Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study

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presenting on behalf of

ARTEMIS Investigators

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

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Guidelines – DAPT after ACS

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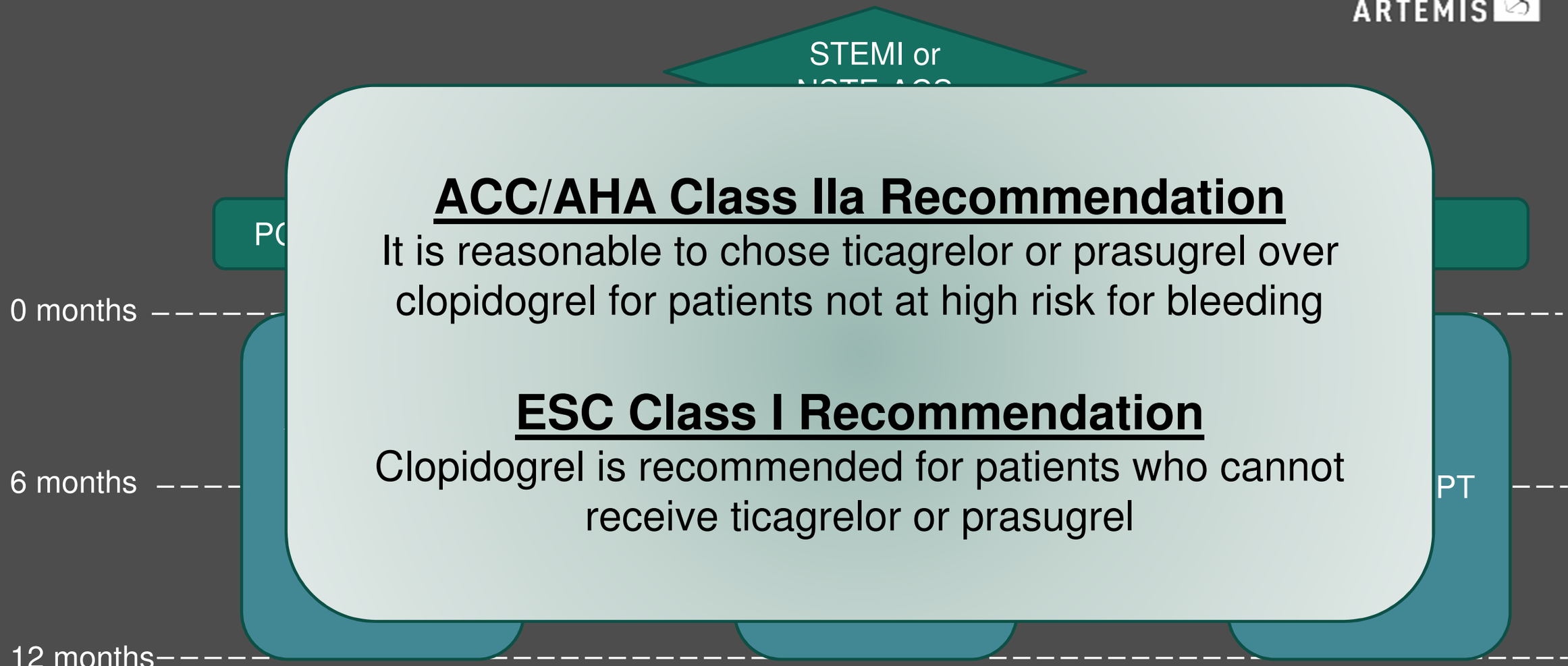

ACC/AHA Class IIa Recommendation

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

$P2Y_{12}$ Inhibitor Use and Persistence in the US

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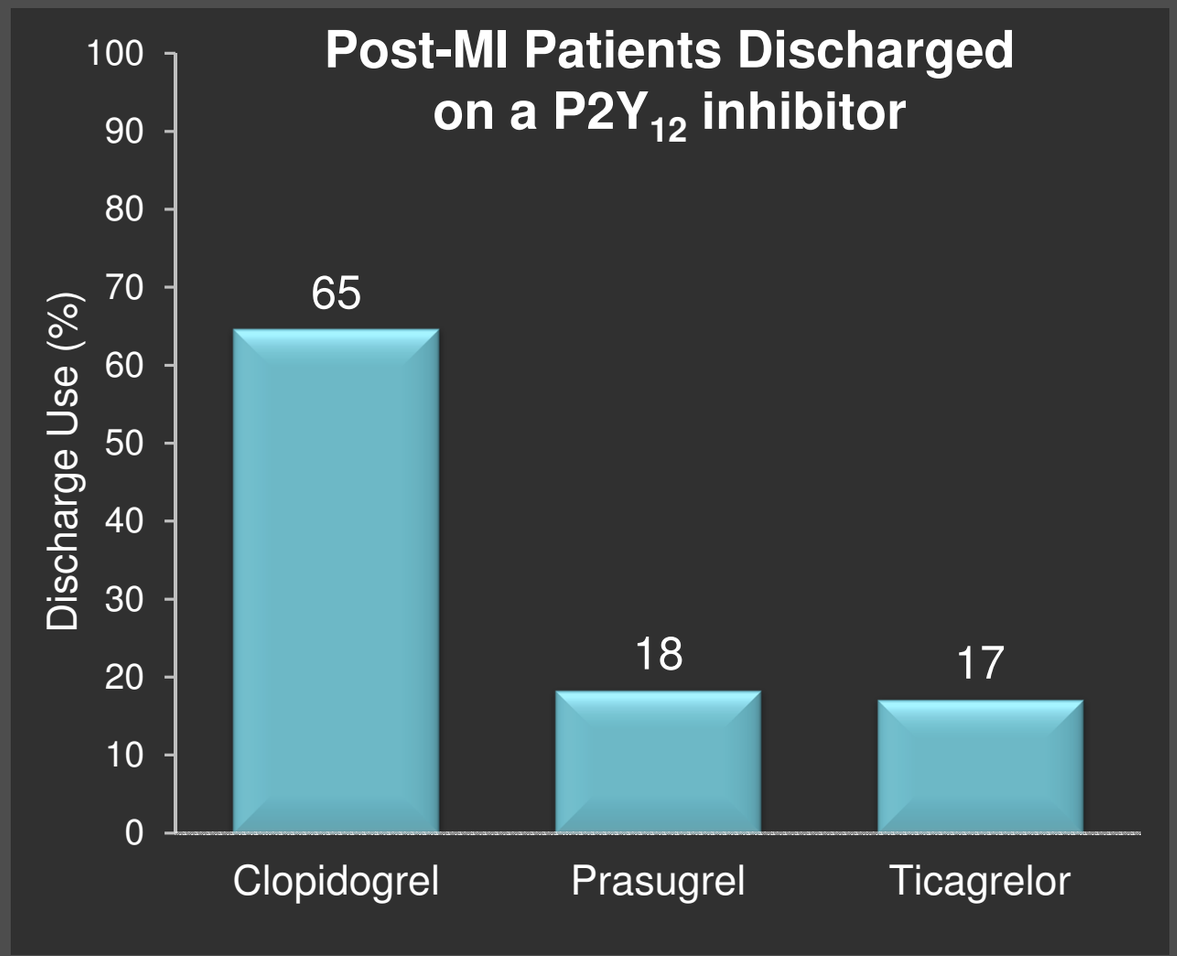

Among post-MI patients in the US:

- Clopidogrel is the most commonly prescribed $P2Y_{12}$ inhibitor
- 30-60% of patients stop $P2Y_{12}$ inhibitor treatment within 1 year
- Affordability thought to be a key factor for 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*

Hypotheses

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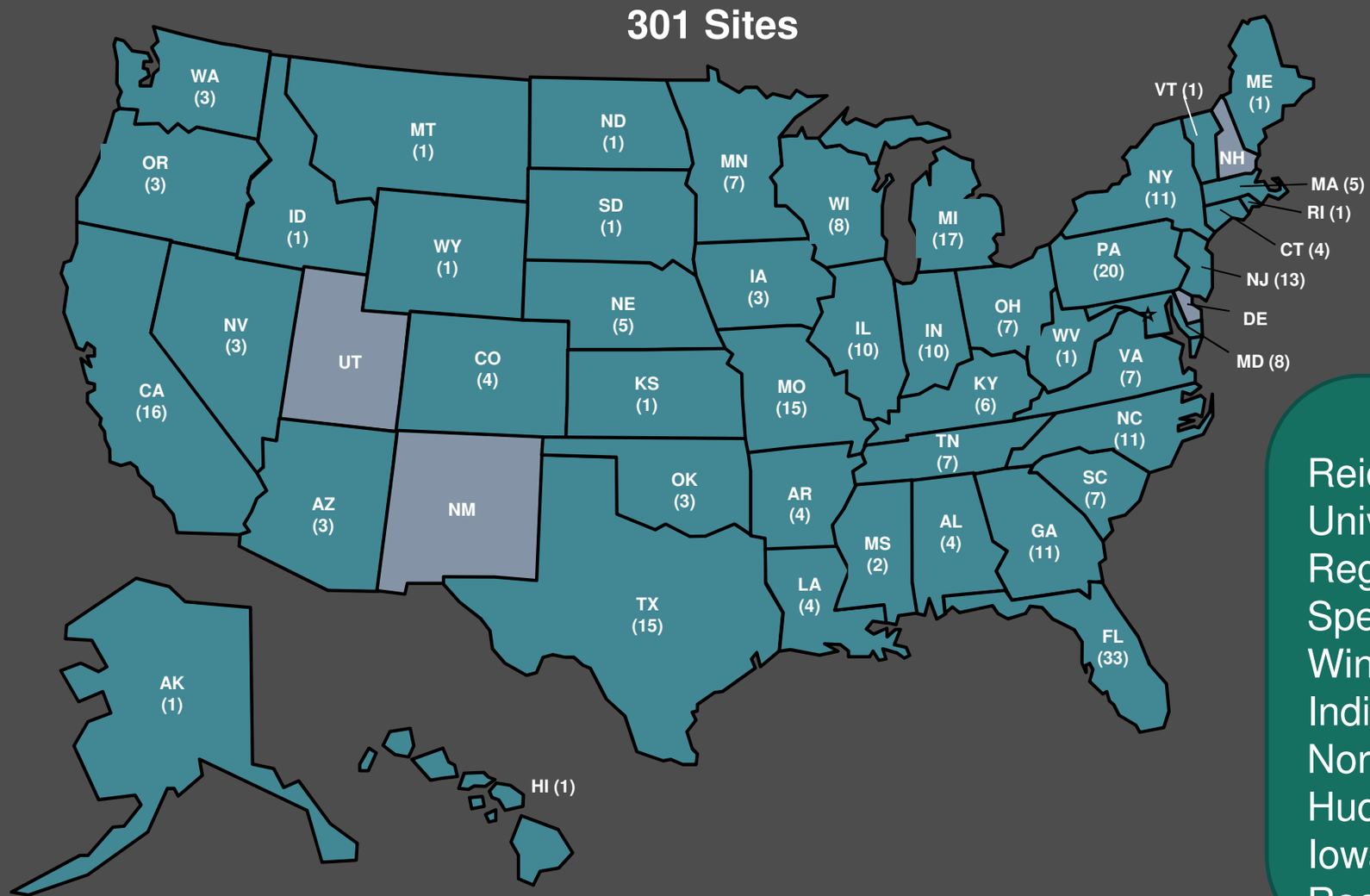
By reducing and equalizing the out-of-pocket cost for generic and brand antiplatelet agents

- 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

ARTEMIS Sites



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Top 10 Enrolling Sites

Reid Hospital (Z. Mirza)
University of Massachusetts (N. Kakouros)
Regions Hospital (W. Nelson)
Spectrum Health (R. McNamara)
Winchester Medical Center (J. Call)
Indiana University (A. Ferguson)
Norton Cardiovascular (V. Panchal)
Hudson Valley Heart Center (L. Kantaros)
Iowa Heart Center (M. Tannenbaum)
Rockford Cardiovascular (A. Sheikh)

Study Design

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STEMI or NSTEMI patients on $P2Y_{12}$ inhibitor therapy
enrolled before discharge
US-based health insurance (commercial or government)

Cluster Randomization *

Copayment Intervention

Usual Care

*Randomization stratified by annual MI volume and baseline % ticagrelor use

Copayment Intervention

- $P2Y_{12}$ inhibitor choice and duration of therapy determined by the treating physicians
  - Enrolled patients could be treated with any $P2Y_{12}$ inhibitor
- Intervention site patients provided a copayment voucher card for either a generic (clopidogrel) or brand (ticagrelor) $P2Y_{12}$ inhibitor
- No other interventions to improve adherence were given

Endpoints

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Co-Primary Endpoints

- Non-persistence of $P2Y_{12}$ inhibitor therapy, defined as
  - % patients who reported ≥30 days gap in $P2Y_{12}$ inhibitor use within 1 year
- MACE (death, recurrent myocardial infarction, and stroke within 1 year)

Key Secondary Endpoints

- $P2Y_{12}$ inhibitor therapy selection at discharge
  - % of patients prescribed ticagrelor vs. clopidogrel vs. prasugrel
- Non-persistence by pharmacy fill
  - % patients with pharmacy fill supply gap ≥30 days
- Non-persistence by blood levels
  - % patients without drug metabolite in blood on random draw

Analysis

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- Because of the un-blinded cluster design, analyses were adjusted for baseline covariates using a propensity model
- Among patients discharged on clopidogrel or ticagrelor
  - Non-persistence of $P2Y_{12}$ inhibitor - logistic regression model with generalized estimating equations to account for within hospital clustering
  - MACE - Cox proportional hazards model with robust standard errors to account for within hospital clustering
- Intention to treat and as-treated (voucher use)

Enrollment Trend

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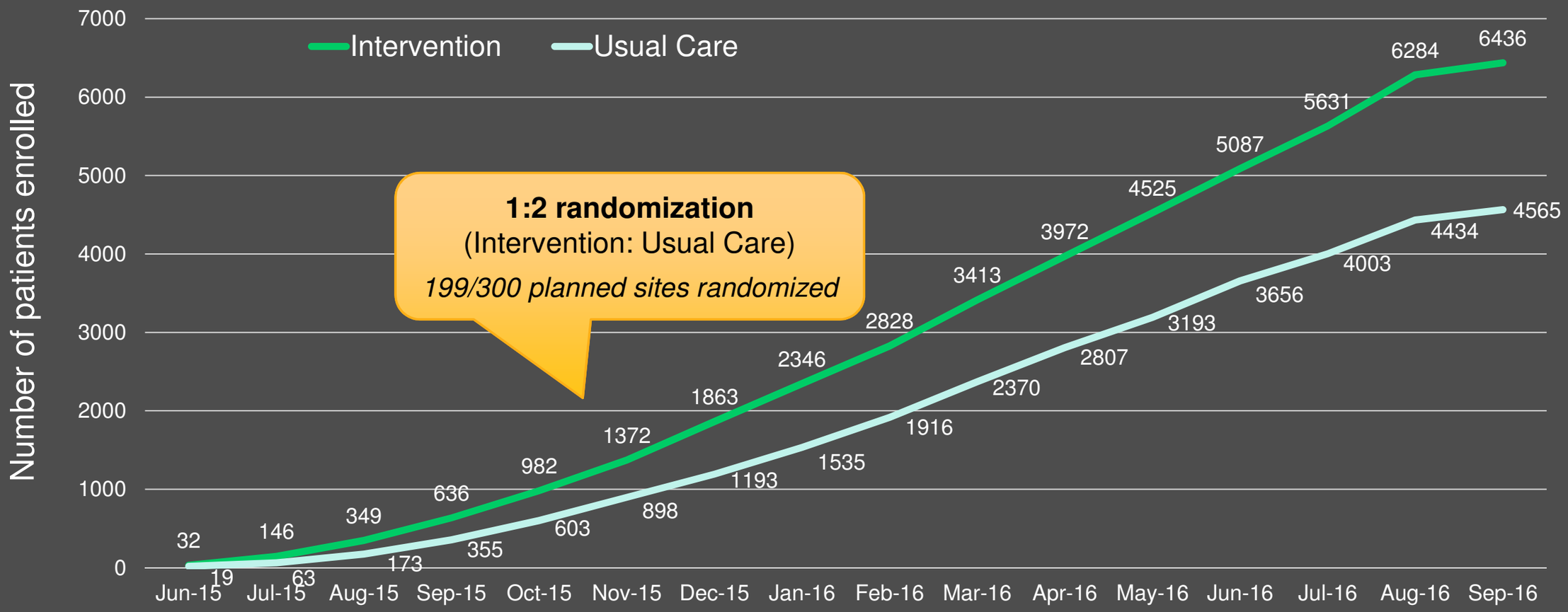

Enrollment and Randomization

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11,001 MI patients at 301 US hospitals

Intervention		**Usual Care**
135 sites randomized, 6,436 patients		166 sites randomized, 4,565 patients
(n=16)	**Died before discharge**	(n=8)
(n=1)	**Withdrew before discharge**	(n=0)
(n=1)	**Discharged without $P2Y_{12}$ inhibitor**	(n=3)
(n=283, 4.4%)	**Discharged on prasugrel**	(n=587, 12.9%)
Intervention		**Usual Care**
131 sites enrolled 6,135 patients		156 sites enrolled 3,967 patients

Hospital Characteristics

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	Intervention N=135	Usual Care N=166	p
Bed size	369 (268, 516)	397 (262, 620)	0.30
Teaching hospital	22.2%	26.5%	0.36
Annual MI volume			0.70
Low (<400)	43.0%	45.2%	
High (≥400)	57.0%	54.8%	
Ticagrelor use before ARTEMIS			0.63
Low (<15%)	43.7%	41.0%	
High (≥15%)	56.3%	59.0%	
# of patients enrolled per site	**37 (18, 66)**	**18 (7, 37)**	**<0.0001**

Patient Demographic Characteristics

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	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**
Private Insurance	63.0%	64.0%	0.02
Employed	46.7%	44.4%	0.08

StdDiff (standardized difference) >0.10 denotes significant difference

Clinical Characteristics

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	Intervention N=6135	Usual Care N=3967	|StdDiff|
STEMI	46.4%	45.2%	0.02
Prior MI	19.6%	21.7%	0.05
Prior CABG	10.7%	12.0%	0.04
Prior stroke/TIA	6.2%	7.5%	0.05
Peripheral artery disease	5.8%	7.1%	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
Home aspirin	42.4%	44.6%	0.04
Home P2Y12 inhibitor	**12.9%**	**16.5%**	**0.10**
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

Discharge $P2Y_{12}$ Inhibitor Selection

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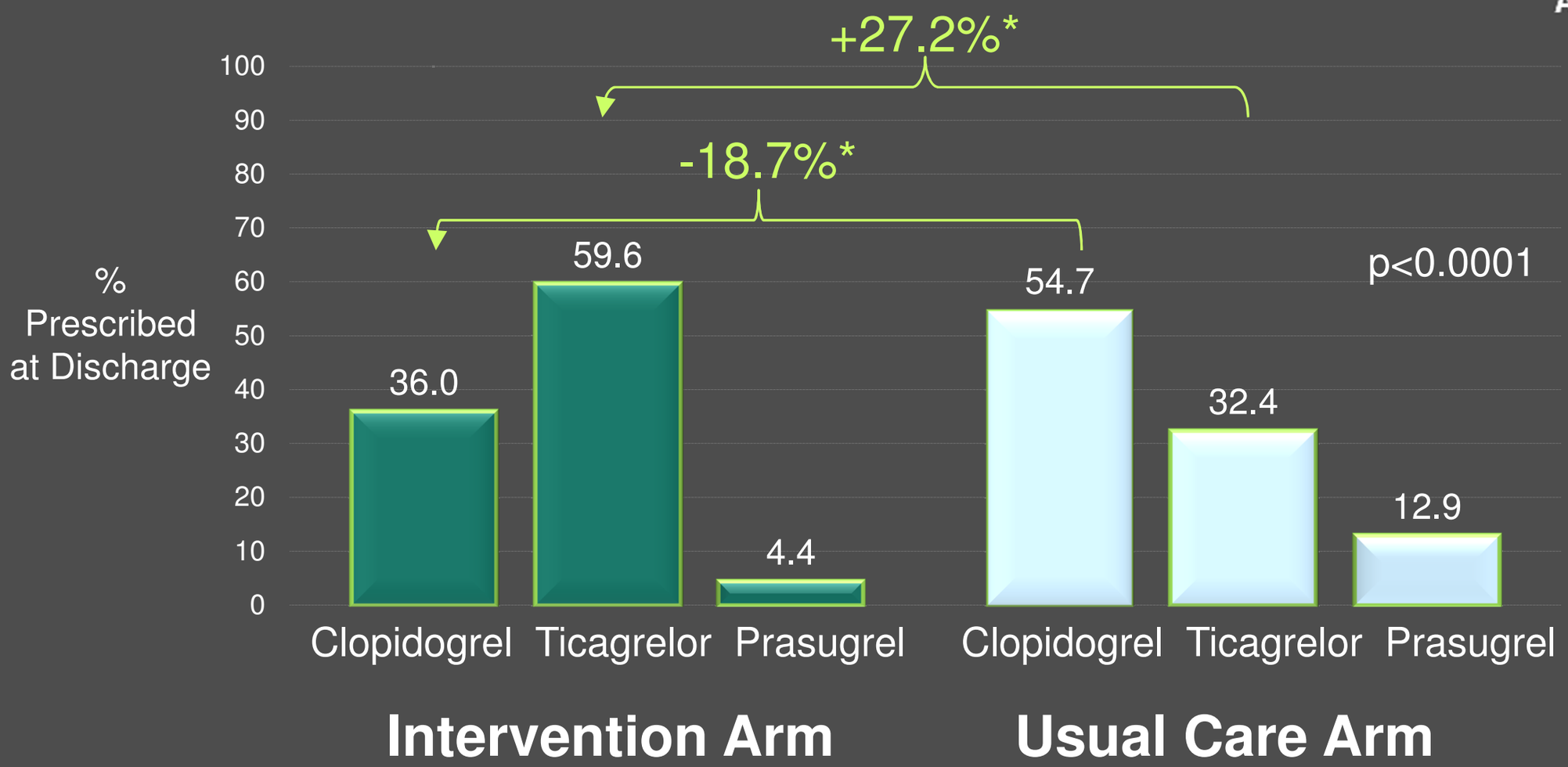

*absolute difference between intervention and usual care arms

Non-Persistence of $P2Y_{12}$ Inhibitor

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	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)**

Major Adverse Cardiovascular Events

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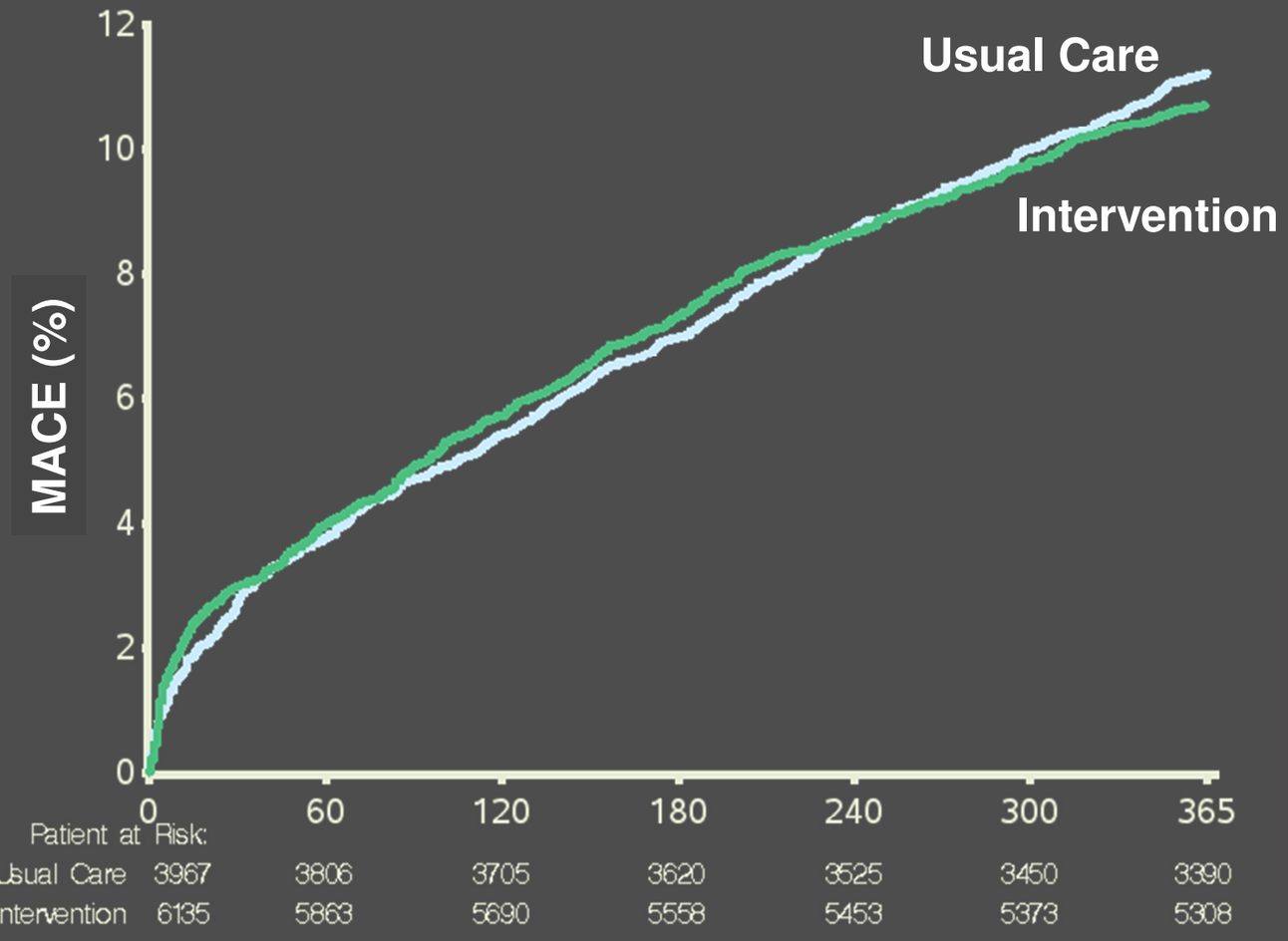

Intervention	Usual Care	p
10.17%	10.63%	0.65
Unadjusted HR:	**0.96**	**(0.80, 1.15)**
Adjusted HR:	**1.07**	**(0.93, 1.25)**

	Intervention	Usual Care	p
Death	3.86%	3.88%	0.98
Recurrent MI	6.91%	7.28%	0.64
Stroke	0.82%	0.95%	0.53

Adjusted comparisons non-significant for each component

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Non-Persistence of $P2Y_{12}$ Inhibitor

As Treated Analysis

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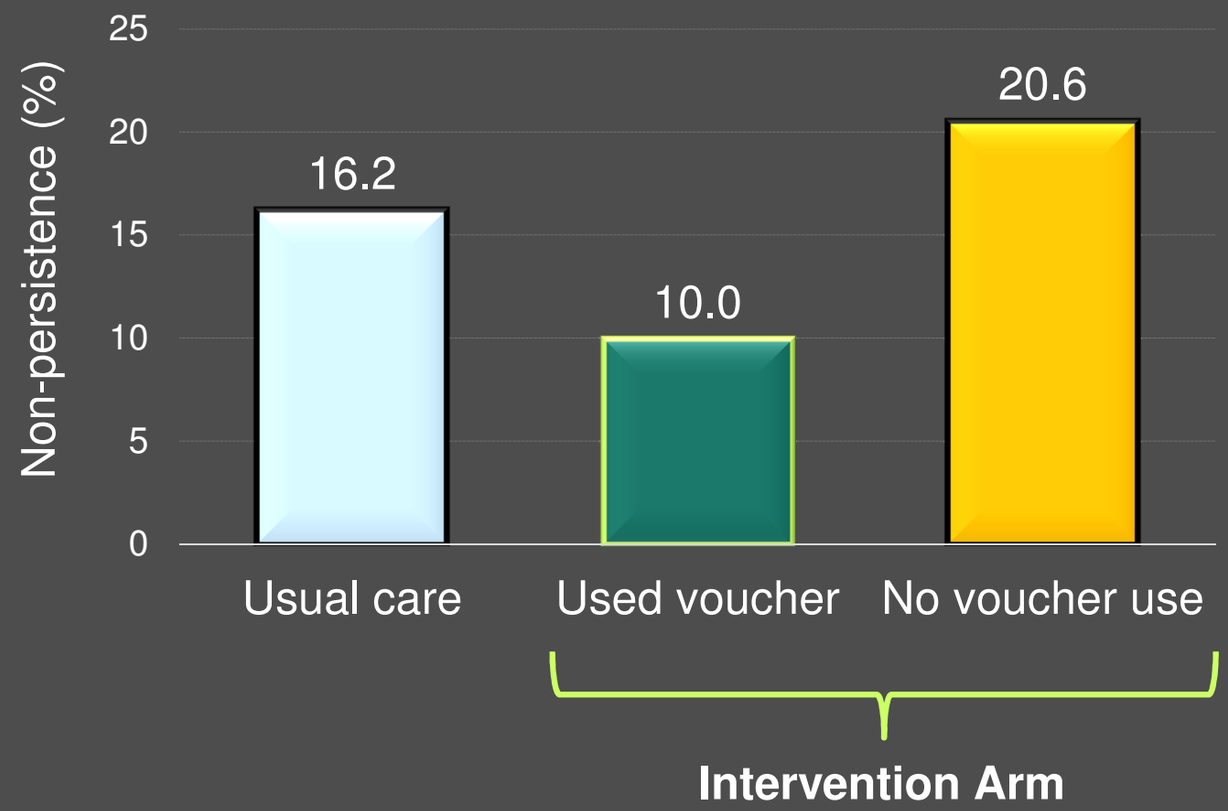
- 1,742 (28%) intervention arm patients did not use study voucher



As Treated* vs. Usual Care

Intervention	Usual Care	p
9.95%	16.21%	<0.0001

Unadjusted OR:	**0.56**	**(0.47, 0.66)**
Adjusted OR:	**0.65**	**(0.55, 0.78)**

*as treated = voucher use

Major Adverse Cardiovascular Events

As Treated Analysis

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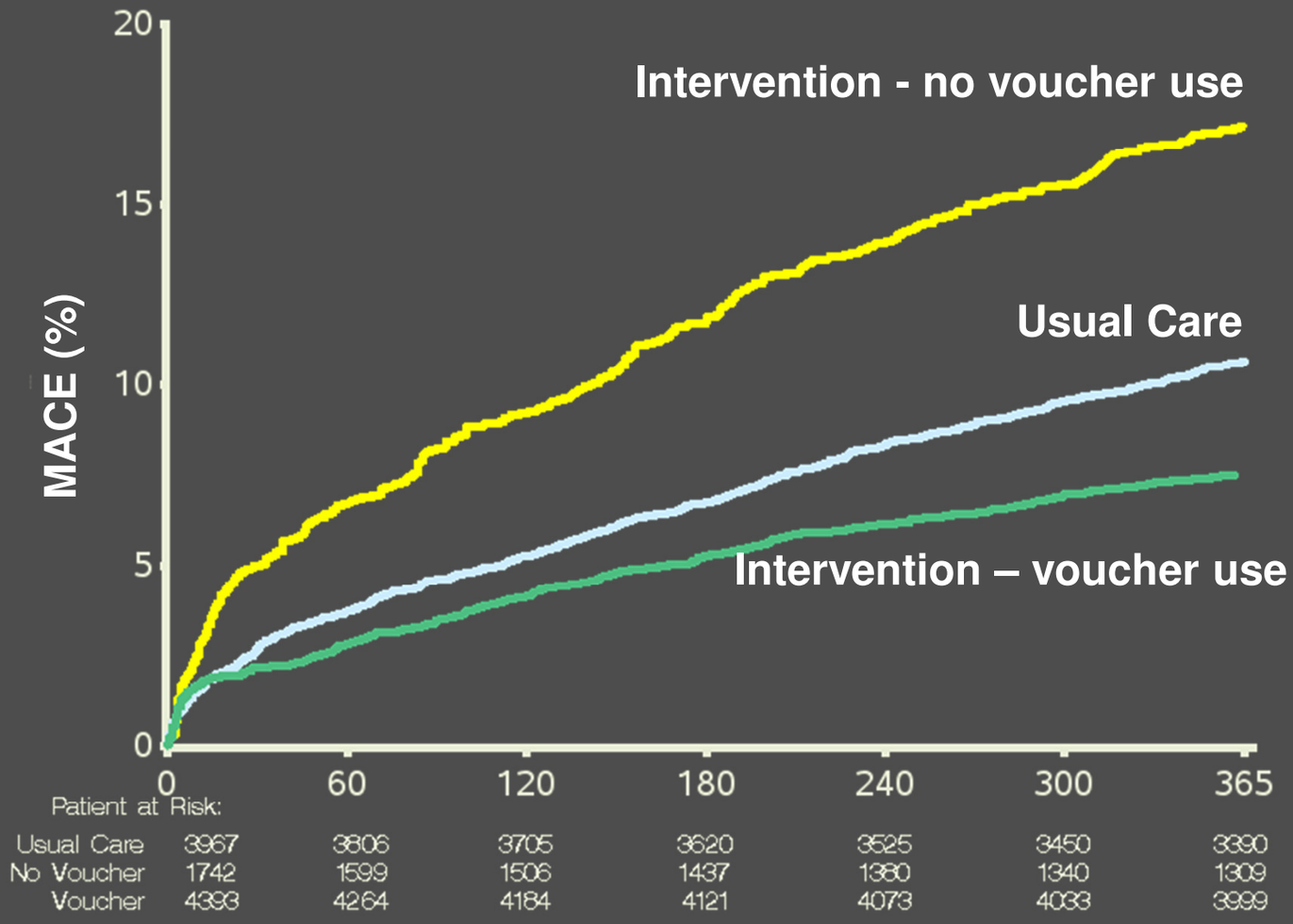

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As Treated* vs. Usual Care

Intervention	Usual Care	p
7.49%	10.63%	0.0001
Unadjusted HR:	**0.70**	**(0.58, 0.84)**
Adjusted HR:	**0.90**	**(0.76, 1.08)**

*as treated = voucher use

Limitations

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- Patient-reported $P2Y_{12}$ persistence rates were high, reflecting the current emphasis on patient adherence education
- Imbalance in enrollment
  - Cluster randomized design intended to study clinician prescribing behavior but gave less incentive to enroll at control sites
  - Possible residual unmeasured confounding between clusters
- No perfect measure of drug persistence
  - Limitations to all measurement methods

Conclusions

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- Copayment reduction significantly
  - Affected clinician choice of treatment
  - Improved persistence to treatment
- Despite increased evidence-based treatment, clinical outcomes were not significantly improved

Implications

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- **Why was copayment reduction alone not enough to change clinical outcomes?**
  - Targeted single drug only
  - Modest co-pay differences and high baseline persistence
  - Incomplete use of co-pay vouchers
  - Significant albeit modest impact on persistence
- **Broad-scale interventions likely needed to further improve medication persistence and patient outcomes**
  - Consider copayment reduction as part of a multi-pronged strategy to enhance medication persistence and outcomes

Acknowledgments

ARTEMIS

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