Pragmatic Clinical Trials – *Shifting to a New Normal*

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The PIONEER & PRIDE Study Teams and the *patients!*

Outline

Pragmatic Clinical Trials (PCTs)

- Current healthcare landscape and the real world
- Definition of a pragmatic clinical trial

Evidence Generation With PCTs

- Design considerations in PCTs
  - PIONEER study example
  - PRIDE study example
- Challenges in PCTs

Regulatory View of PCTs

- Using PCTs for regulatory claims (ACA 2010 and Cures Act 2016)
- Reporting of PCTs
  - an extension of the CONSORT statement

Summary

Pragmatic Clinical Trials (PCTs)

- Current healthcare landscape and the real world
- Definition of a pragmatic clinical trial

Current Healthcare Landscape and the Real World

U.S. healthcare is witnessing four major trends -

Science & technology

- Scientific breakthroughs in drug development, delivery of care and patient-centric tools

Value

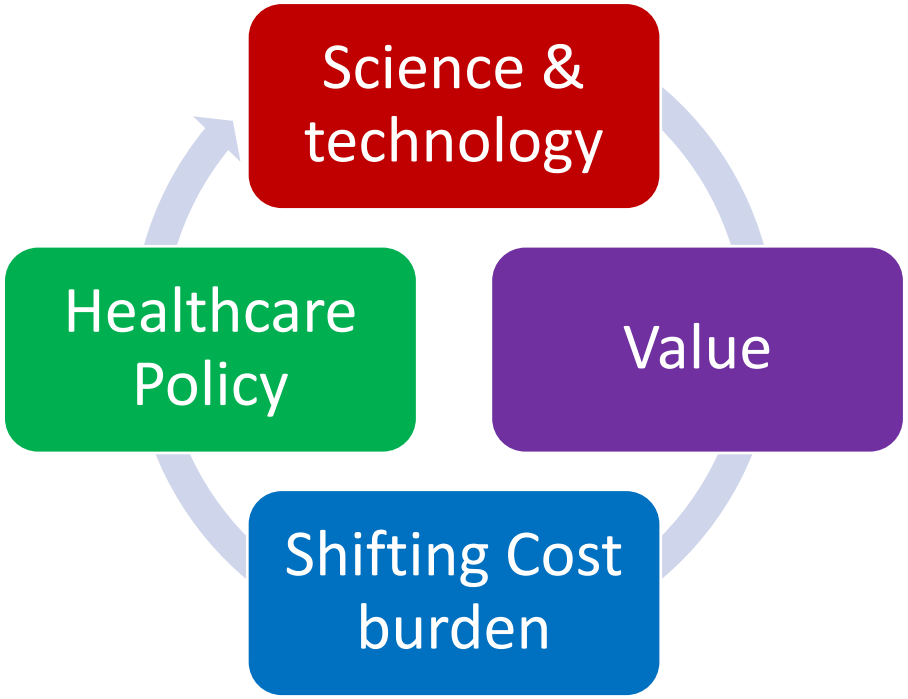
- Significant demand for value-based medicine to improve patient outcomes

Cost burden

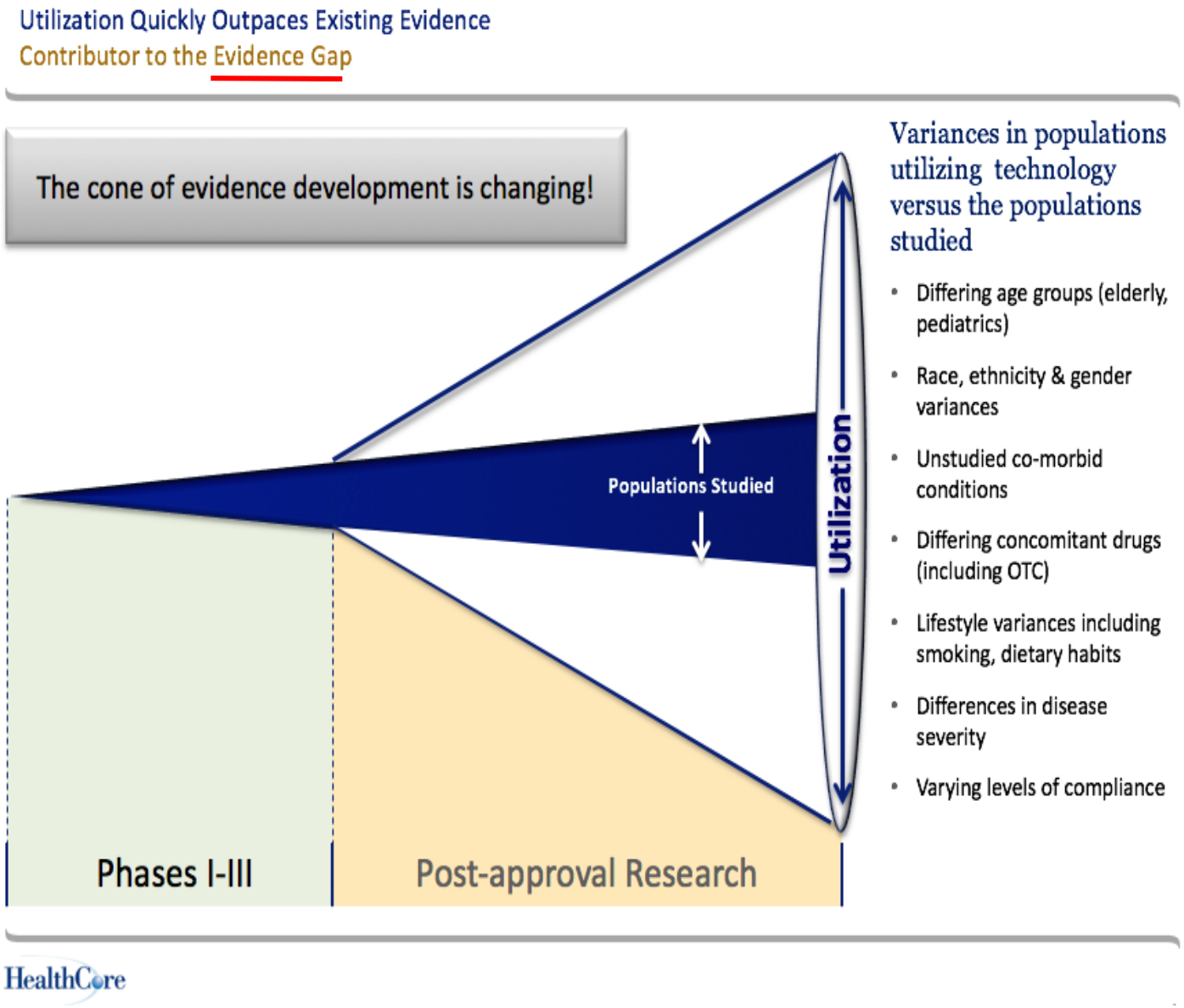
- Aging population dynamics and growth in health care expenditure

Healthcare policy

- Emphasis on wider healthcare access, affordable care and growing evidence base in the real world



Evidence Gap



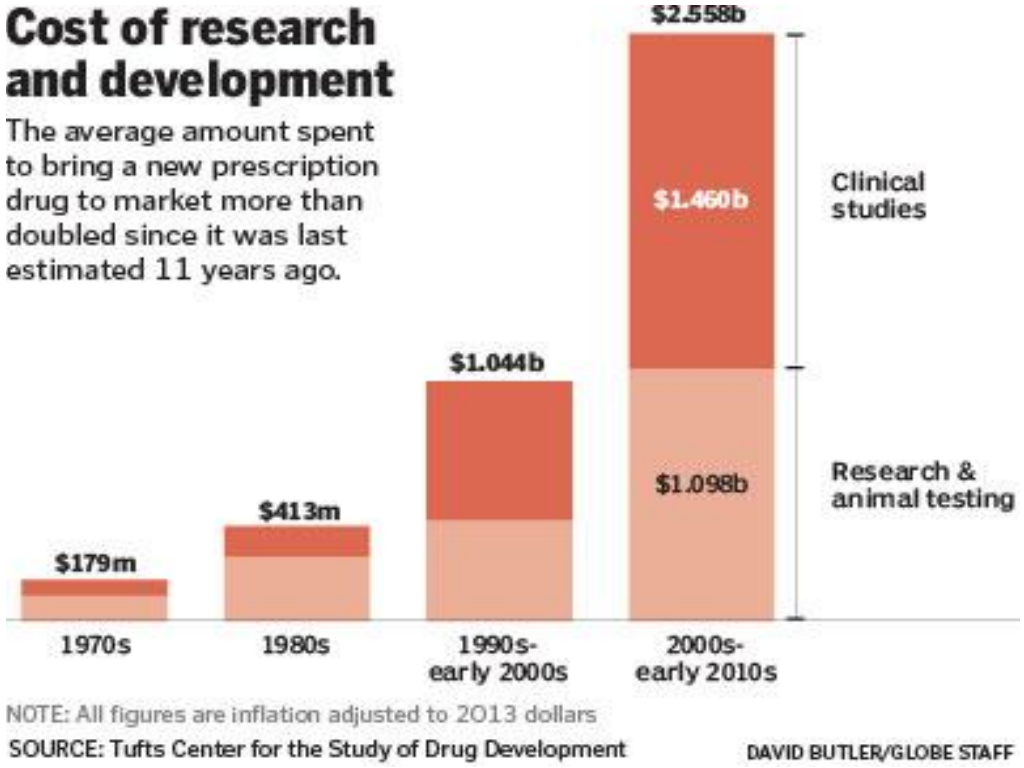
"Voltage drop" phenomenon – highly efficacious treatments in RCTs fail to be replicated in everyday practice

Over ›10,000 traditional explanatory studies published annually – yet systematic reviews point out inadequate (generalizable) evidence for making appropriate clinical recommendations

Clinical practice guidelines mostly developed using lower levels of evidence or expert opinions (need to expand the evidence base!)

Bridging efficacy-effectiveness gap is a serious priority for regulators (Eichler HG, 2011)

Unsustainable Costs?



In 2015, PhRMA member companies spent an estimated **$58.8 billion** to discover and develop new medicines

Estimated 2013 U.S. Industry-Sponsored Clinical Trials (Phrma.org, 2013) and Per-Patient Trial Costs

Phase	# Active Trials	Estimated U.S. Enrollment	Average cost per patient
Phase 0*	35	3,222	$16,500
Phase 1	1,392	119,536	$38,500
Phase 2	2,562	215,740	$40,000
Phase 3	1,680	644,684	$42,000
Phase 4	530	165,158	$16,500
Total	6,199	1,148,340	

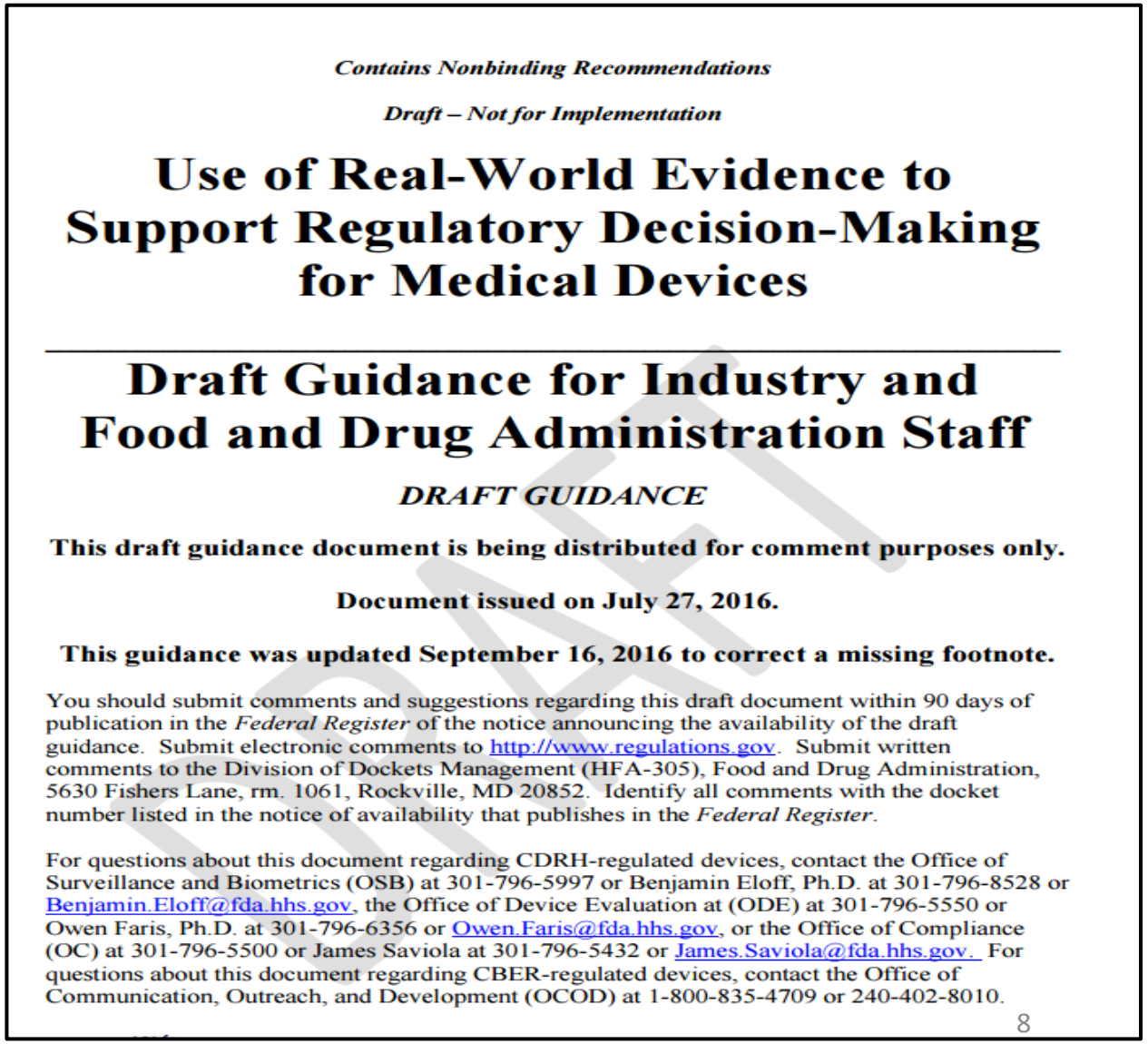
Source: PhRMA 2015; * = used Phase 4 cost estimates for Phase 0

Can RWE play a role?

"*The future of drug development and regulatory approvals must include the use of real world evidence*", according to former FDA Comm. Robert Califf

- "We can't afford to continue doing trials the way we're doing," Califf said during the annual meeting of Friends of Cancer Research.(2016)

- "The average cost of a cardiovascular trial is $500 million, "with 85 percent of the data left unused", Califf said. "**We need a revolution in clinical trials.**"



Contains Nonbinding Recommendations

Draft – Not for Implementation

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on July 27, 2016.

This guidance was updated September 16, 2016 to correct a missing footnote.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or Benjamin Eloff, Ph.D. at 301-796-8528 or Benjamin.Eloff@fda.hhs.gov, the Office of Device Evaluation at (ODE) at 301-796-5550 or Owen Faris, Ph.D. at 301-796-6356 or Owen.Faris@fda.hhs.gov, or the Office of Compliance (OC) at 301-796-5500 or James Saviola at 301-796-5432 or James.Saviola@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

The Evidence Spectrum

Randomization + real world setting expands into a pragmatic clinical trial

Attributes of Different Clinical Study Designs

Clinical Study Design	Design & Data Collection	Patient Population	Potential for Bias	Advantages and Disadvantages
Observational studies (incl. registry studies)	Retrospective or Prospective	Typically unselected population	No randomization	Large population; unmeasured variables or unexplained factors
Traditional RCTs	Prospective design, data collection at selected study clinics	Highly-selected patient population ; not easily generalizable	Randomization eliminates confounding bias	Current gold-standard for comparative efficacy/safety studies
Registry-based RCTs	Prospective; data collection at diverse clinical sites	Pre-specified patient population	Randomization eliminates confounding bias	Large number of outcomes – harness power of already-established clinical registry
Large, pragmatic clinical trials	Prospective; data collection as part of clinical care	Can be broad or selective - depends on EHR/EMR	Randomization eliminates confounding bias	Simple design; large number of subjects & outcomes, requires easy and quick enrollment criteria, infrastructure; require broader range of methodological tools

Source: *Jones et al. JACC v. 68, 17, 2016*

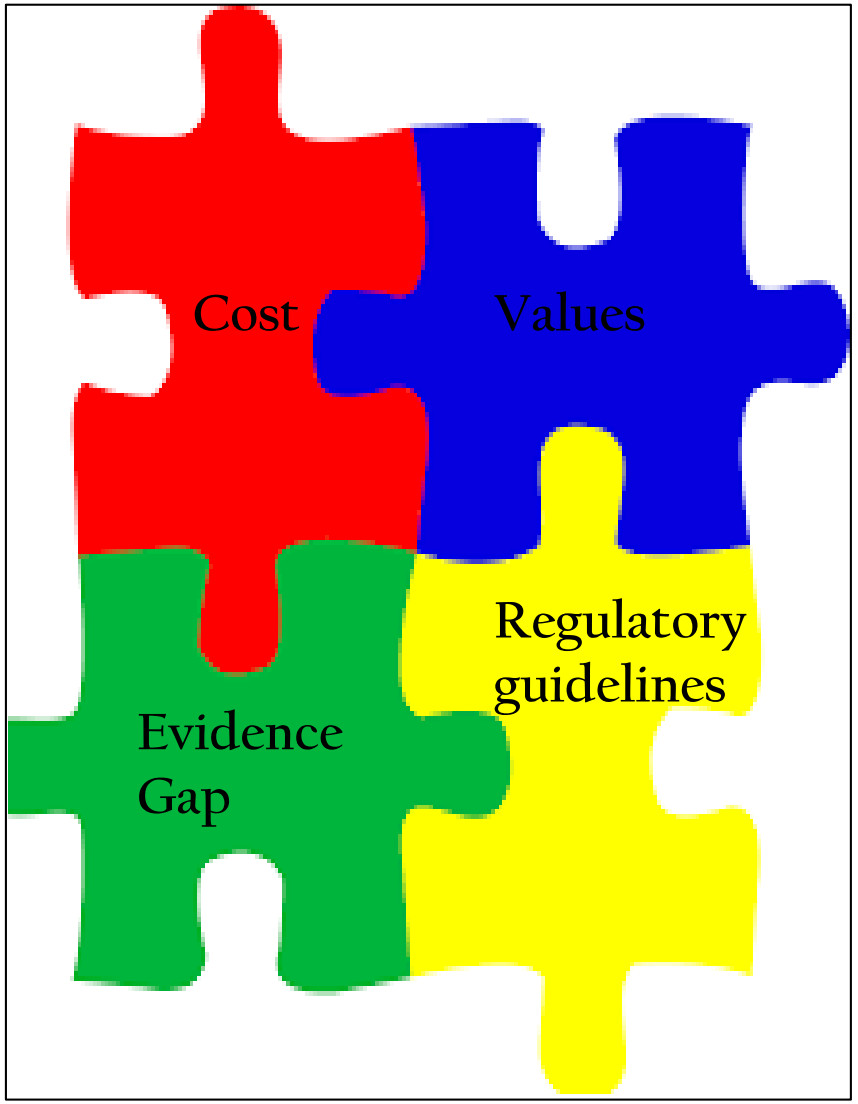
Why Pragmatic Clinical Trials?

Randomized controlled trials (RCTs)

- Typically report an ***average treatment effect*** – not generalizable to much wider pools of patients
- Increasingly *disrupted* by ***cost***, ***values***, ***evidence gap***, and changing ***regulatory guidelines***

Rapid integration of information from pragmatic settings into trial designs significantly improves *value* of a trial to patients and providers

- Do we really need *aspirin* for stroke/ACS patients?
  - ✓ *Anticoagulation* studies - COMPASS, PIONEER, WOEST
- Do *SGLT2-inhibitors* benefit heart failure (HF) patients?
  - ✓ *Type 2 Diabetes Mellitus* (T2 DM) cardiovascular outcome studies - EMPA-REG OUTCOME, CANVAS



Pragmatic Clinical Trials (PCTs)

Concept of PCT was first proposed by Schwartz and Lellouch (1967) to address questions from decision makers in a clinical practice setting

Two key distinctions

- **Explanatory trials** – aim at confirming a physiological or clinical hypothesis
- **Pragmatic trials** – aim to inform a clinical or policy decision by providing evidence for real world use of an intervention

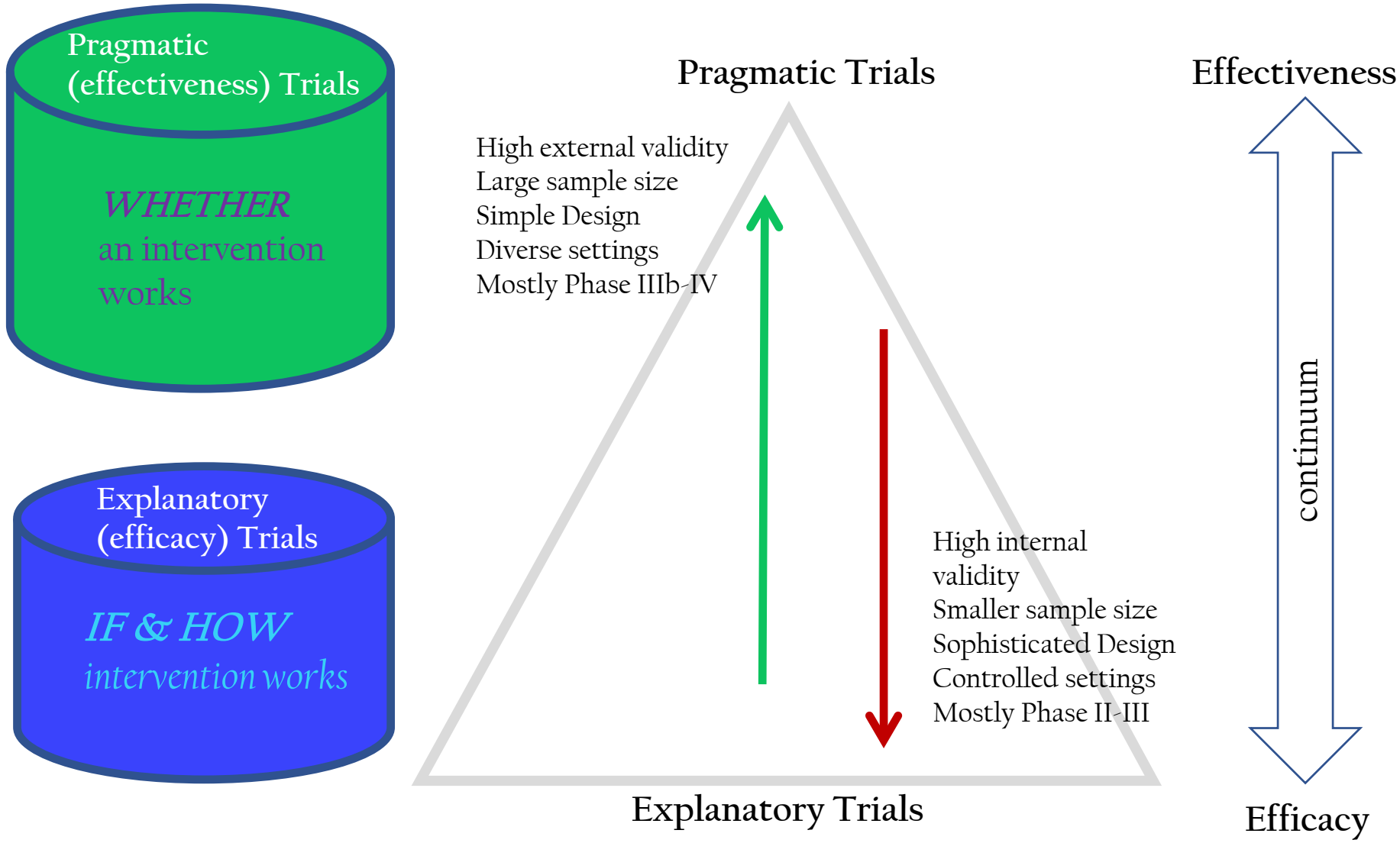
Trial designs vary in 'pragmatism' employed in response to specific objectives - trial design, patient population, interventions, outcomes and analysis

Efficacy vs. Effectiveness Studies

	Efficacy Studies	Effectiveness Studies
Objective	Does it work under optimal circumstances?	Does it work under usual circumstances?
Motivation	Regulatory approval	Formulary approval
Intervention	Fixed regimen / forced titration	Flexible regimen
Comparator	Placebo Arbitrarily chosen comparator	Usual Care Least expensive / most efficacious
Design	Randomized controlled trial – strict control	Randomized controlled trial – or open label – minimum control
Subjects	Selected or "eligible" subjects High compliance	Any subjects Low compliance
Outcomes	Condition specific Strong link to mechanism of action	Comprehensive (incl. PROs: QoL) Weak link to mechanism of action
Analysis	Protocol adherers	Intent-to-treat

(Bombardier and Maetzel, 1999)

Pragmatic vs. Randomized Controlled Trials



Source: *Dialogues Clin Neurosci 2011; 217-224*

Scoring Pragmatism in a Trial

Distinction between an explanatory and a pragmatic trial is not always clear

- Gartlehner (2006) and Thorpe et al (2009) proposed the PRECIS (Pragmatic-Explanatory Continuum Indicator Summary) tool versions
- Thorpe's version is based on a scoring system with 10 key domains to highlight the pragmatic features of a trial
- Key domains of PRECIS include: recruitment of investigators/patients, the intervention and its delivery, follow-up and determination and analysis of outcomes

A modified tool, PRECIS-2 focused on a pragmatic extension to the CONSORT statement (Louden et al. 2015)

Pragmatism is a quality or attribute of the trial – that is simply not dichotomous (absent or present). It's a continuum.

PRECIS-2 Tool for Assessing Pragmatism in a Trial

Dimension	Assessment of Pragmatism
Recruitment of Investigators & participants	
Eligibility	Similarity to patients receiving usual care?
Recruitment	Engagement efforts to recruit and retain patients
Setting	Differences in trial from the practice setting
The intervention and its delivery within the trial	
Organization	Differences in provider expertise and delivery of care
Flexibility in delivery	Flexibility in delivery of intervention
Flexibility in adherence	Flexibility in monitoring and adherence
The nature of follow-up	
Follow up	Intensity of measurement and follow up
The nature, determination, and analysis of outcomes	
Primary outcome	Directly relevant to participants?
Primary analysis	Include all data available in the analysis

Source: Drazen, et al. 2016.

Pragmatic Clinical Trial (PCT) – A definition

Califf and Sugarman (Clinical Trials, 2015)

- Intent to ***inform*** decision makers (patients, clinicians, administrators and policy makers) as opposed to elucidating a biological or social mechanism

- Intent to ***enroll*** a patient population relevant to the decision in practice and representative of the patients/populations and clinical setting for whom the decision is relevant

- Either an intent to:
  - ***Streamline*** procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial or
  - ***Measure*** a broad range of outcomes

Evidence Generation With PCTs

- Design considerations in PCTs
  - PIONEER study example
  - PRIDE study example
- Challenges with PCTs

Design Considerations in PCTs

Study design (randomized and open label)

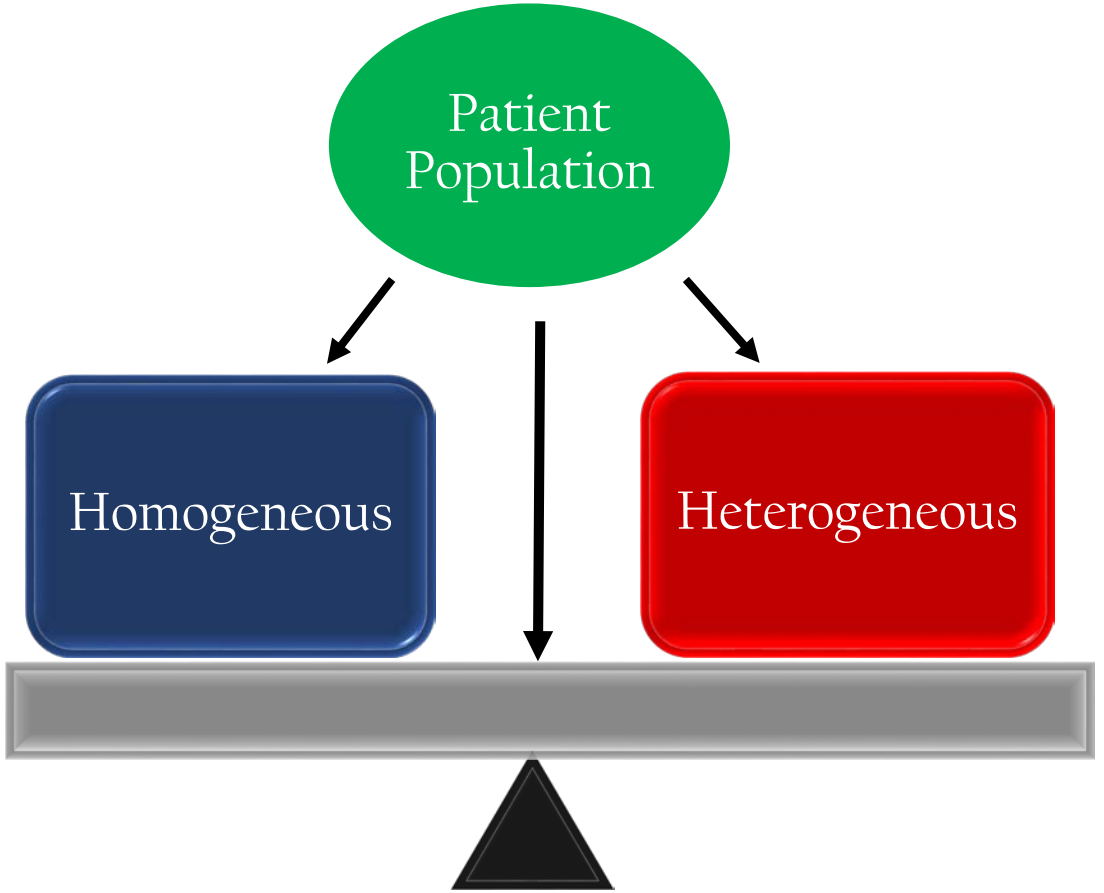
- Clarify the key effectiveness/safety question
- Choose sampling unit – individual patient or a cluster
- Select the pragmatic setting –
  - Prospective practice/site-based recruitment
  - Hospital networks via cluster sampling

Choice of Intervention(s) and outcomes

- Define real-world outcomes/surrogate endpoints
- Select clinically relevant/practice-based interventions
- Decide randomization w/stratification by baseline risk

Patient Recruitment

- Recruit from a broader pool of patients (do not exclude for reasons different from the real practice)
- Identify potential sources of heterogeneity (pt/site/treat)
- Ensure complete (100%) follow-up with electronic data



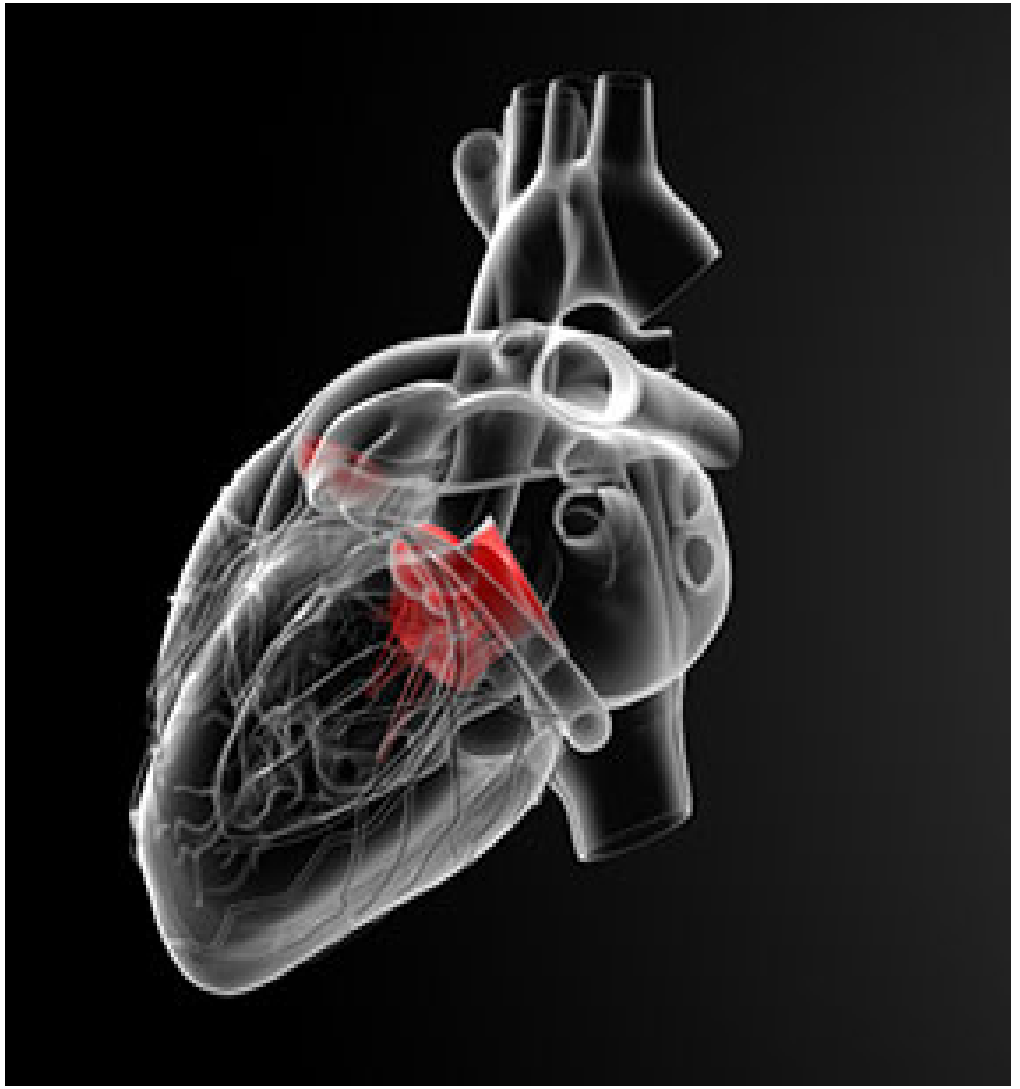
Example 1 - The PIONEER AF-PCI Study

Prevention of Bleeding In Patients with Atrial Fibrillation Undergoing PCI

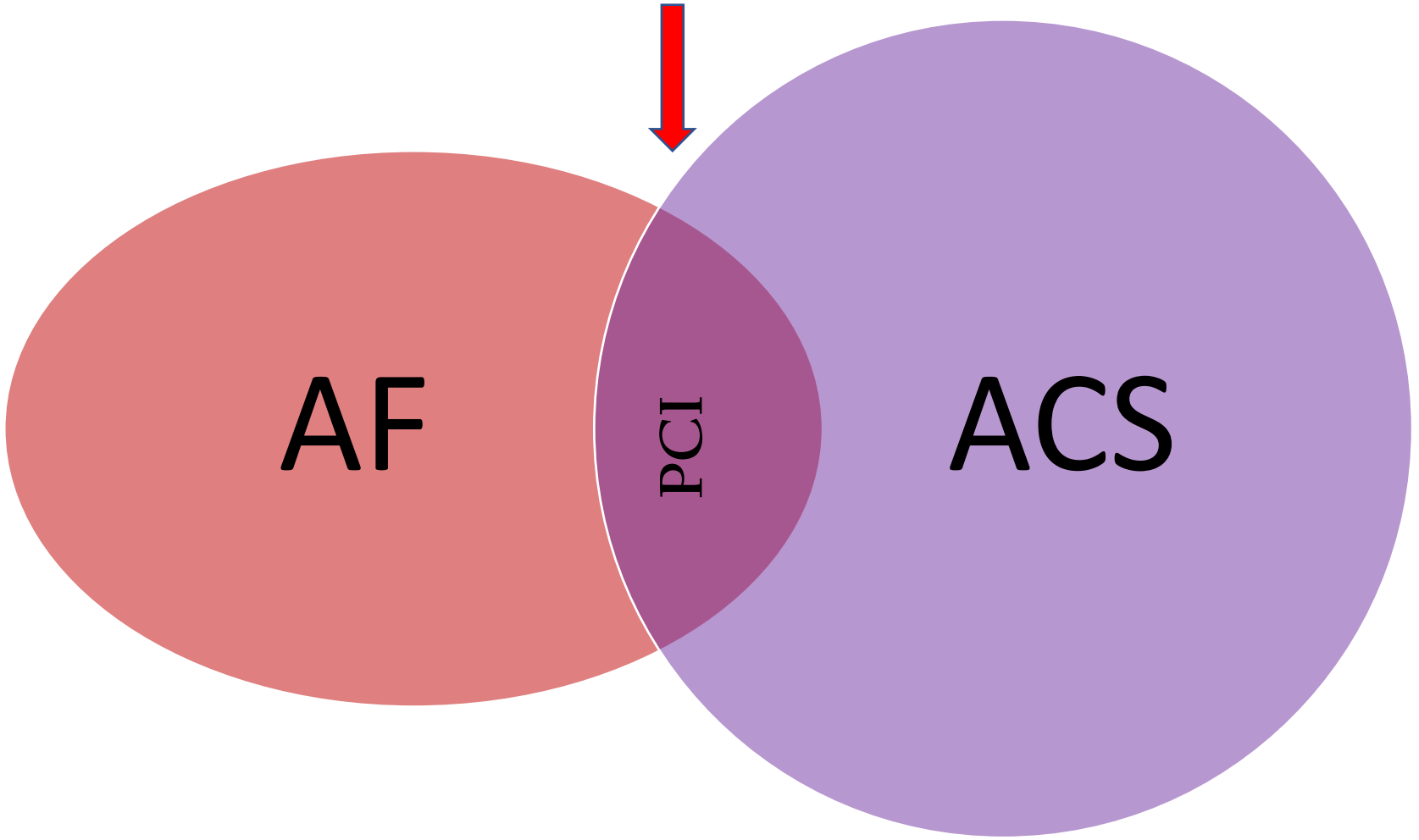
The PIONEER AF-PCI Study

Atrial fibrillation (AFib) is a type of abnormal heart rhythm. In AFib, the heart's two upper chambers (atria) beat irregularly. Instead of beating in a normal, consistent pattern, the atria may quiver rapidly. As a result, some blood that should be moving from the atria to the lower chambers (ventricles) pools in the atria. This can form a clot, which can clog an artery that carries blood to the brain, resulting in a stroke.

Approximately 5% to 21% of patients with acute coronary syndrome (ACS) undergoing PCI also have concomitant AF (Rubboli et al, JIC, 2009)



Patients with Atrial fibrillation and PCI



Treatment Management of AF-PCI patients

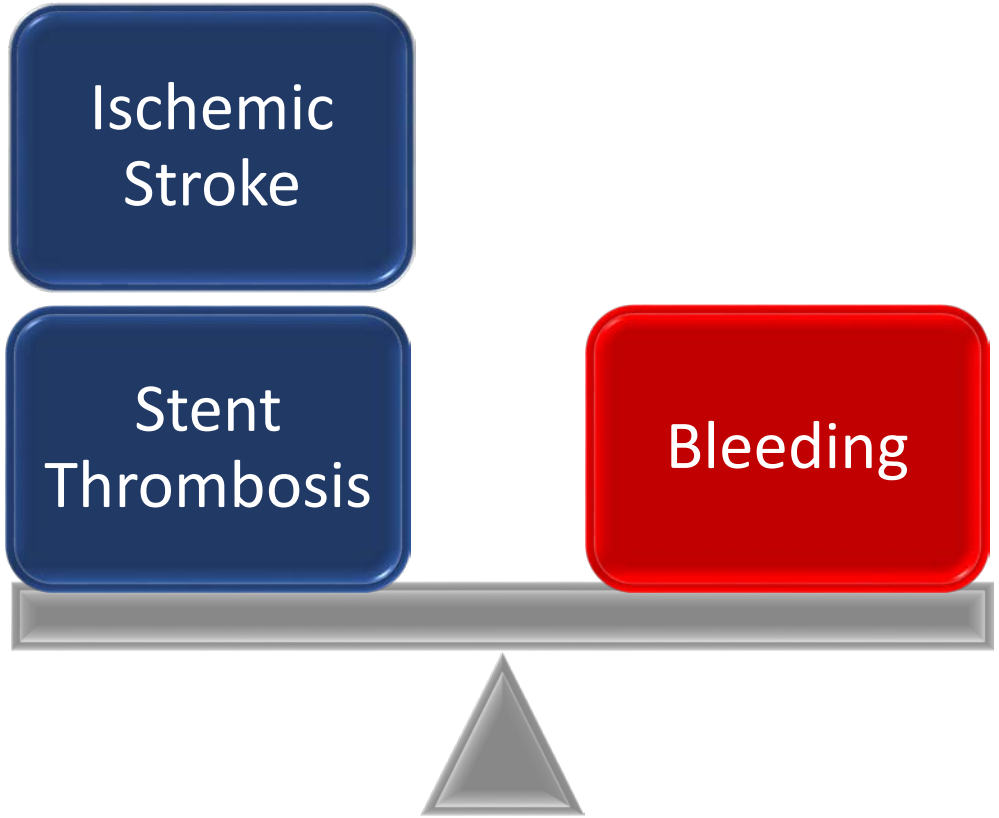
The management of AF patients who undergo stent placement for an ACS is often challenging (Matteo Bertini, 2017)

Need to balance between excess bleeding risk from antithrombotic therapy and higher thrombotic risk posed by the underlying AF condition and stent-thrombosis

Two types of treatments commonly prescribed for AF patients with PCI include –

anticoagulants (NOACs)

antiplatelets (APs)



PIONEER AF-PCI: Design Considerations

Study Question

Can a regimen combining anticoagulant with a single antiplatelet treatment confer better safety to AF + PCI patients when compared to SOC?

Study Design

- Multinational study with sites practicing SOC
- Randomized open label with site-based eCRFs
- Stratification based on intended duration of dual antiplatelet therapy (1 month, 6 months, 12 months)

Intervention/outcomes

- Anticoagulant + 1 antiplatelet vs. anticoagulant + 2 antiplatelets
- Clinically significant bleeding (major/minor/BRMA)

SOC = standard of care

Inclusion

- Men and women at least 18 years of age
- Paroxysmal, persistent, or permanent nonvalvular AF
- Undergone PCI with stent placement
- Documented AF that occurred within 1 year before screening

Exclusion

- History of stroke or TIA
- Clinically significant GI bleeding within 12 months before randomization
- CrCl<30 mL/min
- Anemia of an unknown cause with a Hgb <10 g/dL
- Any other condition known to increase the risk of bleeding

N Engl J Med 2016; 375:2423-34

PIONEER AF-PCI: Pragmatic Considerations

Patient population (with higher disease burden)

- AF+PCI with stenting – more complex patient mix than simply patients with AF or ACS (with/without PCI)

Less established Treatment Paradigm

- Significant variation in post-PCI treatment course ('dual' therapy, 'triple' therapy including combination of anti-platelets with NOACs, length of therapy)
- Intended therapy and anticipated compliance not well defined

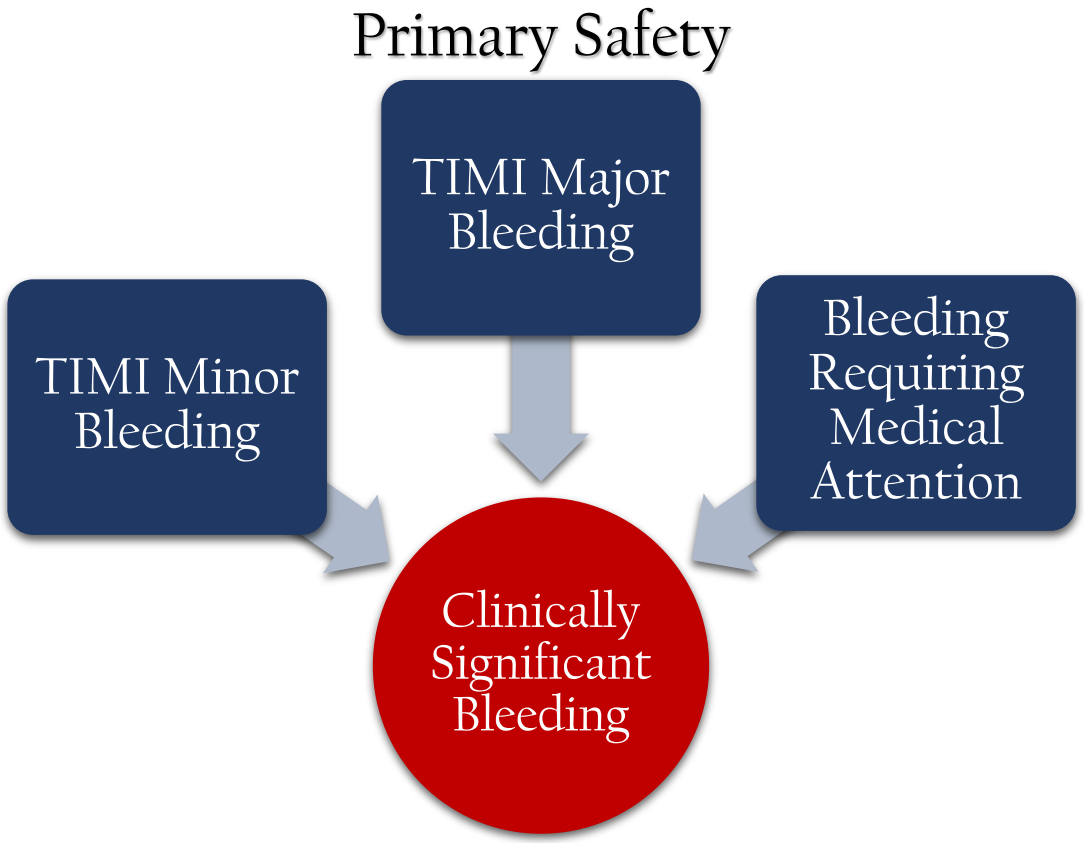
Clinical outcomes not well predicted

- Safety: bleeding rates usually very high with triple therapy
- Efficacy: cardiovascular event rates higher with *potentially* inadequate therapeutic regimen (consisting of lower dose NOAC and anti-platelets and/or insufficient dose-exposure combinations applied)

Significant value to Payer and Provider

- Establishing relevance of "dual" therapy (minus aspirin) as reported in other studies important to inform treatment guidelines and generate value to payer, provider and patient
- Advantage on safety parameters with no appreciable elevation in CV risk with dual/triple therapy adds confidence to practitioners

PIONEER AF-PCI: Study End Points



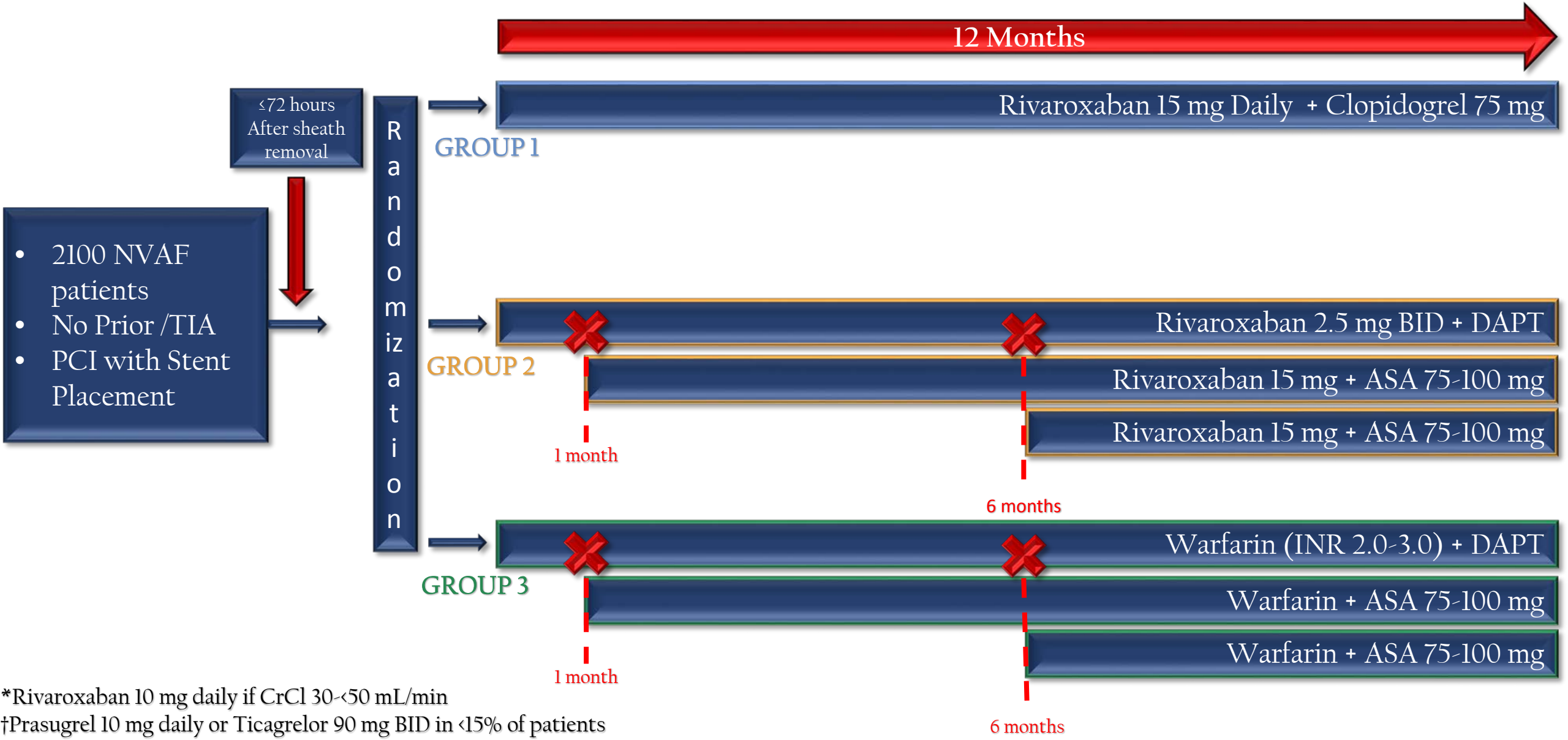
Secondary

Safety	● Each component of the primary safety endpoint
Efficacy	● Major cardiovascular event composite* ● Stent thrombosis
Exploratory	● ISTH Major bleeding ● GUSTO severe bleeding

*Death from cardiovascular cause, MI, Stroke
Each component of the composite

N Engl J Med 2016; 375:2423-34

PIONEER AF-PCI: Study Design



*Rivaroxaban 10 mg daily if CrCl 30-<50 mL/min
†Prasugrel 10 mg daily or Ticagrelor 90 mg BID in <15% of patients

PIONEER AF-PCI: Statistical Analysis

- Analysis based on pooled data across all strata of DAPT duration (1, 6, or 12 months)
- Safety analysis based on data from all randomized participants who received at least 1 dose of trial drug
- Intention-to-treat based on data obtained through follow-up of all randomized participants
- Comparisons of group 1 vs group 3 and group 2 vs group 3 were performed simultaneously with no adjustment for type I error at a rate of 0.05

PIONEER AF-PCI: Findings

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

ABSTRACT

BACKGROUND

In patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) with placement of stents, standard anticoagulation with a vitamin K antagonist plus dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin reduces the risk of thrombosis and stroke but increases the risk of bleeding. The effectiveness and safety of anticoagulation with rivaroxaban plus either one or two antiplatelet agents are uncertain.

METHODS

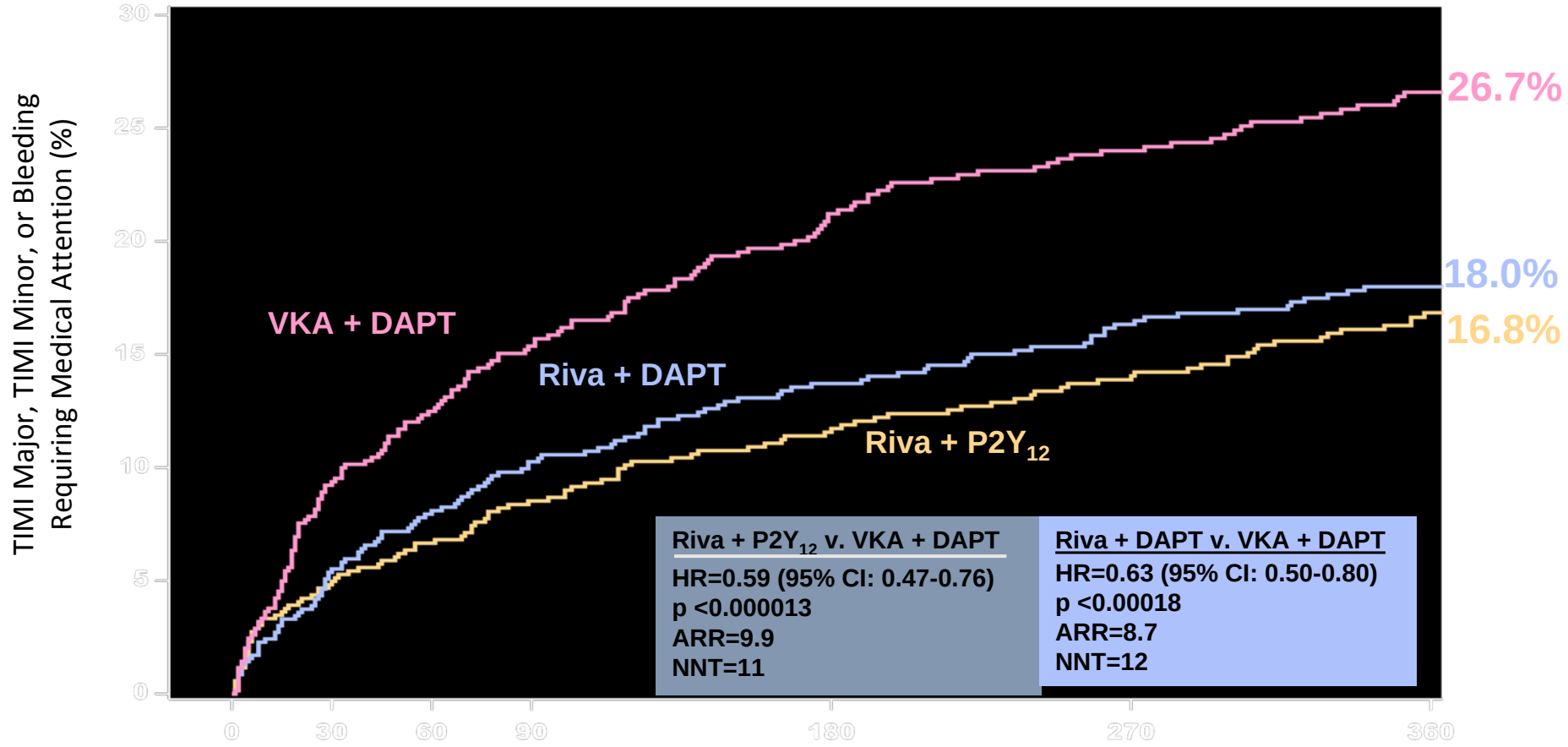
We randomly assigned 2124 participants with nonvalvular atrial fibrillation who had undergone PCI with stenting to receive, in a 1:1:1 ratio, low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (group 2), or standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months (group 3). The primary safety outcome was clinically significant bleeding (a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction [TIMI] criteria or bleeding requiring medical attention).

RESULTS

The rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; hazard ratio for group 1 vs. group 3, 0.59; 95% confidence interval

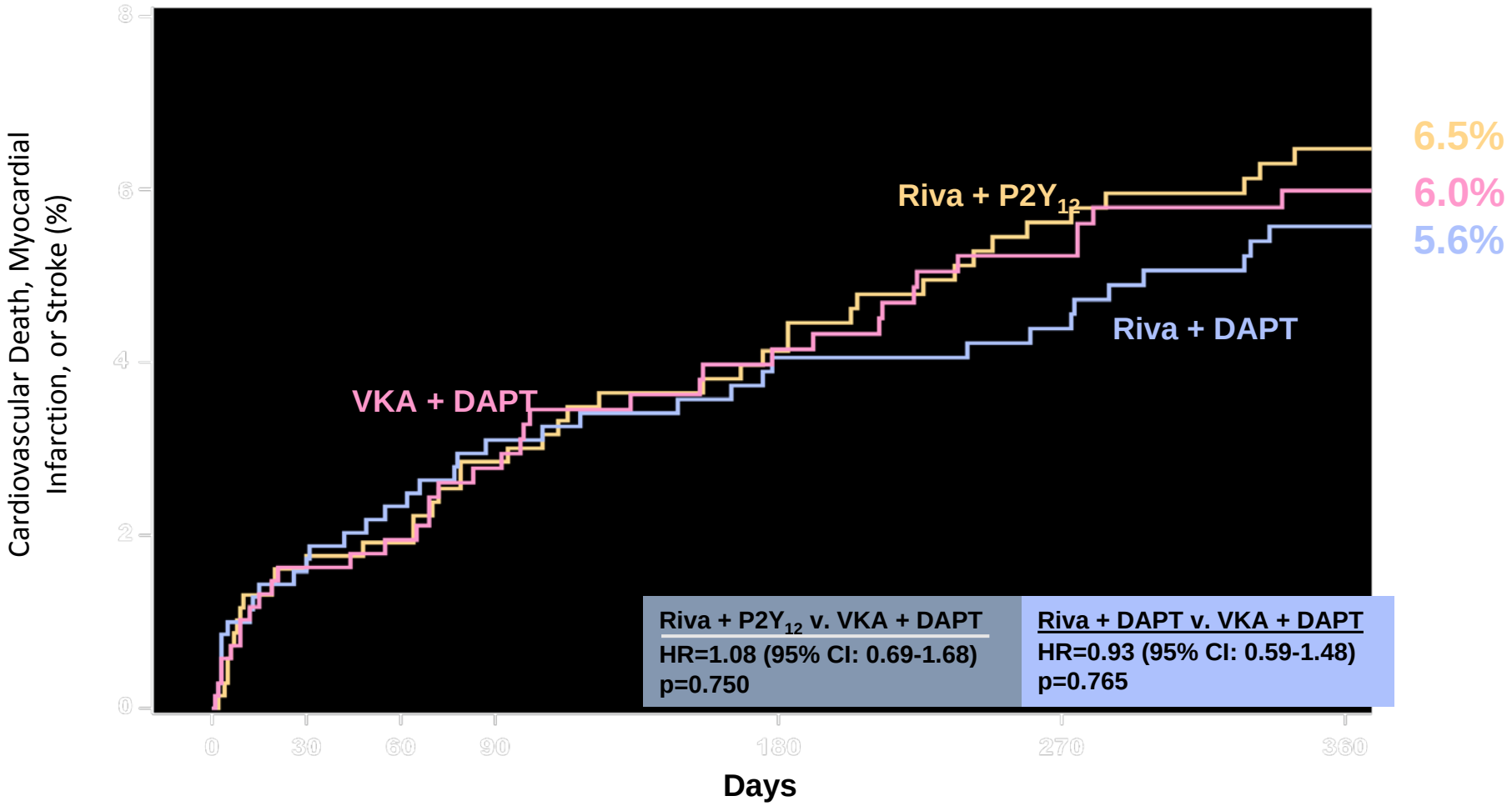
From the Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston (C.M.G., S.K., Y.D.); the Cardiovascular Institute, Mount Sinai Medical Center, Icahn School of Medicine at Mount Sinai, New York (R.M., J.H.); Heart Center, Department for Cardiology and Angiology I, University of Freiburg, Freiburg (C.B.), and Bayer Pharmaceuticals, Leverkusen (M.E.) — both in Germany; Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam (F.W.V.); Janssen Pharmaceuticals, Titusville (P.W., M.B., J.I., P.B.), and the Division of Cardiology, Newark Beth Israel Medical Center, Newark (M.C.) — both in New Jersey; University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom (G.Y.H.L.); Aarhus University Hospital, Medical Department, Hospital Unit West, Herning, Denmark (S.H.); Duke Clinical Research Institute, Durham, NC (E.D.P.); and the Centre for Cardiovascular Sci-

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



Riva + P2Y$_{12}$	696	628	606	585	543	510	383
Riva + DAPT	706	636	600	579	543	509	409
VKA + DAPT	697	593	555	521	461	426	329

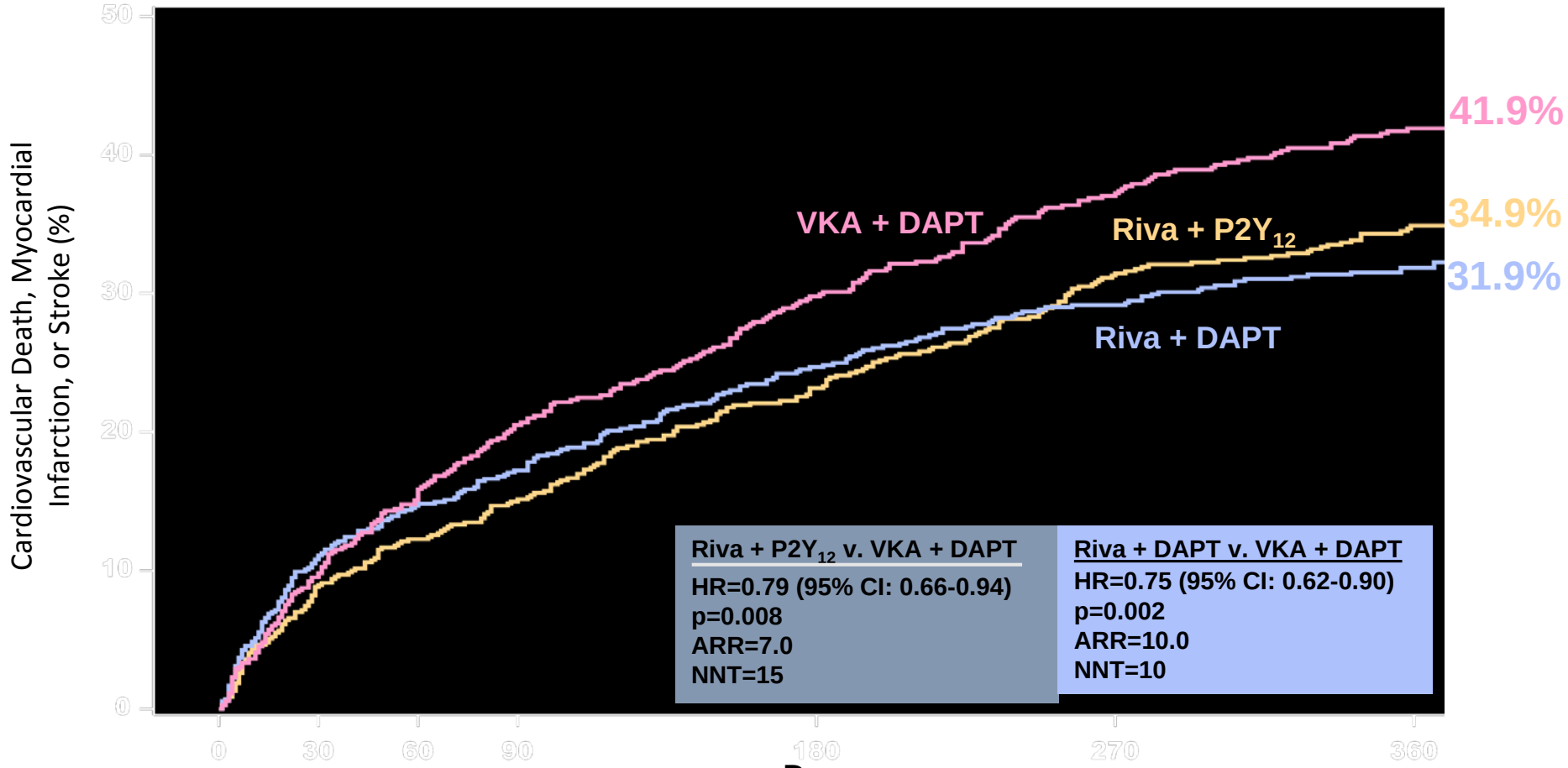
Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke



Riva + P2Y$_{12}$	694	648	633	621	590	562	430
Riva + DAPT	704	662	640	628	596	570	457
VKA + DAPT	695	635	607	579	543	514	408

Note: Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Note: Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test.

Time to First All Cause Death or All Cause Recurrent Hospitalization



Riva + P2Y12	696	609	582	559	496	437	322
Riva + DAPT	706	607	570	548	493	454	367
VKA + DAPT	697	592	540	490	422	369	272

Note: Rehospitalizations do not include first index event
Note: Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.

Influencing the Practice!

EDITORIAL

O PIONEERs!

The Beginning of the End of Full-Dose Triple Therapy with Warfarin?

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

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STRACT

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ORIGINAL RESEARCH ARTICLE

Recurrent Hospitalization Among Patients With Atrial Fibrillation Undergoing Intracoronary Stenting Treated With 2 Treatment Strategies: Rivaroxaban or a Dose-Adjusted Vitamin K Antagonist Treatment Strategy

BACKGROUND: Patients stenting traditionally dual antiplatelet bleeding

PIONEER AF-PCI: Impact on Clinical Practice

Designed with pragmatic features, the PIONEER study suggests that it is safe to treat patients at an increased risk for bleeding with anticoagulation and monotherapy P2Y12 inhibitor

Clinical practice and treatment guidelines are well positioned for early adoption of this pragmatic safety findings on the use of dual therapy with NOAC in AF PCI patient population

Larger PCTs using RWE data sources should be designed to better characterize effectiveness endpoints in addition to safety to ensure positive outcome with regulatory authorities

Example 2 - The PRIDE Study

Paliperidone Palmitate Research In Demonstrating Effectiveness Study

The PRIDE Study

Trends in Mental Health

Deinstitutionalization has **shifted the care** for mental illness and substance disorders

The **largest facilities** housing psychiatric patients in the United States are **not hospitals…but jails**

Philadelphia State Hospital at Byberry

Los Angeles County Jail, CA

PRIDE: Design Considerations

Study Questions

Does the treatment work in patients with a history of incarceration?

Is the treatment safe and effective in patients with clinical diagnoses (rather than persons with formal ICD diagnoses)?

Does the treatment have value beyond that seen with alternative treatment approaches (Compared to other treatments)?

Study Design

- Multicenter study with community sites practicing SOC
- Randomization applied to choice of oral antipsychotics

Intervention/outcomes

- Paliperidone palmitate long acting injectable (LAI)
- Standard of care – multiple oral antipsychotics with poor compliance

Inclusion

- Adults (18 – 65 yrs old) with schizophrenia diagnosis
- MINI confirmation of DSM-IV diagnosis
- History of CJS custody twice or more in the previous 2 years
- Willingness to accept LAI

Exclusion

- Active drug abuse ≤ 3 months of screen
- Unstable medical illness
- Women not pregnant
- Positive urine drug test at screening

Reference: Alphs L et al. *J of Clin Psych*. 2015; 76(5):554-61

PRIDE: Pragmatic Considerations

Patient population

- Included patients normally excluded from trials, such as those at high risk for treatment nonadherence (ie, those with recent criminal justice system involvement, comorbid substance abuse, or unstable living conditions)

Flexibility in treatment/management decisions

- Considerable flexibility in treatment/management decisions by physicians and patients
- "Equipoise" randomization with multitude of oral antipsychotics
- Retain patients for the full planned duration of the trial

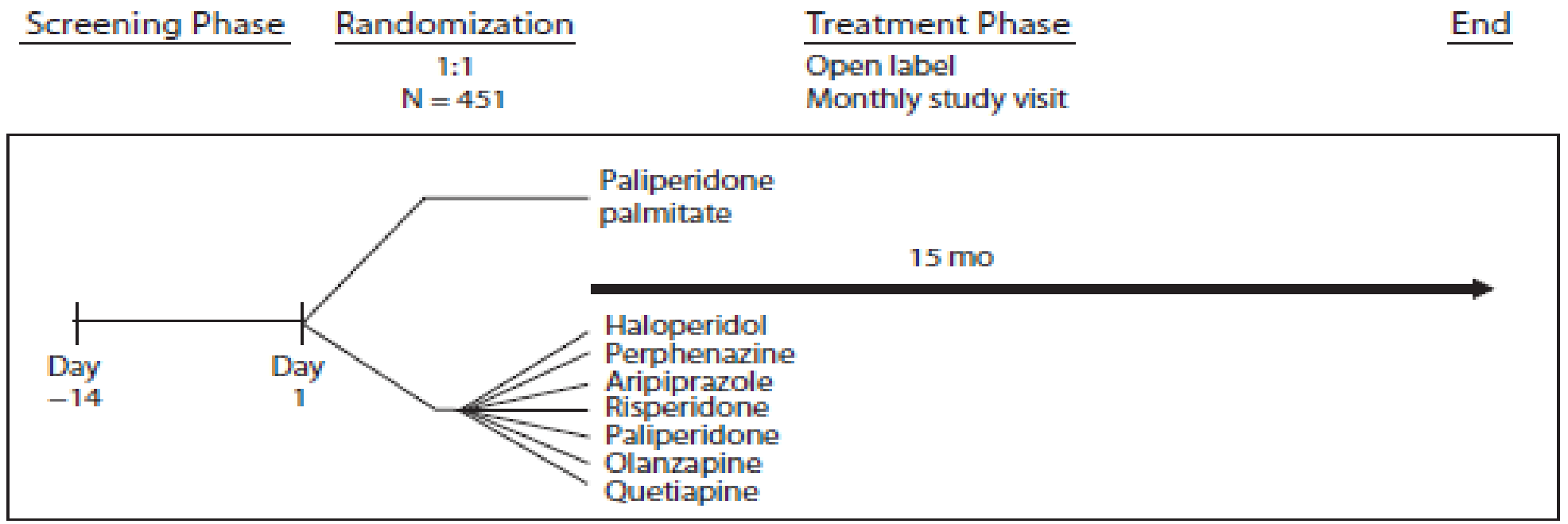
Pragmatic Clinical Outcomes

- Arrest/incarceration, hospitalization, suicide
- Treatment discontinuation

Significant value to Patient and Provider

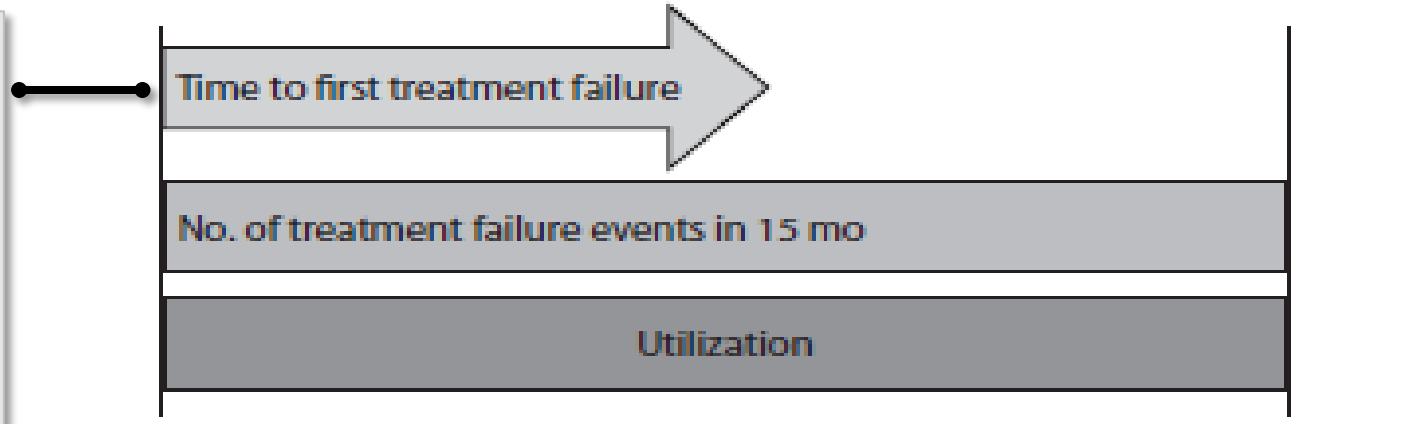
- Reflecting the real world paradigm of schizophrenia as defined by patients, treatments, and outcomes
- Reduced caregiver costs and overall surveillance burden with effective management of schizophrenic patients at the community clinics

PRIDE: Study Design



Protocol-Defined Treatment Failure:

1. **Arrest/Incarceration**
2. **Psychiatric Hospitalization**
3. **Suicide**
4. Increase psychiatric services
5. d/c AP for inadequate efficacy
6. d/c AP for safety or tolerability
7. Supplement AP w/ another AP



1. Alphs L et al. *J of Clin Psych*. 2014;75:1388-1393; 2. Alphs L et al. *J of Clin Psych*. 2015;76(5):554-61.

PRIDE: Study Endpoints

Primary End Point

Time to Treatment Failure (EMB)

First Secondary End Point

Time to first arrest/incarceration or psychiatric hospitalization

Exploratory End Points

Time to discontinuation of treatment

Time to 1st treatment failure for various classifications of arrests

Average number of treatment failure events

Resource utilization

Treatment supplementation

Primary Objective

Compare the effectiveness of paliperidone palmitate treatment with daily oral antipsychotic treatment in delaying time to treatment failure (as defined by several real-world outcomes) over 15 months in subjects diagnosed with schizophrenia who have been incarcerated

Key Secondary Objectives

Compare subjects in each arm (PP vs. oral APs) by:

Subject functioning: change in Personal and Social Performance Scale (PSP)

Time to first psychiatric hospitalization

Symptom improvement: change in Clinical Global Impressions-Severity (CGI-S)

Safety effects of medications

1. Alphs L et al. *J of Clin Psych*. 2014;75:1388-1393; 2. Alphs L et al. *J of Clin Psych*. 2015;76(5):554-61

Analysis Sets in PRIDE Study

- Explanatory Intent-to-Treat (eITT)
  - Relevant end point observed during treatment period with the randomized study medication for all ITT subjects
  - Used for the primary and key secondary end point analyses
- Pragmatic Intent-to-Treat (pITT)
  - End points observed at any time during the study for the full 15-month participation period

Example 3 - The mSToPs Study
mHealth Screening To Prevent Strokes (mSToPs) Study

mHealth Screening To Prevent Strokes (mSToPS) Study

- A home-based clinical research study using wearable sensor technology to identify people with asymptomatic Atrial Fibrillation (AFib), an irregular heartbeat (arrhythmia) that can lead to blood clots, stroke and heart failure.

- **The primary objective** - to determine whether screening select individuals in their homes using wearable medical devices can identify people with asymptomatic AFib more efficiently than routine care.
  - The study, launched in November 2015, is a novel multisectoral collaboration between Scripps Translational Science Institute (STSI), Aetna's Innovation Labs and Healthagen Outcomes units, and Janssen Pharmaceuticals, Inc. Study participants will undergo continuous single-lead electrocardiogram (ECG) monitoring using the ZIO® XT Patch wearable sensor, developed by iRhythm Technologies.

(Source: American Heart Journal, May 2016; Scripps Translational Science Institute)

Challenges with PCTs

Heterogeneity of treatment effect (HTE)

Choice of comparator control group /Confounding bias

Data collection model and recruitment/randomization of participants

Insufficient recording of treatment and/or event history

Heterogeneity of treatment effect

Heterogeneity induced by design choice

Sources of HTE arise due to patient, provider, treatment and environment

Patient level heterogeneity may be described by baseline risk, competing risk, treatment responder/non responder status

Non-random variability in treatment effects attributed to patient, treatment, provider or external factors (changing "environment" for SOC may produce different result)

Population heterogeneity may also reduce assay sensitivity and limit the interpretation of results (Price et al. 2011)

Choice of comparator control group/Confounding bias

Choice of comparator control group

PCTs comparing two or more active treatments with a poorly defined 'standard of care' (heterogeneous) control group may affect the true treatment estimate

[eg, CATIE pragmatic schizophrenia trial – perphenazine has a receptor profile identical to that observed in atypical antipsychotics (Sweet et al. 2000)]

Practitioners with a strong interest in promoting any therapy may raise patient expectations leading to bias ("Hawthorne effect")

Confounding bias induced by intermediate variable(s) (Hernan and Robbins, 2016) in a heterogeneous control group

[eg, decision to receive treatment depends on the risk of the patient which also impacts patient outcome]

Data collection model and recruitment/randomization

Extending traditional site-based eCRFs into patient-centric tools
Randomization in the hospital/clinic based settings with EHRs/EMRs
Handling of large commercial databases (data extraction, statistical analysis)
Hybrids – combining eCRFs and EHR/EMR data (augmentation)

Insufficient recording of treatment and/or event history

Claims data often lack specificity about care needed and exposure history
Disease diagnosis information not comprehensive enough
Different care settings use different coding systems
Limited clinical information (no physiological measurements, including timing of events)

Regulatory View of PCTs

- Using PCTs for regulatory claims -ACA 2010 and Cures Act 2016
- Reporting of Pragmatic Clinical Trials – an extension of the CONSORT statement

Regulatory View of PCTs

The Patient Protection and Affordable Care Act of 2010 mandates

A national comparative effectiveness research (CER) project

CER includes both clinical trials and observational studies

PCTs and CER share many common features

CER compares real world alternatives

[eg, minimal interventions needed to change (MINC)]

Key study designs include – cRCTs, naturalistic follow-up, time series, stepped wedge, etc.

[NIH defines CER as a rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients. Such a study may compare similar treatments, such as competing drugs, or it may analyze very different approaches, such as surgery and drug therapy and may include the development and use of clinical registries, clinical data networks and other forms of EHRs that can be used to generate or obtain outcomes data as they apply to CER]

The 21st Century Cures Act 2016

FDA required to develop a framework and guidance for evaluating real world evidence (RWE) to support approvals of new indications for previously approved drugs, and to support or fulfill post-approval study requirements

> FDA must establish a framework for RWE program in collaboration with relevant stakeholders in the drug industry, and implement that framework within two years
>
> FDA must issue draft guidance describing 1) the circumstances under which sponsors of drugs may rely on RWE, and 2) acceptable standards and methodologies for collecting and analyzing RWE within five years

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Expected: FDA guidance document for drugs and biologics (similar to devices)

Impact: More concrete designs and data advice may be prescribed for PCT trialists

Reporting of Pragmatic Clinical Trials
An extension of the CONSORT statement

Guidance for reporting PCTs as a specific extension of the CONSORT statement

Goal: Report results from PCTs pertinent to users in determining acceptability of the intervention and correctly interpret trial findings

Original CONSORT statement (last revised in 2001) has 22-item checklist - detailing the flow of participants through the trial

In 2005, it was recommended to add specific text to 8 items (2-4,6,7,11,13, and 21) to the CONSORT checklist

Summary

Pragmatic clinical trials signal a shift from the normal to address real-world effectiveness & safety questions relevant to decision making

- Aim at maximizing generalizability of the study results by recruiting a diverse set of patients from heterogeneous practice settings
- More likely to yield a *null* average treatment effect than efficacy trials
- A broader evidence-base helps to support development of treatment guidelines

Analyses should focus on highlighting relationship between treatment benefit and individual patient disease-specific baseline risk, likely treatment-emergent harm and competing risks

Heterogeneity of treatment effect (HTE) in PCTs can be natural but requires thorough understanding and careful examination

Statisticians have an important role to play in the methodology development to fully tease out benefits of the pragmatic trial features

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