Pragmatic Trial Design to Study Health Policy Interventions: Lessons Learned from ARTEMIS

Tracy Y. Wang, MD, MHS, MSc, FACC, FAHA

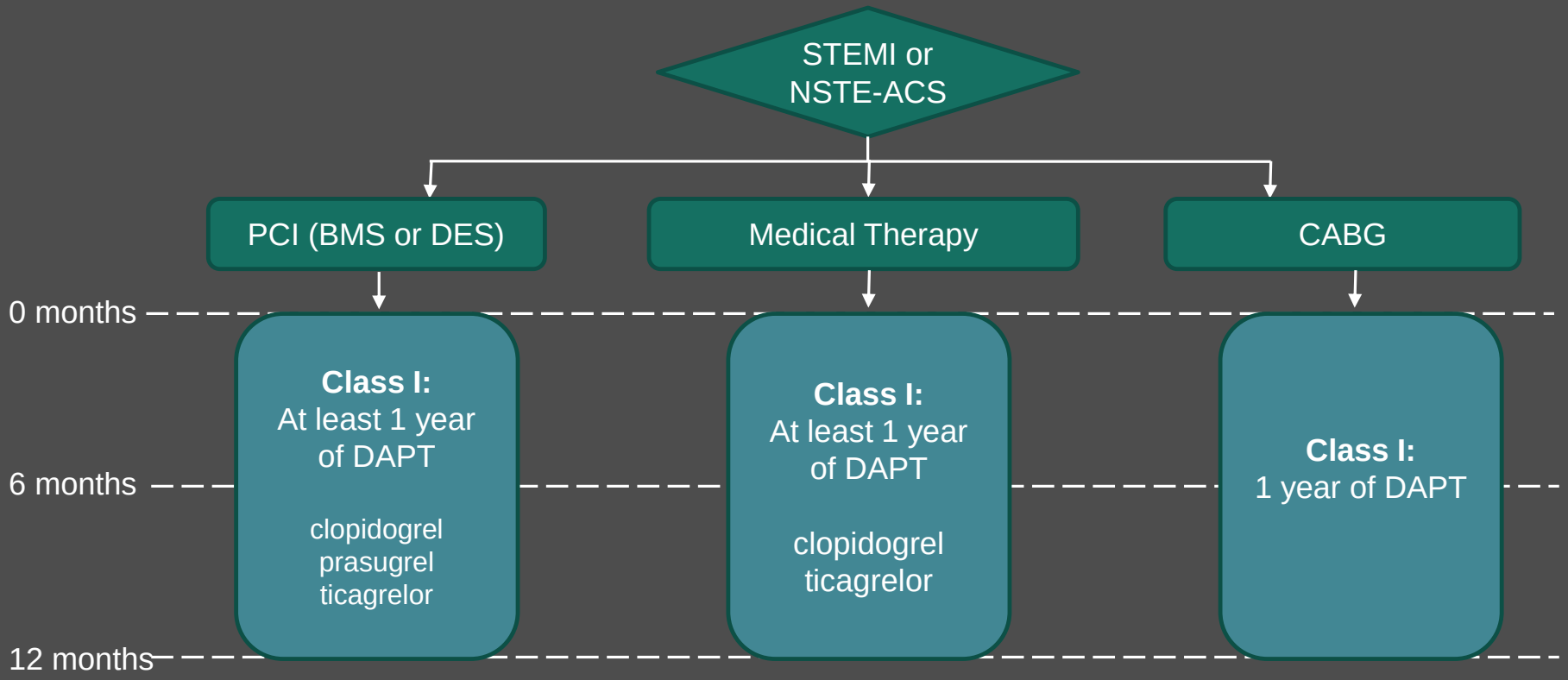
Associate Professor of Medicine, Duke University
Director of Health Services Research, Duke Clinical Research Institute
June 22, 2018

ARTEMIS
Affordability and Real-world antiplatelet Treatment Effectiveness after Myocardial Infarction Study

Disclosures

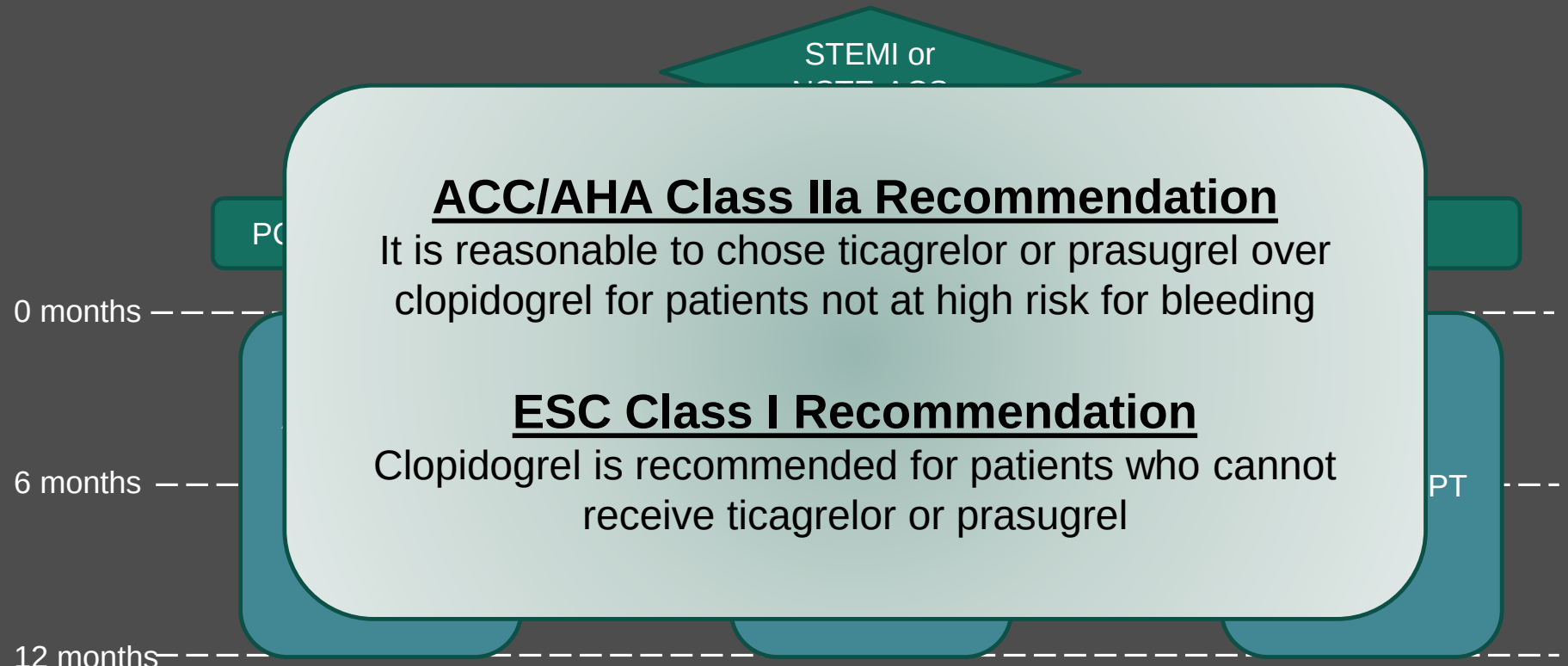
- Research grants to the Duke Clinical Research Institute from
  - NIH, PCORI, AHRQ, FDA
  - Amgen, AstraZeneca, Bristol Myers Squibb, Cryolife, Novartis, Pfizer, Portola and Regeneron
- Consulting honoraria from
  - Grifols and Gilead.

Guideline Recommendations



2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy
2015/2017 ESC Guidelines for the Management of Acute Coronary Syndrome and STEMI

Guideline Recommendations



ACC/AHA Class IIa Recommendation

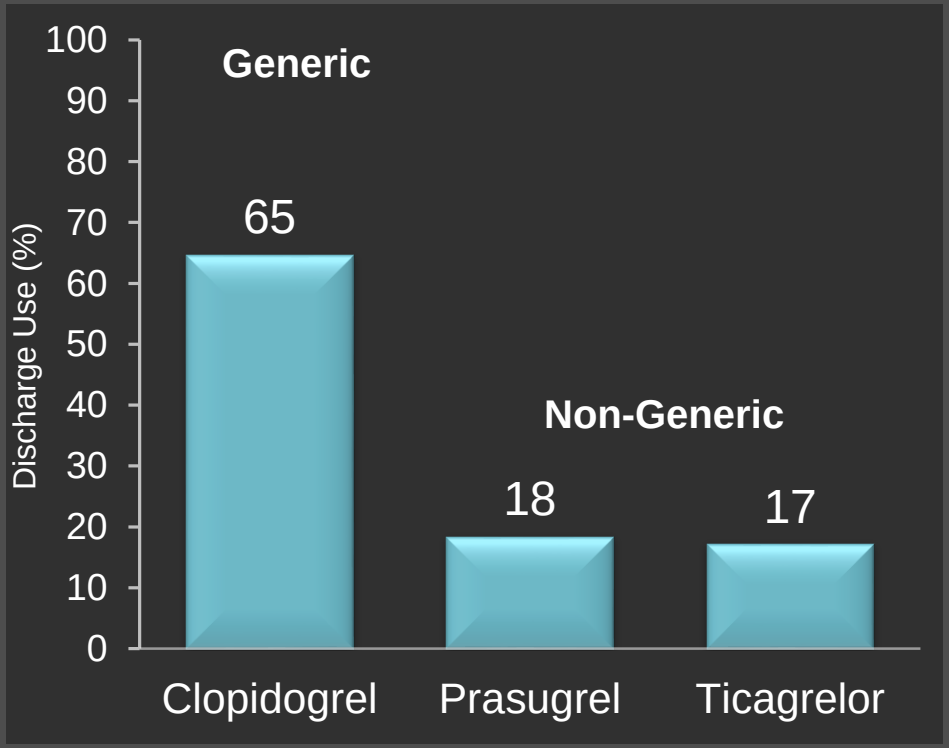
It is reasonable to chose ticagrelor or prasugrel over clopidogrel for patients not at high risk for bleeding

ESC Class I Recommendation

Clopidogrel is recommended for patients who cannot receive ticagrelor or prasugrel

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy
2015/2017 ESC Guidelines for the Management of Acute Coronary Syndrome and STEMI

Medication Use and Persistence

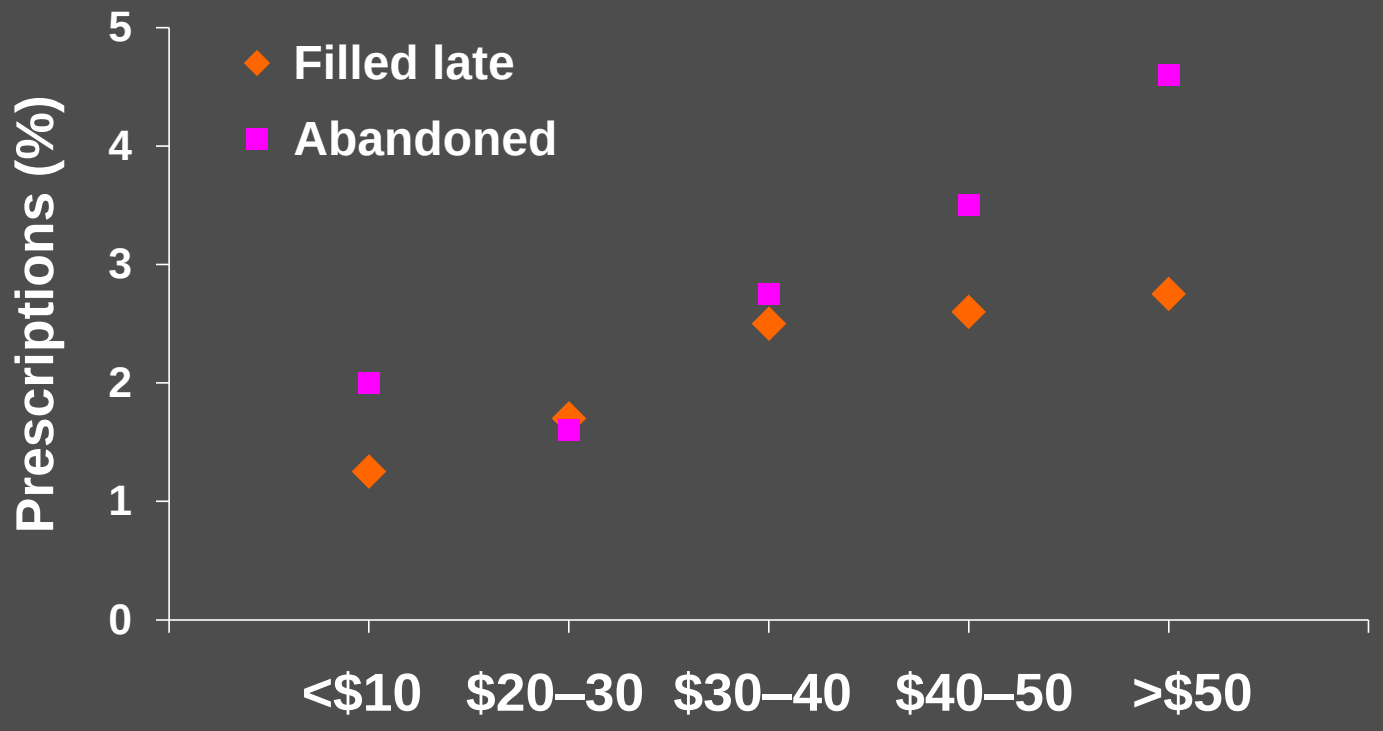


In the US:

- Higher potency (non-generic) $P2Y_{12}$ inhibitors under-utilized
- 30-60% of patients stop treatment within 1 year
- Patients' inability to afford medications is frequently cited as a barrier to both

Basra S. et al, *NCDR data 2013-2015, AHA QCOR 2016*
Czarny MJ et al, *Clin Cardiol 2014,* Fosbol EL et al, *Cath Cardiovasc Interv 2016*

Prescription Cost Affects Adherence



- New medication users 3x more likely to fill late/abandon
- >$50 prescription cost 5x more likely to abandon

Shrank et al. *Ann Intern Med*. 2010.

Hypotheses

By reducing and equalizing the out-of-pocket cost for generic and brand $P2Y_{12}$ inhibitors

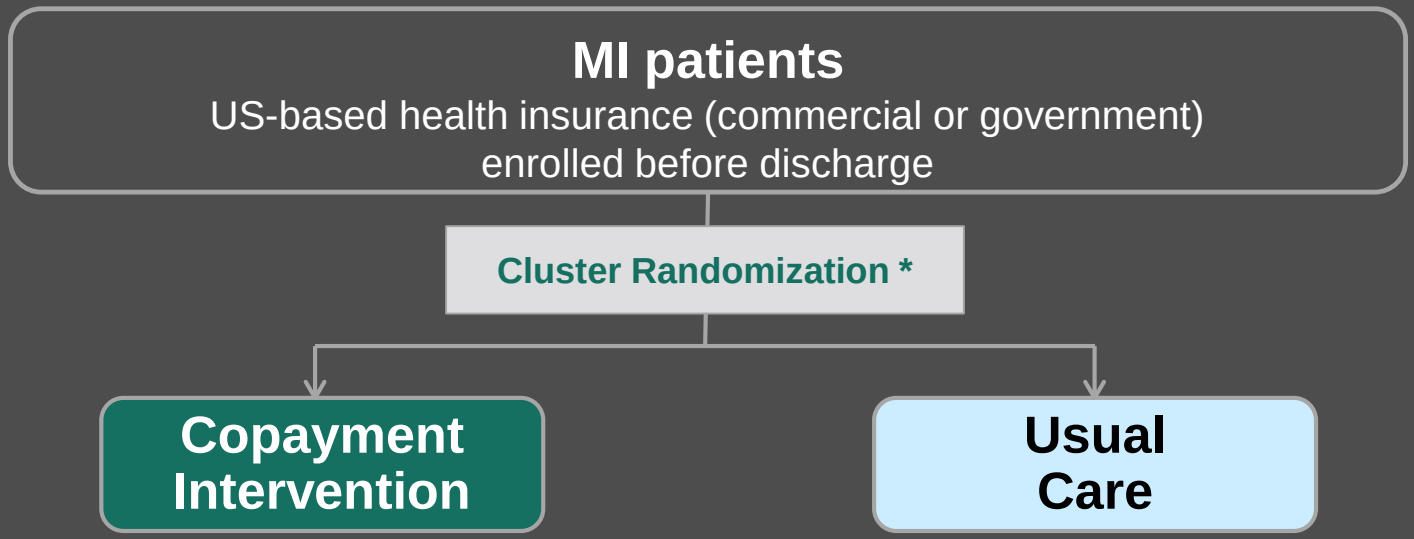
- Antiplatelet medication choice will be driven more by evidence than patient affordability
- Patients will be more likely to complete 1 year of therapy as recommended by practice guidelines
- Improved persistence to $P2Y_{12}$ inhibitor therapy will lead to better clinical outcomes

Doll JA et al., ARTEMIS design paper. *Am Heart J* 2016; 177: 33

Why This Study?

- Stimulate health system and payer consideration of novel cost-sharing models to
  - promote patient and provider adherence to evidence based therapies
  - Allow choice of therapies to be driven by differences in risk-benefit rather than the cost of the intervention
  - Improve patient outcomes
- Can we innovate the design of pragmatic health policy trials?

Study Design



- Treatment choice and duration of therapy determined by the treating physicians
- Intervention site patients provided a copayment voucher card for either generic clopidogrel or brand ticagrelor

Cluster Randomization

- Hospital- vs. patient-level randomization
  - Not dangling benefit in front of the patient
  - Preserves provider treatment decision-making
  - Patient-level randomization was considered impossible
    - unacceptably higher lost-to-follow-up rate for patients who were consented and randomized to no co-payment reduction

Cluster Randomization

- Hospital- vs. patient-level randomization
  - Not dangling benefit in front of the patient
  - Preserves provider treatment decision-making
  - Patient-level randomization was considered impossible
    - unacceptably higher lost-to-follow-up rate for patients who were consented and randomized to no co-payment reduction
- Vulnerable to imbalances in enrollment rate and type of enrolled

Trial Design Considerations

- Need to ensure both arms enroll as consecutively as possible with similar follow-up rates between groups
  - Make enrollment criteria as inclusive as possible
  - Make enrollment burden as light as possible for sites
  - Reduce patient barriers to enrollment and follow-up
  - Reduce loss to follow-up even in the group of patients not benefiting from an intervention

Broad Inclusion Criteria

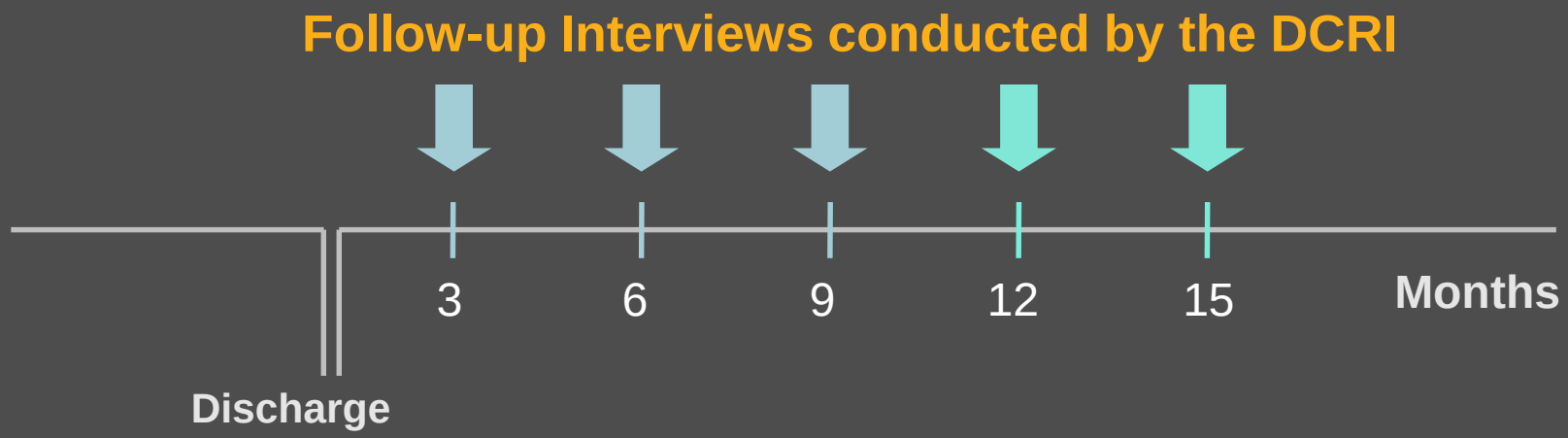
- MI patients ≥18 years of age treated with a $P2Y_{12}$ receptor inhibitor at the time of enrollment
- Have United States-based health insurance coverage with prescription drug benefit
- Able to provide consent for longitudinal follow-up
  - Do we need this requirement for future pragmatic trials when linkage to clinical data sources may be sufficient?

Reducing Site Burden

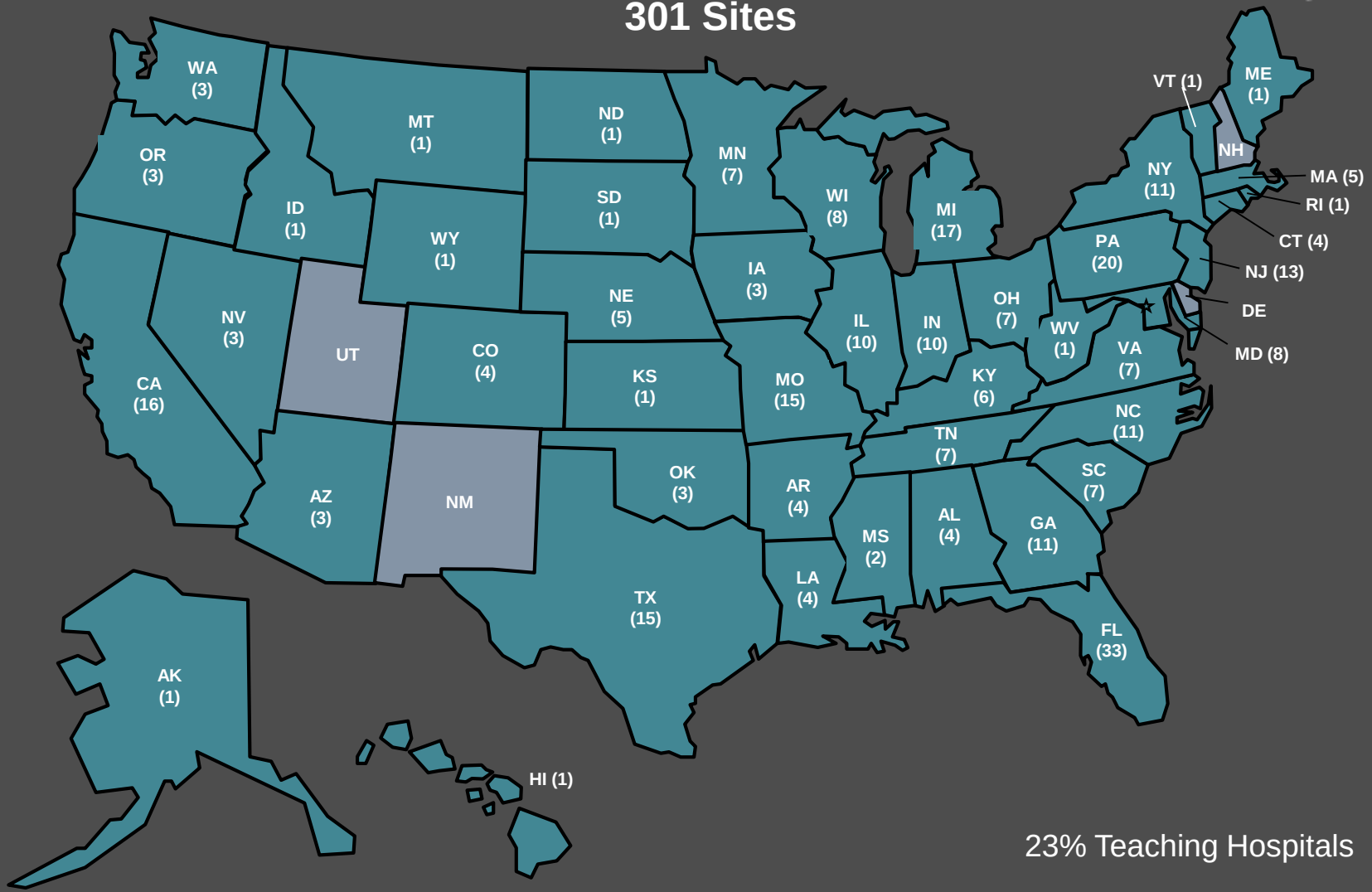
- Site responsibilities:
  - Identifying patients
  - Obtain consent
  - Baseline case report form
  - Medical record query 1 year later

Reducing Site Burden

- Site responsibilities:
  - Identifying patients
  - Obtain consent
  - Baseline case report form
  - Medical record query 1 year later



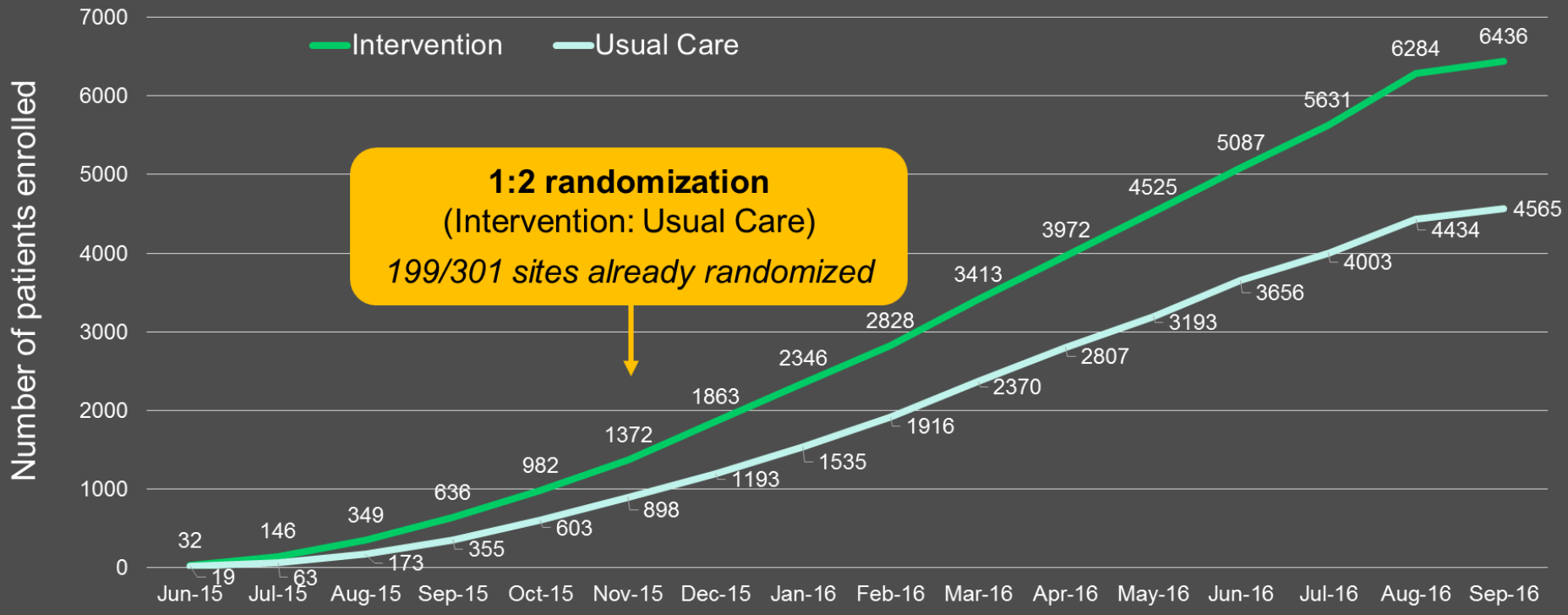
US Representation



23% Teaching Hospitals

Balancing Enrollment

11,001 patients (42%) enrolled among screen eligible



Patients declined more at usual care hospitals (29% vs. 26%, p<0.01)

Patient Characteristics

	Intervention N=6135	Usual Care N=3967	|StdDiff|
Age	62 (54, 70)	62 (54, 70)	0.00
Female	31.7%	32.4%	0.02
Non-white race	**10.4%**	**13.9%**	**0.11**
STEMI	46.4%	45.2%	0.02
Prior MI	19.6%	21.7%	0.05
Prior stroke/TIA	6.2%	7.5%	0.05
Diabetes	31.6%	34.0%	0.05
Creatinine clearance (ml/min)	71 (53, 90)	69 (52, 87)	0.04
Weight (kg)	89 (77, 103)	89 (76, 104)	0.01
Multivessel disease	47.2%	45.2%	0.02
PCI during index MI	90.1%	87.6%	0.08

StdDiff (standardized difference) >0.10 denotes significant difference

Reduce Patient Barriers

- No need to return to enrolling site for follow-up
- Follow-up interviews kept short
- Patients can choose phone- or web- follow-up
- Rescue mechanisms to complete follow-up

Reduce Patient Barriers

- No need to return to enrolling site for follow-up
- Follow-up interviews kept short
- Patients can choose phone- or web- follow-up
- Rescue mechanisms to complete follow-up

Patient Contact: 87% through 1 year

Lost-to-follow-up for MACE assessment: 1.8%

Web vs. Phone Follow-up

- 34% patients elected web-based follow-up

	Phone (n=7288)	Web (n=3688)
Age	63 (55,72)	59 (52,66) Max 98
Female	35%	24%
Non-white	14%	7%
Employment status **full time** **part time**	 32% 7%	 55% 8%
College of higher education	40%	66%
Low Health Literacy	17%	8%
EQ5D VAS	70	70

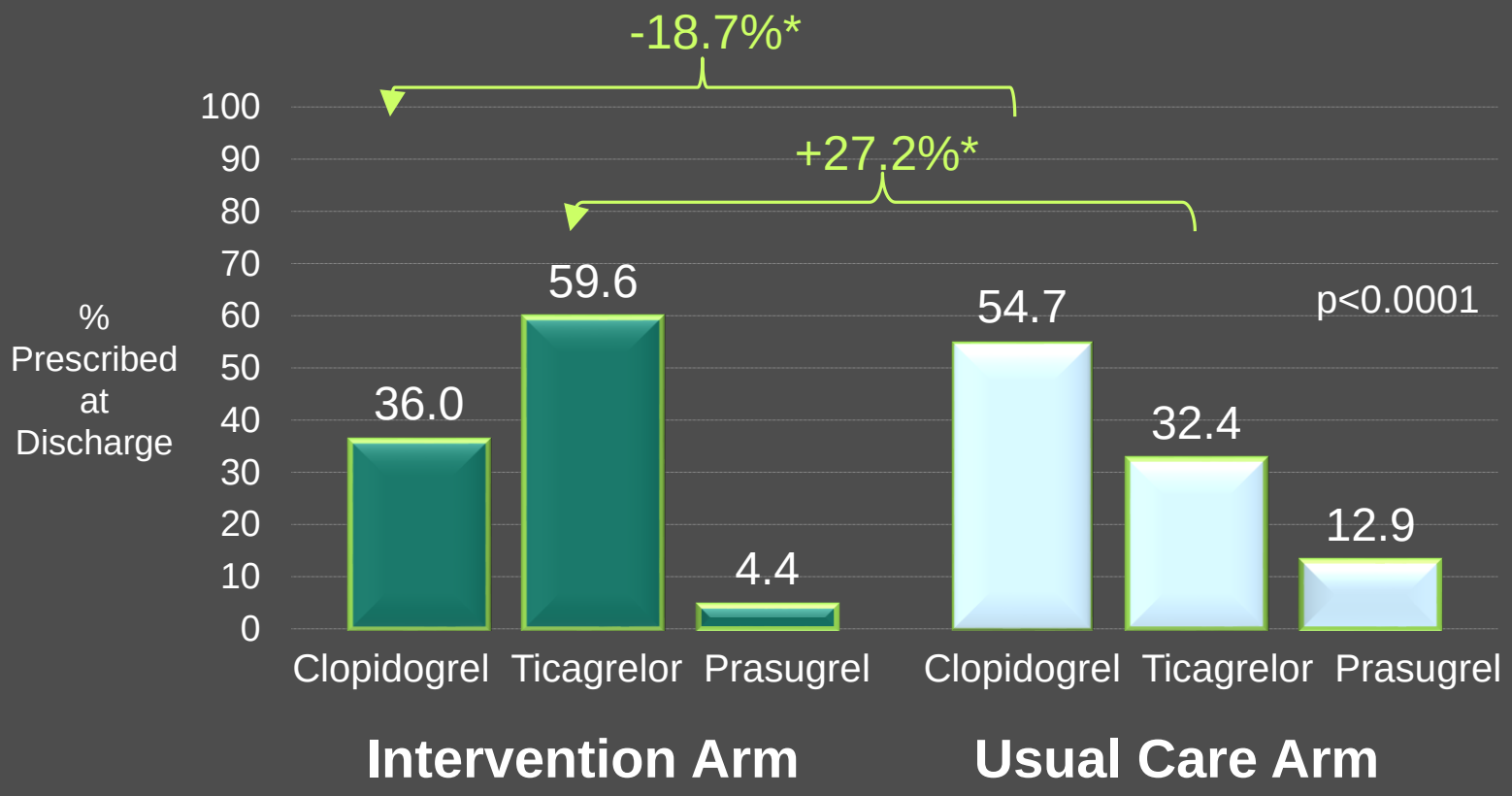
All p <0.001

Rescus for Web-Based Follow-up

- 72% patients needed rescue
  - Most of these (75%) needed rescue more than once

	Rescued >1x (n=2039)	Mostly Web (n=1649)	p
Age	58 (50,66)	60 (53,67)	<0.001
Female	25%	22%	0.11
Non-white	9%	5%	<0.001
Not working	35%	41%	<0.001
College of higher education	62%	70%	<0.001
Low Health Literacy	9%	6%	<0.001
Depression	10%	6%	<0.001
EQ5D VAS	70	74	<0.001

Intervention Increased Guideline Adherence



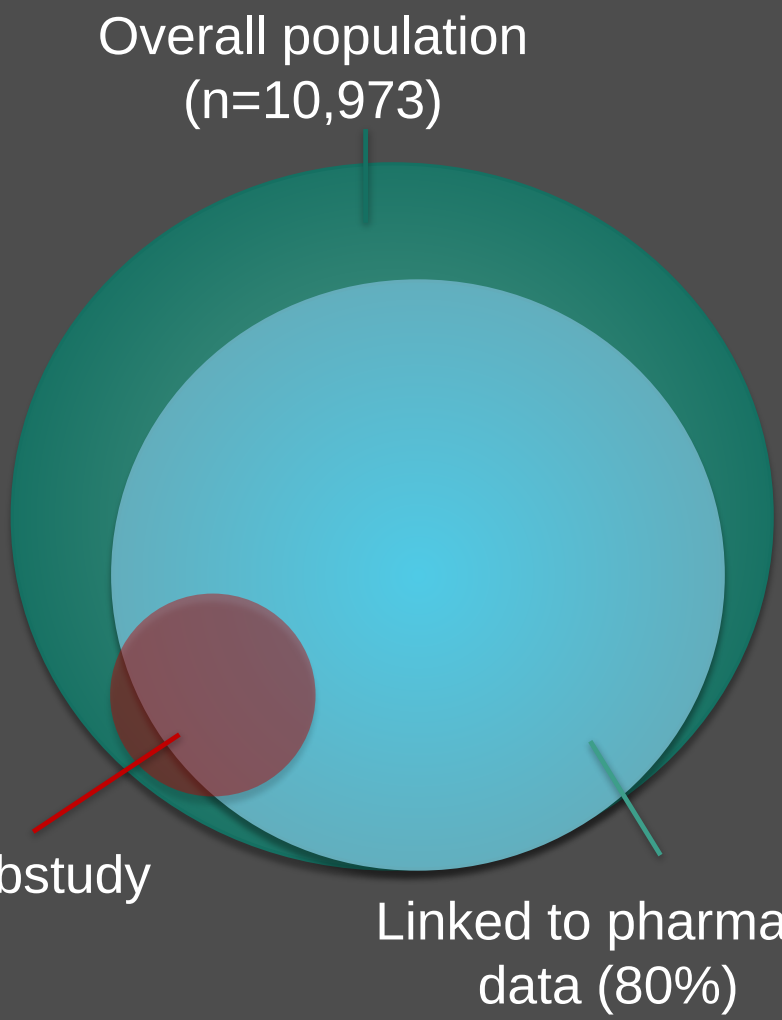
*absolute difference between intervention and usual care arms

Measuring Medication Use

- **Patient report**
  - % of patients who reported ≥30 days gap in use
- **Pharmacy fill**
  - % patients with pharmacy fill supply gap ≥30 days
- **Blood levels**
  - % patients without drug metabolite in blood draw

Measuring Medication Use

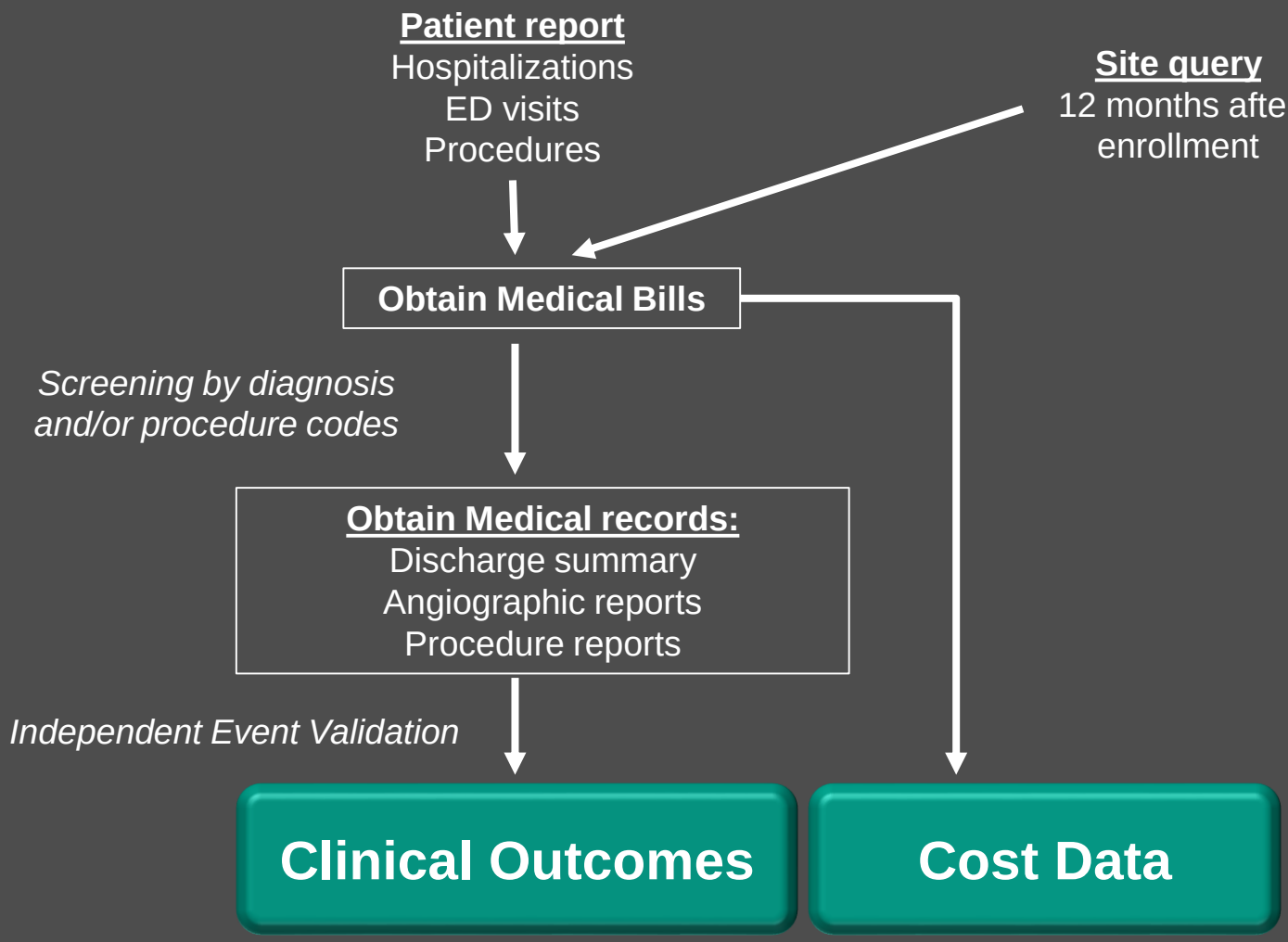
- **Patient report**
  - % of patients who reported ≥30 days gap in use
- **Pharmacy fill**
  - % patients with pharmacy fill supply gap ≥30 days
- **Blood levels**
  - % patients without drug metabolite in blood draw



Effect on Medication Persistence

	Intervention	Usual Care	p		OR (95% CI)
Primary Analysis					
Patient-Reported n=10,102	12.96%	16.21%	<0.0001	Unadjusted Adjusted	**0.76 (0.65, 0.89)** **0.84 (0.72, 0.98)**
Secondary Analyses					
Pharmacy Fills n=8,360	44.80%	53.71%	<0.0001	Unadjusted Adjusted	**0.64 (0.57, 0.73)** **0.68 (0.60, 0.77)**
Randomly-Selected Blood Draws n=944	8.23%	12.35%	0.04	Unadjusted	**0.64 (0.42. 0.98)**

Centralized Data Collection



American Heart Association | American Stroke Association

How Reliable are Patient-Reported Rehospitalizations? Implications for the Design of Future Practical Clinical Studies

Arun Krishnamoorthy, MD; Eric D. Peterson, MD, MPH; J. David Knight, MS; Kevin J. Anstrom, PhD; Mark B. Effron, MD; Marjorie E. Zettler, PhD, MPH; Linda Davidson-Ray, MS; Brian A. Baker, PharmD; Patrick L. McCollam, PharmD; Daniel B. Mark, MD, MPH; Tracy Y. Wang, MD, MHS, MSc

Background—Longitudinal clinical investigations often rely on patient reports to screen for postdischarge adverse outcomes events, yet few studies have examined the accuracy of such patient reports.

Methods and Results—Patients with acute myocardial infarction (MI) in the TRANSLATE-ACS study were asked during structured interviews at 6 weeks, 6 months, and 12 months postdischarge to report any rehospitalizations. The accuracy of patient-reported rehospitalizations within 1 year of postdischarge was determined using claims-based medical bill validation as the reference standard. The cumulative incidence of rehospitalizations was compared when identified by patient report versus medical bills. Patients were categorized by the accuracy in reporting events (accurate, under-, or over- reporters) and characteristics were compared between groups. Among 10 643 MI patients, 4565 (43%) reported 7734 rehospitalizations. The sensitivity and positive predictive value of patient-reported rehospitalizations were low at 67% and 59%, respectively. A higher cumulative incidence of rehospitalization was observed when identified by patient report versus medical bills (43% vs 37%; $P<0.001$). Overall, 18% of patients over-reported and 10% under-reported the number of hospitalizations. Compared with accurate reporters, under-reporters were more likely to be older, female, African American, unemployed, or a non-high-school graduate, and had greater prevalence of clinical comorbidities such as diabetes and past cardiovascular disease.

Conclusions—The accuracy of patient-reported rehospitalizations was low with patients both under- and over-reporting events. Longitudinal clinical research studies need additional mechanisms beyond patient report to accurately identify rehospitalization events.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT01088503. (***J Am Heart Assoc*. 2016;5: e002695 doi: 10.1161/JAHA.115.002695**)

Key Words: myocardial infarction • patient outcome assessment • validation studies

Patient Report of Hospitalizations

Among 10,643 patients

- 4,565 patients (43%) reported 7,734 hospitalizations
- 5,015 patients had 6,786 bills collected

	Follow-up Interval			
	6 Weeks	6 Months	12 Months	Total
Patient-reported hospitalizations confirmed by medical bills	1304 (63%)	1654 (60%)	1621 (56%)	4579 (59%)
Confirmed medical bills not patient-reported	403 (24%)	889 (35%)	915 (36%)	2207 (33%)

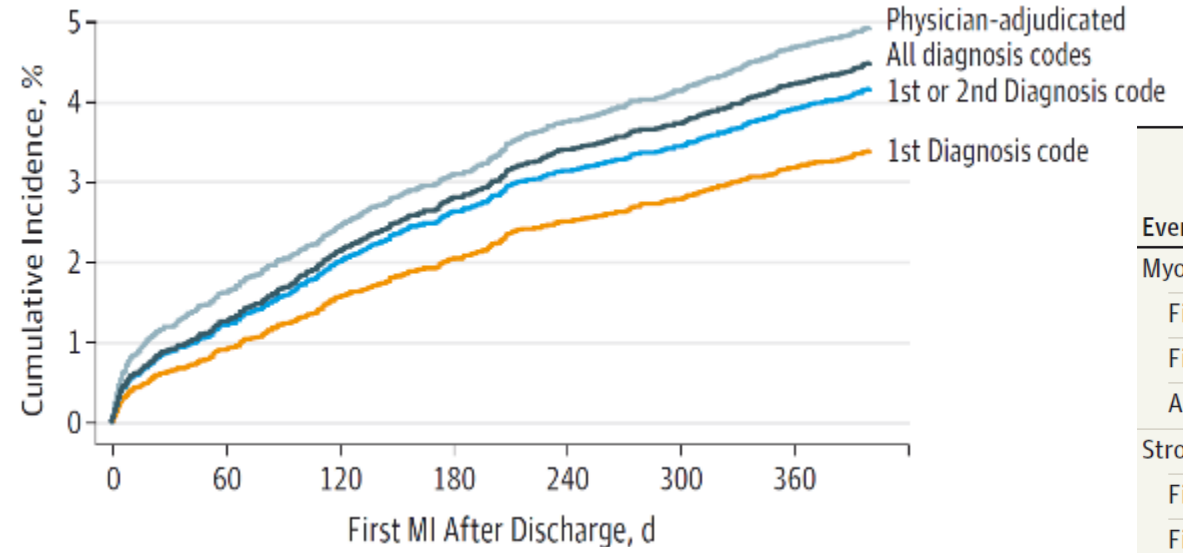
- 72% accurately reported # hospitalizations
  - 18% (n=1,911) over-reported
  - 10% (n=1,012) under-reported

Can Patients Accurately Report MI/Stroke?

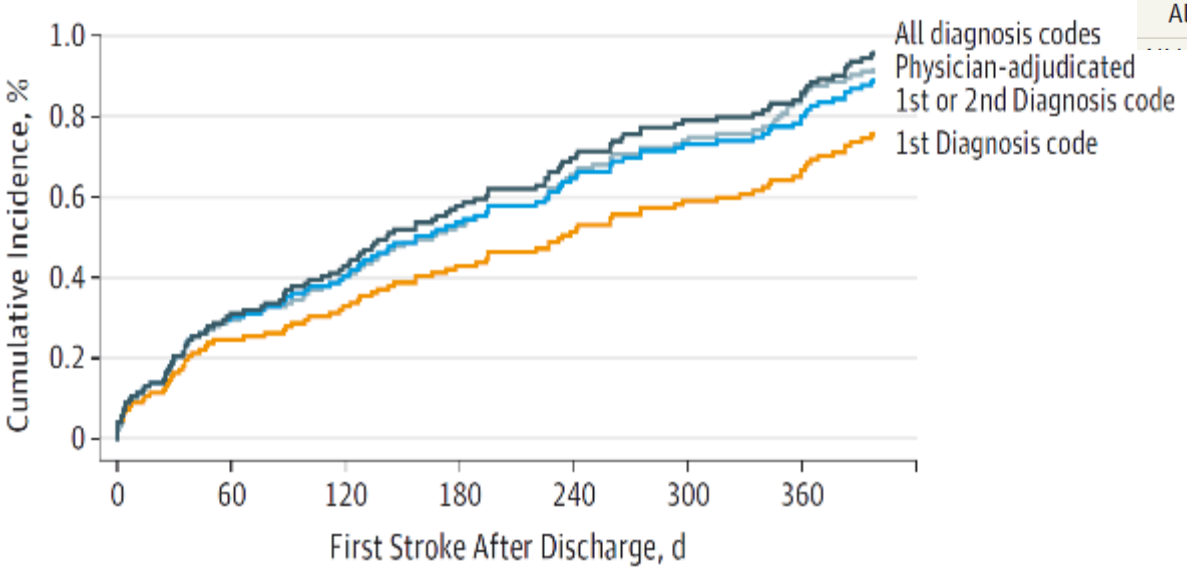
Table 2. Comparison Between Patient-Reported Rehospitalization for MI and Stroke and Physician-Validated Recurrent MI and Stroke

	Physician Validated MI: Yes	Physician Validated MI: No
Patient-reported MI: yes	103	257
Patient-reported MI: no	254	N/A
Sensitivity	29%	
Positive predictive value	29%	
	Physician Validated Stroke: Yes	Physician Validated Stroke: No
Patient-reported stroke: yes	19	57
Patient-reported stroke: no	36	N/A
Sensitivity	35%	
Positive predictive value	35%	

Are Claims Data Any Better?

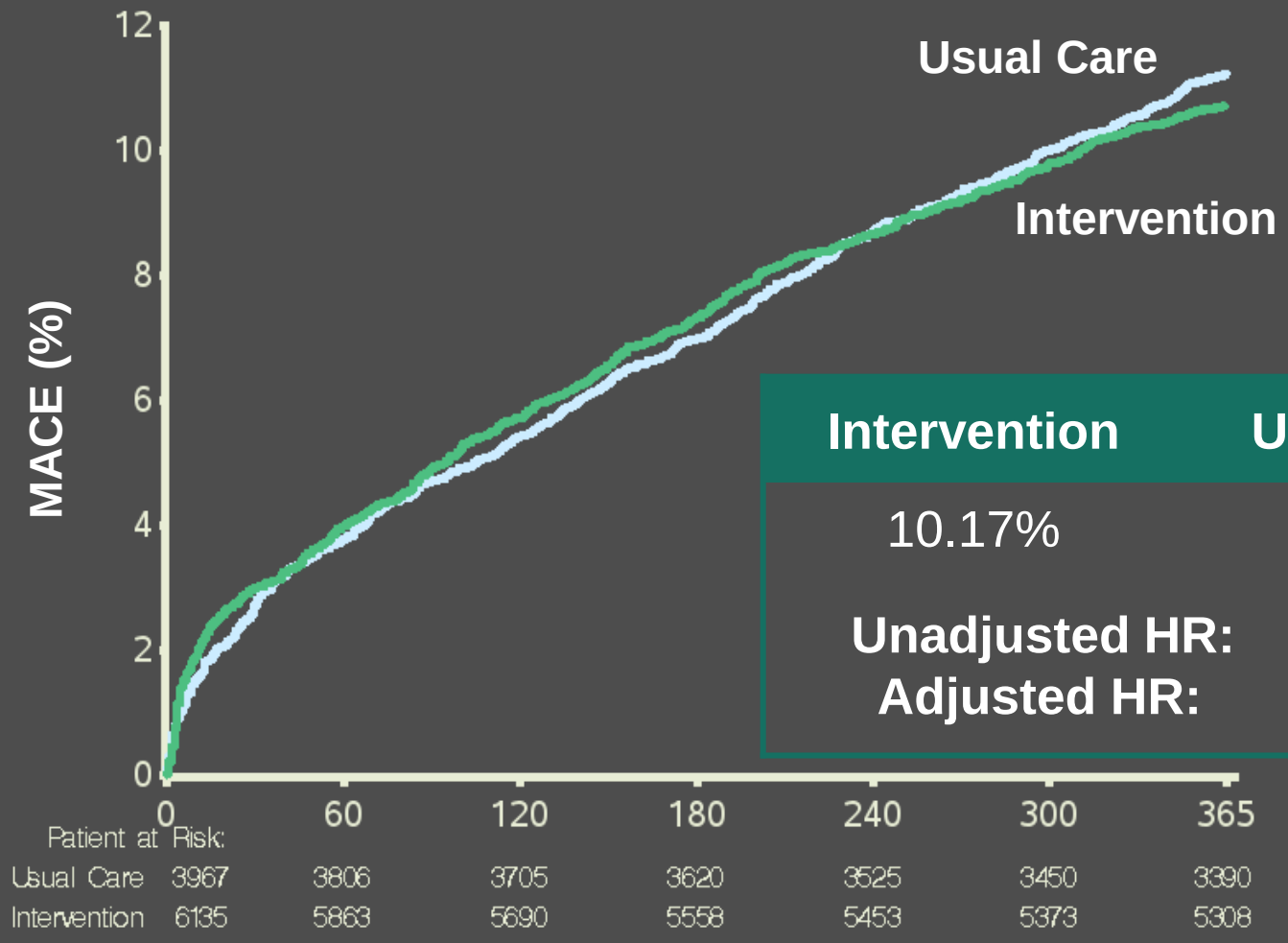


Events	Incidence Rate, %	
	Medical Claims	Physician Adjudication
Myocardial infarction		
First diagnosis code	3.2	4.7
First or second diagnosis code	4.0	4.7
All diagnosis codes	4.3	4.7
Stroke		
First diagnosis code	0.7	0.9
First or second diagnosis code	0.8	0.9
All diagnosis codes	0.9	0.9



Guimaraes P, Wang TY. JAMA Cardiology, published May 23, 2017

Clinical Outcomes



Intervention	Usual Care	p
10.17%	10.63%	0.65
Unadjusted HR:	**0.96 (0.80, 1.15)**	
Adjusted HR:	**1.07 (0.93, 1.25)**	

Take Home Messages

- Health policy and implementation studies require pragmatic trial design
- Cluster randomized design may be uniquely suited but more likely present operational challenges compared with patient-randomized designs
- Lessons learned on
  - how to enhance site and patient participation in research
  - Practically but accurately assess outcomes