	8,691	19.8
	<b>80+</b>	94,459	39.2	47,248	39.2	47,211	39.2	18,267	41.7
<b>Female</b>		112,500	46.7	56,085	46.5	56,415	46.8	21,171	48.3
<b>CHADS-VASC</b>	<b>Mean (SD)</b>	5 (1.7)		5 (1.6)		5 (1.7)		5 (1.7)	NA

## 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 CHA<sub>2</sub>DS<sub>2</sub>-VASc calculates stroke risk for patients with atrial fibrillation.
- Complete the following CHA<sub>2</sub>DS<sub>2</sub>-VASc calculator to determine your personal risk.
- If you have AFib and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or greater, you have an increased risk of stroke.



CHA <sub>2</sub> DS <sub>2</sub> -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
<b>MY TOTAL</b>	

# 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 CHA<sub>2</sub>DS<sub>2</sub>-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](http://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)

# Reasons for not using OAC for AF with risk factors

## Legitimate

- Very high risk of major/life-threatening bleeding
- Unable to tolerate warfarin and unable to afford NOAC
- Patient decision after thorough review of risks, benefits, concerns

## Illegitimate

- Aspirin is effective
- Belief that asymptomatic or minimal AF has a low stroke risk
- Some risk of bleeding that does not outweigh stroke reduction benefit (prior bleeding, typical falls, etc)
- Lack of a reversal agent