ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events): A Study to Assess the Efficacy and Safety of Aspirin in Patients at Moderate Risk of Cardiovascular Disease

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For the ARRIVE Executive Committee

European Society of Cardiology

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ARRIVE Executive Committee: *JM. Gaziano, C. Brotons, R. Coppolecchia, C. Cricelli, H. Darius, PB. Gorelick, G. Howard, TA. Pearson, PM. Rothwell, LM. Ruilope, M. Tendera, G. Tognoni.*

Declaration of Interest

- Consulting/Royalties/Owner/Stockholder of a healthcare company (Consulting – Bayer)

- All voting members of the ARRIVE Executive Committee (EC) received personal fees from Bayer during the conduct of the study.
- R. Coppolecchia is an employee of Bayer Healthcare.
- The following EC members report additional relationships:
  - PMR: personal fees from Bristol-Meyers Squibb
  - LMR: personal fees from Novartis, Sanofi, Medtronic, Daiichi-Sanyo and grants from Astra-Zeneca
  - MT: personal fees from Celyad, Janssen Cilag, Kowa, Perfuse Group, Servier
- Role of the sponsor and executive committee are provided in detail in the paper in the *Lancet.*

ARRIVE Study Design

- **Design:** Randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy and safety of aspirin among those at moderate estimated risk of a cardiovascular event.

- **Setting:** Primary care offices in 7 countries: Germany, Poland, UK, Italy, Spain, Ireland, US

- **Study Population:** Subjects had no known history of CVD or diabetes and were considered at moderate risk (estimated 10-year risk of major CHD events of 10-20% corresponding to a 10-year CVD risk of 20-30%)
  - Men ≥55 years with 2 or more CV risk factors
  - Women ≥60 years with 3 or more CV risk factors

- **Intervention:** 100 mg enteric-coated aspirin daily versus placebo

ARRIVE Study Design

- **Primary Efficacy Endpoint:** Time of first occurrence of composite endpoint: cardiovascular disease (CVD) death, myocardial infarction (MI), stroke, unstable angina (UA), transient ischemic attack (TIA)

- **Secondary Efficacy Endpoints:** Composite of CVD death, MI or stroke; all-cause death; and incidence of each of components of the primary endpoint

- **Safety Endpoints:** Bleeding events and incidence of adverse events

- **Protocol amendments driven by lower than expected event rates:**
  - Moved from event driven (1488 events) to common study end date (11/15/16)
  - Extended treatment and follow-up to 72 months to acquire 60,000 person-years
  - Addition of TIA and UA to primary composite endpoint

ARRIVE Study Design

Demographics
(Intent-to-Treat Population)

	Placebo Arm (n= 6276)	Aspirin Arm (n= 6270)
Age at Randomization (year)		
Mean	63.9	63.9
SD	7.05	7.10
Median	63.0	63.0
Min – Max	50 - 97	50 - 91
Categorical Distribution of Age at Randomization, %		
<= 59 years old	25.75%	25.89%
60 to 69 years old	52.36%	52.70%
>= 70 years old	21.89%	21.42%
Gender, %		
Female	29.59%	29.52%
Male	70.41%	70.48%

Note: Percentages based on number of subjects randomized to the indicated treatment group

Demographics
(Intent-to-Treat Population)

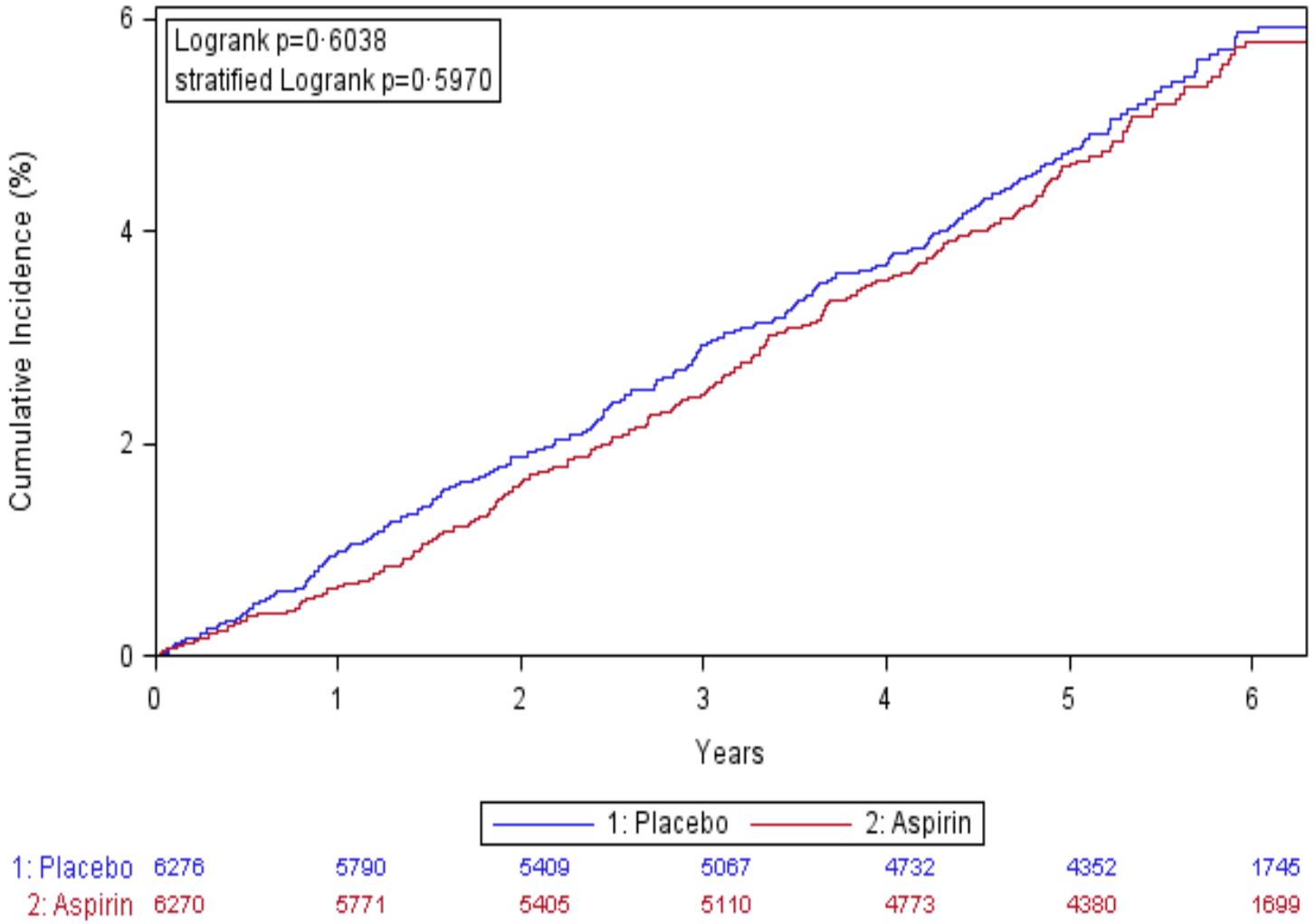
	Placebo Arm (n= 6276)	Aspirin Arm (n= 6270)
Weight at Randomization (kg)		
Median	82.0	82.0
Min – Max	43-177	35-163
BMI		
Mean	28.5	28.3
SD	4.3	4.3
White, %	97.9	97.8
Current antihypertensive medication, %	65.3	64.4
Elevated total cholesterol, %	58.3	58.2
Mean Framingham 10-year CHD risk score	14.1%	13.9%
Mean ACC/AHA 10-year ASCVD risk score	17.4%	17.3%

Note: Percentages based on number of subjects randomized to the indicated treatment group

Observed ASCVD event rate normalized to 10 years	**8.43%**	**8.80%**

Primary Efficacy Endpoint: CVD Death, MI, UA, Stroke or TIA

Time to First Occurrence of CV Death, MI, UA, Stroke or TIA (Intent-to-Treat population)



HR (95% CI)*
0.96 (0.81;1.13)

p-Value*
0.6038

*Comparison: Aspirin vs Placebo

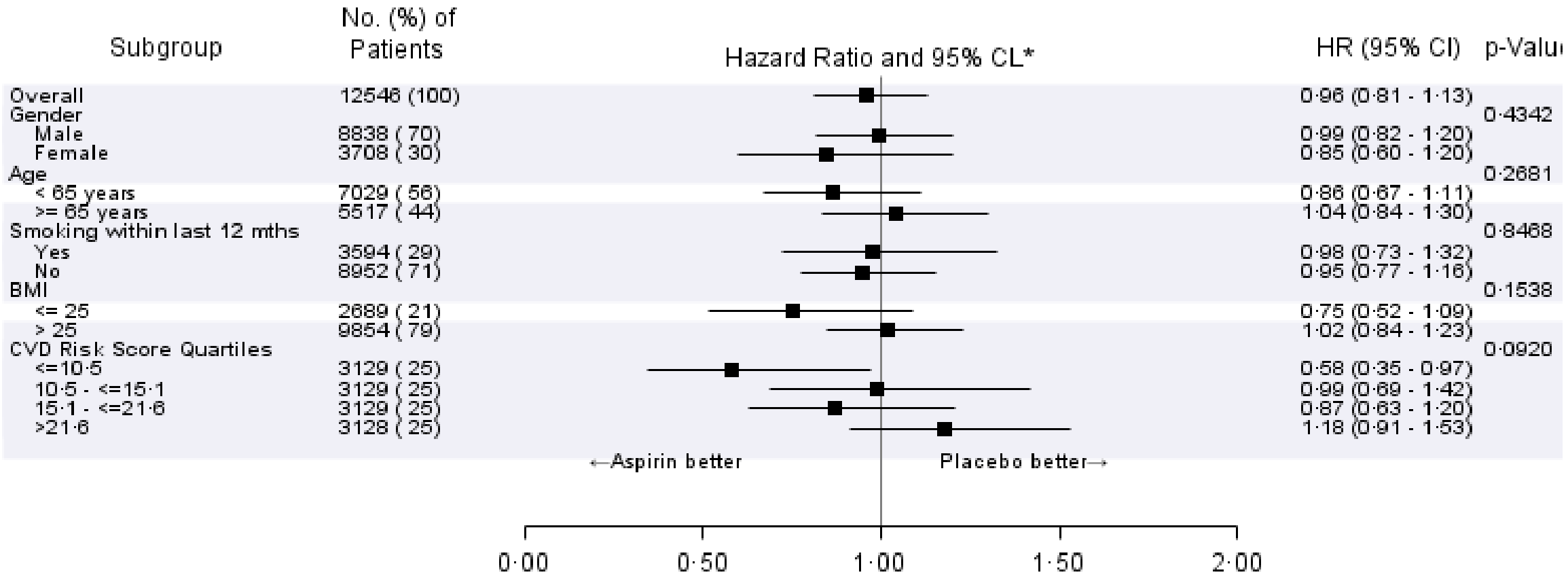
Overview Efficacy Endpoints
(Intent-to-Treat Population)

Event	Treatment Assignment	Number of Events (%)†	Hazard Ratio (95% CI) ‡	p-Value¥
MI, Stroke, CV Death, UA, or TIA	Aspirin Placebo	269 (4.29%) 281 (4.48%)	0.96 (0.81;1.13)	0.6038
MI, Stroke or CV Death	Aspirin Placebo	208 (3.32%) 218 (3.47%)	0.95 (0.79;1.15)	0.6190
Myocardial Infarction[a]	Aspirin Placebo	95 (1.52%) 112 (1.78%)	0.85 (0.64;1.11)	0.2325
Non-Fatal Myocardial Infarction	Aspirin Placebo	88 (1.40%) 98 (1.56%)	0.90 (0.67;1.20)	0.4562
Stroke[b]	Aspirin Placebo	75 (1.20%) 67 (1.07%)	1.12 (0.80;1.55)	0.5072
CV Death	Aspirin Placebo	38 (0.61%) 39 (0.62%)	0.97 (0.62;1.52)	0.9010
Unstable Angina	Aspirin Placebo	20 (0.32%) 20 (0.32%)	1.00 (0.54;1.86)	0.9979
Transient Ischemic Attack	Aspirin Placebo	42 (0.67%) 45 (0.72%)	0.93 (0.61;1.42)	0.7455
Any Death	Aspirin Placebo	160 (2.55%) 161 (2.57%)	0.99 (0.80;1.24)	0.9459
Cancer Events[c]	Aspirin Placebo	252 (4.02%) 236 (3.76%)	1.07 (0.89;1.27)	0.4750

†Percentages based on number of subjects randomized to the indicated treatment group; ‡ Comparison: Aspirin vs Placebo; ¥ (Log-Rank Test

[a] Fatal or non-fatal myocardial infarction; [b] Fatal or non-fatal Stroke; [c] All cancers excluding non-melanoma skin cancer

Time to first occurrence of CV Death, MI, UA, Stroke, or TIA by Subgroups (Intent-to-Treat Population)



* unstratified Hazard Ratio

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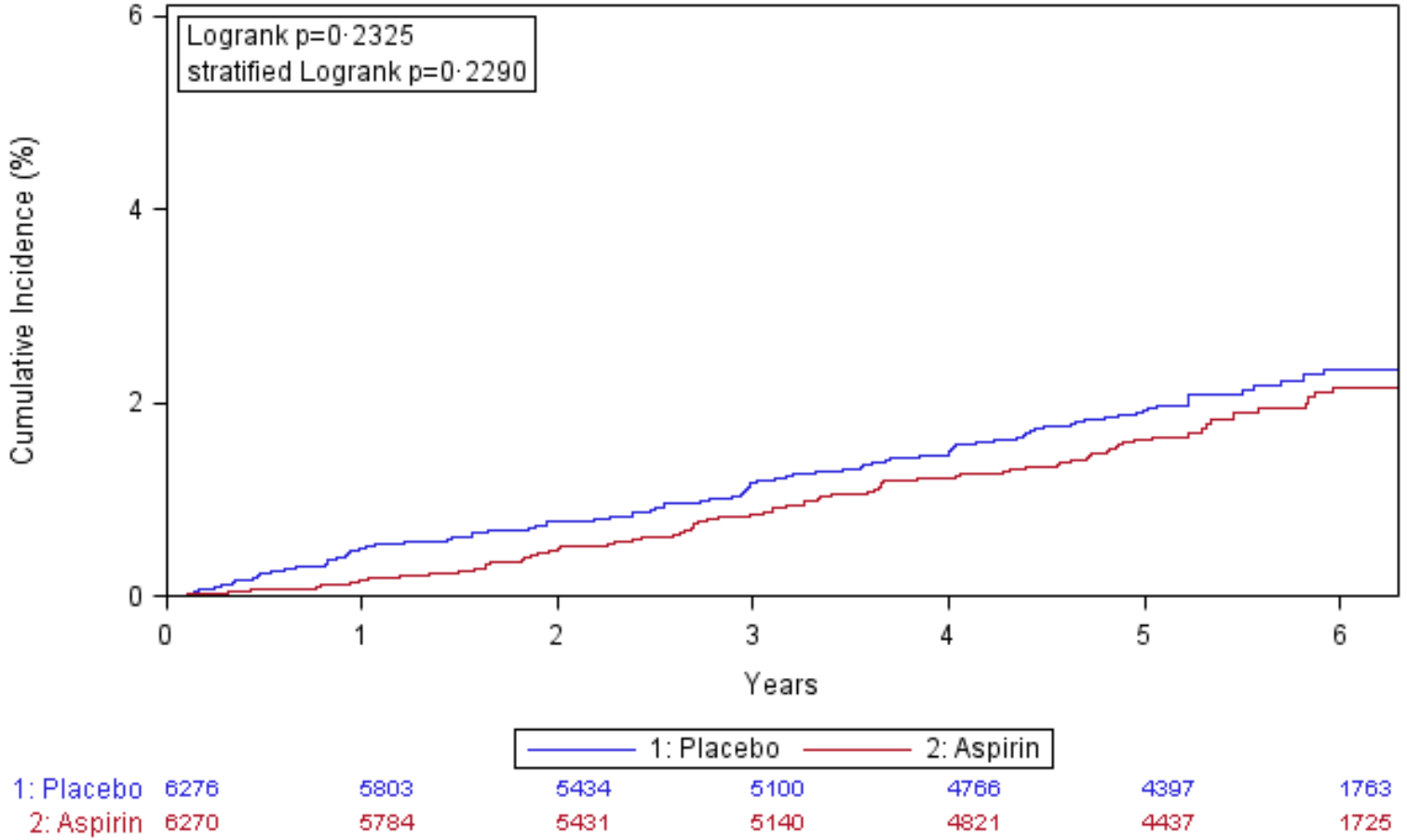
Cumulative Incidence Curve for Time to Fatal or Non-Fatal MI (Intent-to-Treat Population)

Time to first occurrence of Fatal or Non-Fatal MI (Intent-to-Treat population)



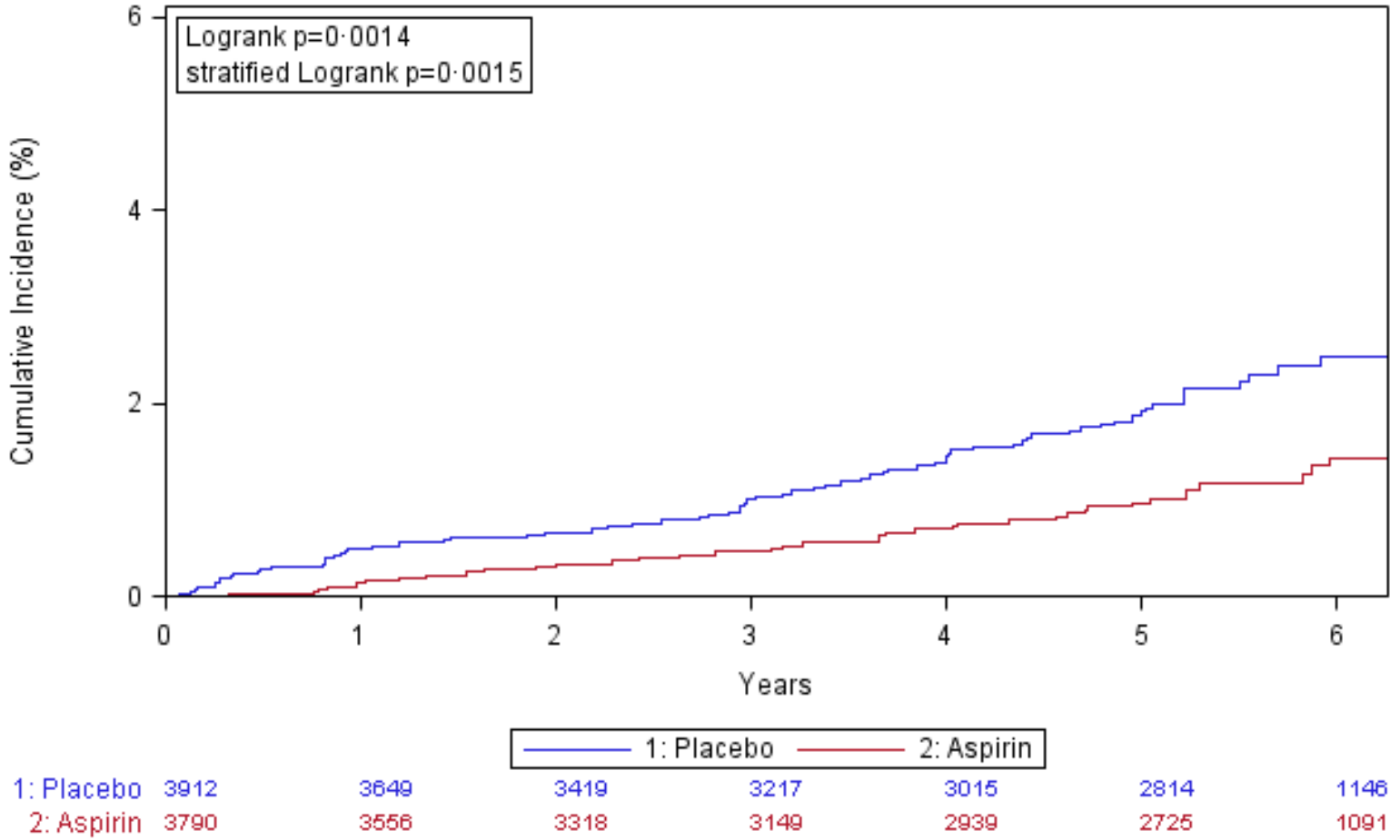
HR (95% CI)*
0.85 (0.64;11)

p-Value*
0.2325

*Comparison: Aspirin vs Placebo

Cumulative Incidence Curve for Time to Fatal or Non-Fatal MI (Per-Protocol Population [a])

Time to First Occurrence of Fatal or Non-Fatal MI (Per-Protocol Population)



HR (95% CI)*
0-53 (0-36;0-79)

p-Value*
0·0014

*Comparison: Aspirin vs Placebo

[a] Per protocol: Correct number of risk factors at study entry, no concomitant anticoagulant therapy, and ≥60% compliant

Primary Efficacy Endpoints By Age Group (Intent-to-Treat and Per Protocol Populations)

Age Group	Intent-to-Treat Population				Per Protocol Population			
	Placebo Event Rate	Aspirin Event Rate	Hazard Ratio* (95% CI)	RRR†	Placebo Event Rate	Aspirin Event Rate	Hazard Ratio* (95% CI)	RRR†
50-59	3.53%	2.71%	0.76 (0.51, 1.13)	23.2%	3.32%	1.81%	0.54 (0.31,0.96)	45.5%
60-69	4.02%	3.84%	0.95 (0.60, 1.19)	4.5%	3.52%	3.00%	0.85 (0.60,1.19)	14.8%
>=70	6.70%	7.30%	1.11 (0.83, 1.47)		6.99%	6.44%	0.92 (0.63,1.34)	7.9%
Overall results	4.48%	4.29%	0.96 (0.81, 1.13)	4.2%	4.19%	3.40%	0.81 (0.64,1.02)	18.9%

*Comparison: Aspirin vs Placebo
†RRR: Relative Risk Reduction

Gastrointestinal Bleeding
(Intent-to-Treat Population)

Gastrointestinal Bleeding Adjudication	Placebo Arm (n=6276)	Aspirin Arm (n=6270)
Time to First GI Bleeding		
Patients with events, n (%)	29 (0.46%)	61 (0.97%)
Hazard Ratio (95% CI)*	2.11 [1.36;3.28]	
p-Value*	0.0007	
Severity of adjudicated first GI Bleeding		
Mild, n (%)	22 (0.35%)	42 (0.67%)
Moderate, n (%)	5 (0.08%)	15 (0.24%)
Severe, n (%)	2 (0.03%)	4 (0.06%)

*Comparison: Aspirin vs Placebo; p-Value from log-rank test of time to first event
Note: Percentages based on number of subjects randomized to the indicated treatment group

Overview of Treatment Emergent Adverse Events (Intent-to-Treat Population)

Event	Placebo Arm (n=6276)	Aspirin Arm (n=6270)
Subjects with Adverse Events		
Any AEs	5129 (81.72%)	5142 (82.01%)
Serious AEs	1311 (20.89%)	1266 (20.19%)
Severe AEs	759 (12.09%)	724 (11.55%)
AEs leading to death	78 (1.24%)	81 (1.29%)
AEs leading to permanent discontinuation of study drug	1238 (19.73%)	1277 (20.37%)
Subjects with Adverse Events Related to Treatment		
Any AEs	850 (13.54%)	1050 (16.75%)
Serious AEs	49 (0.78%)	76 (1.21%)
Severe AEs	30 (0.48%)	55 (0.88%)
AEs leading to death	1 (0.02%)	4 (0.06%)
AEs leading to permanent discontinuation of study drug	325 (5.18%)	441 (7.03%)

Note: Percentages based on number of subjects randomized to the indicated treatment group

ARRIVE: Selected Endpoints (ITT Population) Compared to Other Primary Prevention Trials*

*Raju et al. Updated Meta-Analysis of Aspirin in Primary Prevention of Cardiovascular Disease. Am J Med. 2016 May;129(5):e35-6.
Trials: PHS, BDT, HOT, TPT, PPP, WHS, JPAD, POPADAD, AAA, JPPP

ARRIVE: Selected Endpoints (Per Protocol Population) Compared to Other Primary Prevention Trials*

Major CV Events	**PP trials**	**0.89 (0.82 – 0.97)**
	ARRIVE	**0.81 (0.64 – 1.02)**
CV Mortality	**PP trials**	**0.95 (0.84 – 1.07)**
	ARRIVE	**1.03 (0.60 – 1.77)**
MI	**PP trials**	**0.78 (0.65 – 0.94)**
	ARRIVE	**0.53 (0.36 – 0.79)**
Non fatal MI	**PP trials**	**0.80 (0.64 – 0.99)**
	ARRIVE	**0.55 (0.36 – 0.84)**
All-cause Stroke	**PP trials**	**0.94 (0.84 – 1.06)**
	ARRIVE	**1.12 (0.71 – 1.75)**
Hemorrhagic Stroke	**PP trials**	**1.43 (1.10 – 1.86)**
	ARRIVE	**0.69 (0.19 – 2.44)**
All-cause Mortality	**PP trials**	**0.94 (0.89 – 1.00)**
	ARRIVE	**1.10 (0.84 – 1.45)**

Favors Intervention **Favors Control**

*Raju et al. Updated Meta-Analysis of Aspirin in Primary Prevention of Cardiovascular Disease. Am J Med. 2016 May;129(5):e35-6.
Trials: PHS, BDT, HOT, TPT, PPP, WHS, JPAD, POPADAD, AAA, JPPP

Summary of Study Findings

- ARRIVE attempted to address the the role of aspirin in primary prevention of CVD in patients at moderate risk, however, the actual rate was much lower than anticipated in contrast to many previous studies.
- There was no overall reduction in major CVD events in the intent-to-treat population. However, the risk of first MI was lower among those on aspirin in subjects who were at least 60% compliant (the per-protocol analysis)
- Rates of GI bleeding were higher in the aspirin treatment group, but not higher than expected, rates of severe GI bleeding were extremely low, and there was no difference in the incidence of fatal events
- There was no reduction in the risk of cancer among those assigned aspirin.

Conclusions and Clinical Implications

- ARRIVE demonstrates challenges in conducting long-term primary prevention trials in the current era of aggressive management of CV risk factors and treatment and in estimating risk.
- While no overall reduction was observed in the primary composite endpoint of CV events, results from ARRIVE are generally consistent with many other previous primary studies that tended to demonstrate aspirin's ability to lower the risk of first nonfatal MI without affecting risk of total stroke.
- Safety results also were consistent with previous studies showing an increased risk of GI bleeding most of which were mild with a low rate overall and of severe events.
- ARRIVE adds relevant information on efficacy and safety of aspirin in primary prevention of CVD adding more data on older individuals and women. More data are coming from other completed trials.
- *The use of aspirin remains a decision that should involve a thoughtful discussion between a clinician and a patient given the need to weigh the CV and cancer benefits against the bleeding risks, patient preferences, cost, and other factors.*

Back Up

ARRIVE
Inclusion Criteria

Males aged 55 years and above with 2 to 4 risk factors	Females aged 60 and above with 3 or more risk factors
• Elevated **cholesterol** [total cholesterol >200 mg/dL or low-density lipoprotein (LDL) cholesterol >130 mg/dL; as measured at screening] irrespective of current treatment • Current **smoking**: defined as any cigarette smoking in the past 12 months • High-density lipoprotein (HDL) cholesterol (HDL <40 mg/dL; as measured at screening) • Elevated **blood pressure** [systolic blood pressure (SBP) >140 mmHg; as measured at screening] • Currently on any medication to treat high blood pressure • Positive **family history** of early CHD [a first-degree relative (father, mother, brother, sister, son, daughter) suffered a heart attack (MI) before the age of 60 years]	• Elevated **cholesterol** (total cholesterol >240 mg/dL or LDL >160 mg/dL; as measured at screening) irrespective of current treatment • Current **smoking**: defined as any cigarette smoking in the past 12 months • HDL cholesterol (HDL <40 mg/dL; as measured at screening) • Elevated **blood pressure** (SBP >140 mmHg; as measured at screening) • Currently on any medication to treat high blood pressure • Positive **family history** of early CHD [a first-degree relative (father, mother, brother, sister, son, daughter) suffered a heart attack (MI) before the age of 60 years]

- An understanding and willingness to comply with trial procedures and has given written informed consent to participate in the trial

ARRIVE Study Design

Primary Efficacy Endpoint

- Time to first occurrence of composite: cardiovascular death, myocardial infarction, unstable angina, stroke or transient ischemic attack

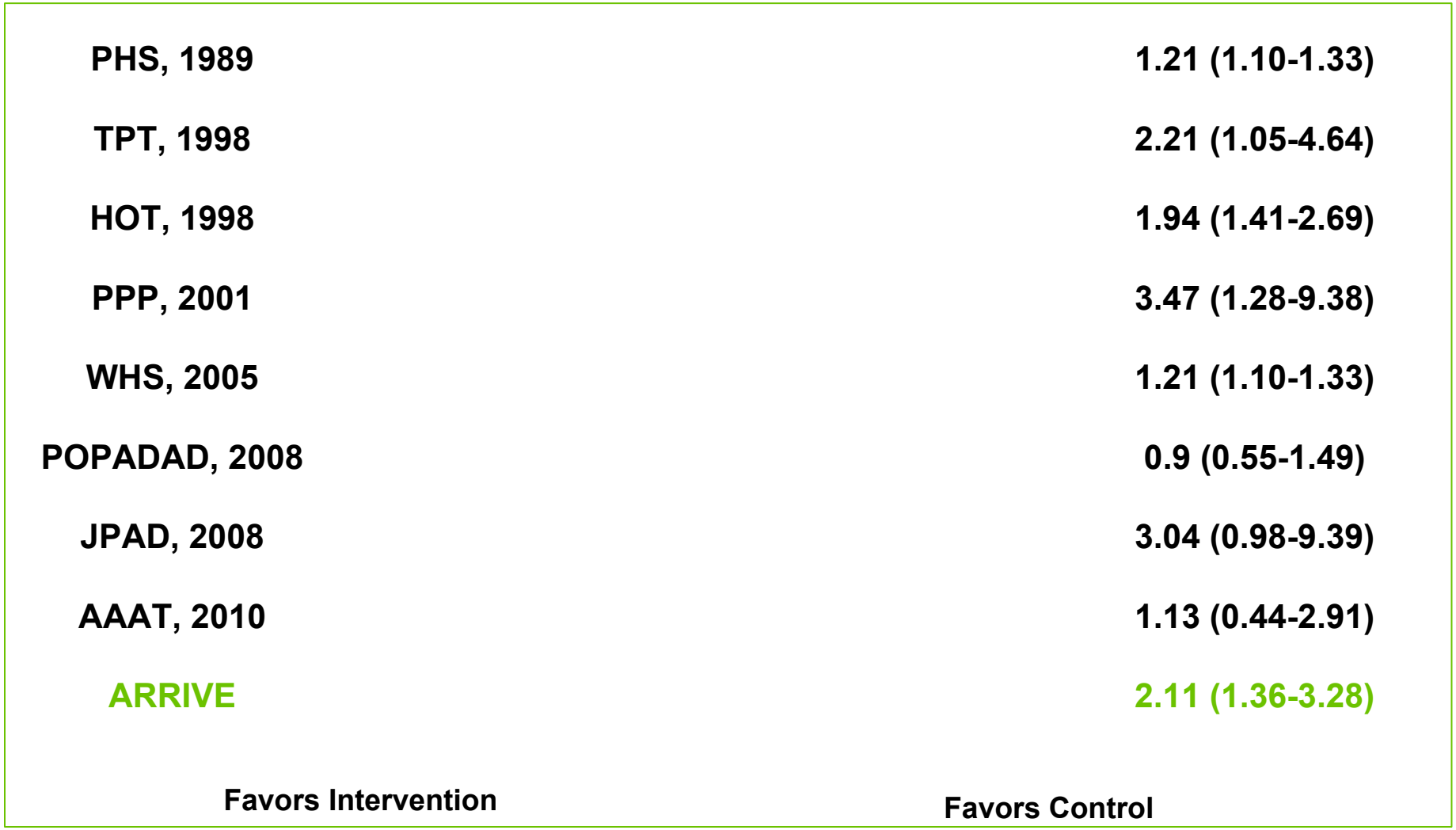
Secondary Endpoints

Time to first occurrence/incidence of:	Time to first occurrence/incidence of:	
• Composite outcome MI, Stroke, CVD death	• All cause mortality	• Colon cancer
• Individual components of primary endpoint	• All cancers, (excluding non melanoma skin cancer)	

Protocol Assumptions and Amendments

Original Protocol	Amended Protocol (Amendment 3-4)
• Age eligibility (lower limit): 50 years of age with 2 or 3 cardiovascular risks	• Age eligibility (lower limit): 55 years and above with 2 to 4 cardiovascular risks
• 1° Endpoint: Time to first occurrence of the composite outcome of MI, stroke or CV death	• 1° Endpoint: Time to first occurrence of the composite outcome of MI, stroke, CV death, TIA and ACS/UA
• Study duration: ~ 5 years • Event-driven Trial : study will end when 1488 events are reached • Sample size: N=12,000 patients	• Extend 12 months to acquire approximate patient years 60,000 (common study end date) • Event: interim at 744 events • Sample size: FPFV July 2007, n=12,551
• Event rate: 2.48% per year • RRR:14.9% • Power: 90%	• Event rate (revised):1.5% per year • RRR:17.5% • Power: ~ 80%

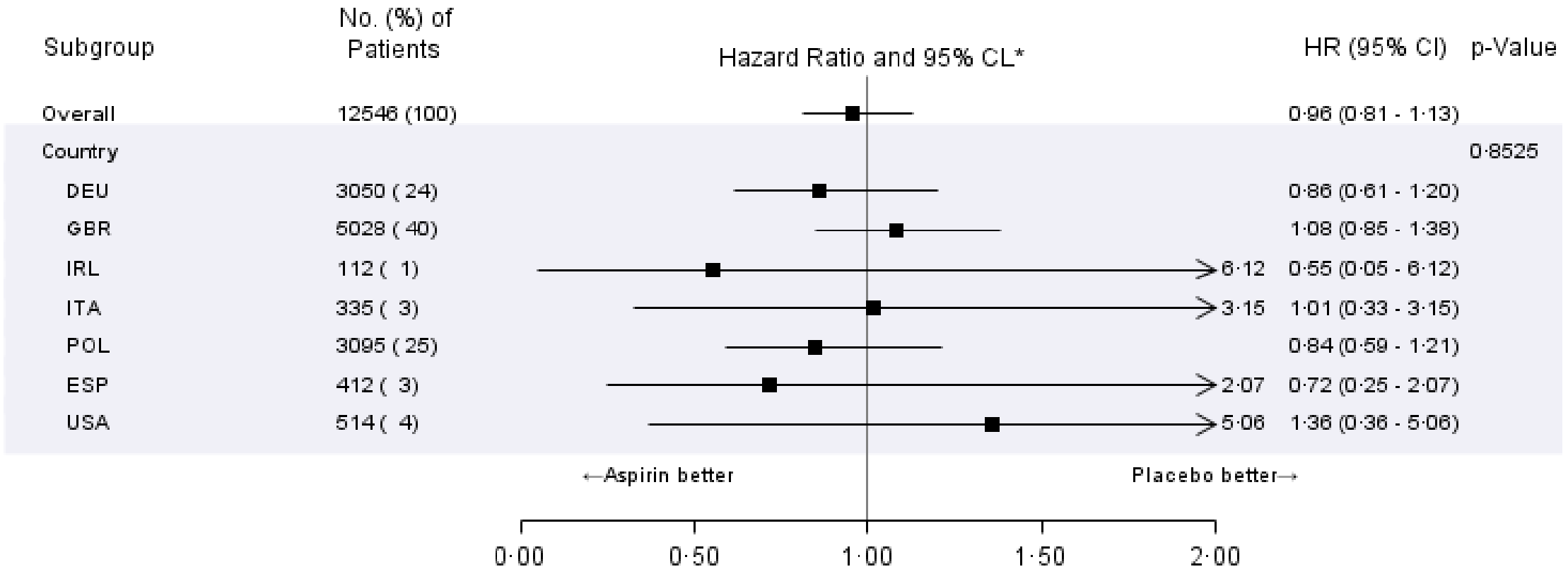
ARRIVE: Gastrointestinal Bleeding (adjudicated cases) (ITT Population) Compared to Other Primary Prevention Trials



* Raju et al.. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. Am J Med. 2011 Jul;124(7):621-9.

Time to First Occurrence CV Death, MI, UA, Stroke, or TIA by Subgroups

(Intent-to-Treat Population) (Cont.)



* unstratified Hazard Ratio

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