10.1161/CIRCULATIONAHA.122.062770

# Aspirin vs. Clopidogrel for Chronic Maintenance Monotherapy after Percutaneous Coronary Intervention: the HOST-EXAM Extended Study

**Running title:** *Kang et al.;Antiplatelet Monotherapy after PCI*

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**This work was presented as an abstract at AHA Scientific Sessions, November 5-7 in Chicago, IL

**Abstract**

**Background:** Long term outcomes of antiplatelet monotherapy in patients who receive percutaneous coronary intervention (PCI) are unknown. The HOST-EXAM Extended study reports the post-trial follow-up results of the original HOST-EXAM trial.

**Methods:** From March 2014 through May 2018, 5438 patients who maintained dual antiplatelet therapy without clinical events for 12±6 months after PCI with drug-eluting stents (DES) were randomly assigned in a 1:1 ratio to receive clopidogrel 75mg once daily or aspirin 100mg once daily. The primary endpoint (a composite of all-cause death, nonfatal myocardial infarction (MI), stroke, readmission due to acute coronary syndrome (ACS), and BARC type ≥3 bleeding), secondary thrombotic endpoint (cardiac death, non-fatal MI, ischemic stroke, readmission due to ACS, and definite or probable stent thrombosis), bleeding endpoint (BARC type ≥2 bleeding) were analyzed during the extended follow-up period. Analysis was performed on the per-protocol population (2431 patients in the clopidogrel group and 2286 patients in the aspirin group).

**Results:** During median follow-up of 5.8 years (interquartile range, 4.8 and 6.2 years), the primary endpoint occurred in 12.8% and 16.9% in the clopidogrel and aspirin groups, respectively (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.63 to 0.86, p<0.001). The clopidogrel group had a lower risk for the secondary thrombotic endpoint (7.9% vs. 11.9%; HR 0.66, 95% CI 0.55 to 0.79, p<0.001) and secondary bleeding endpoint (4.5% vs. 6.1%; HR 0.74, 95% CI 0.57 to 0.94, p=0.016). There was no significant difference in the incidence of all-cause death between the two groups (6.2% vs. 6.0%; HR 1.04, 95% CI 0.82 to 1.31, p=0.742). Landmark analysis at 2 years showed that the beneficial effect of clopidogrel was consistent throughout the follow-up period.

**Conclusion:** During an extended follow-up of over 5 years after randomization, clopidogrel monotherapy as compared with aspirin monotherapy was associated with lower rates of the composite net clinical outcome in patients without clinical events for 12±6 months after PCI with DES.

**Clinical Trial Registration:** HOST-EXAM trial, ClinicalTrials.gov Identifier: NCT02044250

**Key Words:** Antiplatelet monotherapy, Long term outcome, Chronic maintenance period, Percutaneous coronary intervention

**Non-standard Abbreviations and Acronyms**

ACS; Acute coronary syndrome
BARC; Bleeding Academic Research Consortium
CI; Confidence interval
DES; Drug-eluting stent
HOST-EXAM; Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy
HR; Hazard ratio
ICD-10-CM; International Classification of Disease-10th Revision-Clinical Modification
MI; Myocardial infarction
PCI; Percutaneous coronary intervention

## Clinical Perspective

### What is new?

- From the HOST-EXAM Extended study, clopidogrel monotherapy as compared to aspirin monotherapy, significantly reduced the risk of the composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and BARC type ≥3 bleeding in patients without clinical events for 12±6 months after coronary stenting.
- Clopidogrel monotherapy was associated with a lower risk in both thrombotic endpoints and bleeding endpoints with no significant difference in the risk of all-cause death, compared to aspirin monotherapy.
- During the extended follow-up duration, the discontinuation rate was higher for aspirin monotherapy, implying a higher compliance of clopidogrel monotherapy.

### What are the clinical implications?

- Long-term treatment with clopidogrel monotherapy leads to a consistent reduction in cardiovascular events compared with aspirin monotherapy.
- The HOST-EXAM Extended study supports clopidogrel as the preferable antiplatelet agent prescribed for secondary prevention of coronary artery disease.

## Introduction

Antiplatelet therapy is an integral component of pharmacotherapy for secondary prevention of atherothrombotic cardiovascular events, especially after percutaneous coronary intervention (PCI).[1] The Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy (HOST-EXAM) trial showed superiority of clopidogrel monotherapy over aspirin monotherapy in prevention of the composite of all-cause death, nonfatal myocardial infarction (MI), stroke, readmission due to acute coronary syndrome (ACS), and major bleeding during 24-months of follow-up in patients that received PCI with drug-eluting stents (DES) and had successfully completed 6 to 18 months of dual antiplatelet therapy without events.[2] The results of this study challenged the notion that aspirin is the antiplatelet agent of choice in the chronic maintenance period post-PCI. Clopidogrel monotherapy was also associated with a lower risk of both thrombotic and bleeding endpoints. However, there was a numerical increase, which did not yield statistical significance, for all-cause death in the clopidogrel arm, adding confusion to the interpretation of the results.

Given that antiplatelet monotherapy is often prescribed lifelong for secondary prevention,[3, 4] the potentially conflicting results at 2 years of significantly lower rates of composite net clinical events and a numerically higher rate of mortality needs clarification and warrants longer term follow-up. Therefore, the HOST-EXAM Extended study was designed to perform a post-trial extended follow-up of the patients enrolled in the HOST-EXAM trial to compare the longer-term outcomes between clopidogrel and aspirin monotherapy.

## Methods

The data that support the findings of this study are available from the corresponding author

upon reasonable request.

**Trial Design and Oversight**

Details regarding the design of the HOST-EXAM trial have been described previously.[5] Briefly, the HOST-EXAM trial was an investigator-initiated, prospective, randomized, open-labeled, multicenter trial done at 37 study sites in Korea. In March 2020, an extended follow-up was planned and the study protocol was submitted to the National Evidence-based Healthcare Collaborating Agency of Korea. All investigators were invited in the post-trial extended follow-up analysis. The extended follow-up study was named the HOST-EXAM Extended study which was composed of the HOST-EXAM in-trial period and post-trial follow-up period (**Figure S1**). Because the original study was terminated before the initiation of the extended study, and because some patients had experienced additional clinical events (including mortality events) or were being followed-up in a different medical center when the extended study was initiated, we could not obtain informed consent prospectively in all of the patients. Obtaining data from all of the patients that were enrolled in the original HOST-EXAM trial would be of paramount importance to understand the full impact of antiplatelet therapy during the extended follow-up of these patients. Therefore, the patients who performed clinical follow-up in the original center were enrolled in the prospective cohort after obtaining informed consent, while those who could not provide informed consent (already had events before study initiation or were being followed up at centers other than the original participating hospitals) were enrolled in the retrospective cohort. As the original HOST-EXAM trial mandated allocated antiplatelet therapy up to 24 months post-enrollment, the post-trial follow-up antiplatelet prescription was at the discretion of the treating physician.

The Seoul National University Hospital Clinical Trial Center and Medical Research Collaborating Center were responsible for the scientific conduct of the trial. All events were

adjudicated by an independent clinical-event committee whose members were unaware of the trial-group assignments. Members of the independent clinical-event committee received medical records of adverse events after removing any reference to the treatment groups.

The trial protocol of the HOST-EXAM Extended study was approved by the institutional review board at each participating site. This study was conducted in accordance with the standards specified in the International Council for Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.

**Study Population, Randomization and Follow-up**

Patients 20 years or older who underwent PCI with DES and maintained dual antiplatelet therapy without any clinical events during 12 ± 6 months after PCI were eligible for the HOST-EXAM study.[2, 5] There was no restriction regarding the clinical diagnosis at the index PCI period, stenosis location, length, or numbers of lesions/vessels at the time of PCI. Patients who met all the inclusion criteria and none of the exclusion criteria, were randomly assigned in consecutive order to either the clopidogrel group (75mg once daily) or aspirin group (100mg once daily) in a ratio of 1:1. Detailed inclusion and exclusion criteria of the HOST-EXAM study are described in the **Supplementary appendix.** After the initial 2-year follow-up of this trial, the single antiplatelet agent was determined by the treating physician with no mandatory designation. Clinical follow-up was performed according to standard therapy. For those patients who did not visit the outpatient clinic, a telephone interview was permitted. The final clinical status was ascertained at March, 2022. Additionally, the vital status of all patients was cross-checked through the National Health Insurance Service system of Korea and the Korea National Statistics System. Regarding mortality cases, the definite cause of death was confirmed by the recorded data classified by the International Classification of Disease-10th Revision-Clinical Modification (ICD-10-CM) codes.

**Trial Endpoints and Definitions**

The trial endpoints and definitions were identical to the HOST-EXAM trial.[2] The primary endpoint was a composite of all-cause death, nonfatal MI, stroke, readmission due to ACS, and major bleeding complications during the follow-up period. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) type ≥3 bleeding. Secondary composite endpoints included the thrombotic composite endpoint (defined as cardiac death, non-fatal MI, ischemic stroke, readmission due to ACS, and definite or probable stent thrombosis) and any bleeding (defined as BARC type ≥2 bleeding). Endpoints were defined according to the Academic Research Consortium definition.[6] The individual components of the primary endpoint, secondary composite endpoint, and revascularization were also analyzed as secondary endpoints. Detailed definitions of each clinical events are described in the **Supplementary appendix**.

**Statistical Analysis**

The working hypothesis of the HOST-EXAM study was that clopidogrel would be superior to aspirin as a chronic maintenance monotherapy agent, which required 5530 patients to ensure a power of at least 80% with a 2-sided α of 5% based on event rate assumptions. The current study was an extended follow-up of the HOST-EXAM population, therefore, no additional sample size calculation was performed. The primary analysis was performed on the basis of per-protocol analysis, including those who received the allocated single antiplatelet therapy for the full duration of follow-up unless they experienced an adverse clinical event. The intention-to-treat analysis was also performed, including all patients randomized to a treatment arm in the former study.

Continuous variables were reported as mean ± standard deviations, and categorical variables were presented as absolute values and their proportions. Differences between continuous variables were compared by Student's t-test for independent data. The primary

endpoint was analyzed by a Cox proportional-hazards model and Kaplan-Meier survival curves to estimate the risk of clinical events according to the type of antiplatelet agent. No other factor variables than the trial group was used for stratification. Event-free survival with incomplete follow-up was counted as censored data for all time-to-event analyses. A Cox proportional-hazards model was used for analysis of subgroups, defined according to age (<65 years or ≥65 years), sex (male or female), body mass index (≥25kg/$m^2$ or <25kg/$m^2$), renal function, diabetes, clinical presentation (acute MI or not, ACS or not), angiographic severity (single vessel disease vs. multivessel disease), complex PCI,[7] high bleeding risk[8] and proton-pump inhibitor usage. The specific definition of complex PCI and high bleeding risk are shown in the **Supplementary appendix**. Statistical tests were performed using SPSS, V24 (SPSS Inc.) and R programming language, version 4.0.4 (R Foundation for Statistical Computing).

**Role of Funding Source**

The study funder had no role in trial design; data collection, analysis, interpretation; writing of the manuscript; and the decision to submit.



## Results

### Participants and Follow-up

From March 2014 through May 2018, a total of 5438 patients who were event-free for 6~18 months after PCI and successfully received the intended duration of dual antiplatelet therapy (DAPT) were successfully randomized from 37 centers (**Figure 1**). Among the total population, 9 patients withdrew informed consent, 618 patients used a different antiplatelet regimen from the allocated arm (including 583 patients who used a different antiplatelet regimen in the post-trial period), and 94 patients were lost to follow-up (including 3 patients who were lost to follow-up in the post-trial period), leaving 4717 patients analyzed in the per

protocol population (2431 patients in the clopidogrel group and 2286 patients in the aspirin group). The vital status was cross-checked in the total population. The clinical follow-up status was ascertained in March 2022, and the median follow-up duration was 5.8 years (interquartile range, 4.7 and 6.2 years).

Baseline characteristics of each group are shown in **Table 1** and the concomitant medications are shown in **Table S1**. The mean age was 63.3 ± 10.7 years and the mean body mass index was 24.8 ± 3.2 kg/m$^2$. Among the study population, 33.8% had diabetes mellitus, 12.4% had chronic kidney disease, and the clinical diagnosis at the time of PCI was ACS in 71.9%. The demographics, laboratory data and angiographic data were well balanced between the two groups.

Among 721 patients who were excluded from the per protocol analysis, 583 were excluded during the post-trial follow-up period due to medication change. The baseline clinical characteristics for those who were excluded from per protocol analysis are shown in **Table S2**. The discontinuation rate was significantly higher in the aspirin group (8.0% (216 out of 2648 patients) vs. 13.5% (367 out of 2710 patients), p<0.001 in the clopidogrel and aspirin groups, respectively), and the reason for deviation from originally allocated antiplatelet agent are provided in **Table S3**.

**Clinical Endpoints**

During the follow-up duration, the primary endpoint occurred in 311 patients (12.8%) who received clopidogrel monotherapy, and in 387 patients (16.9%) who received aspirin monotherapy (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.63 to 0.86; p<0.001). The absolute risk reduction related with clopidogrel usage was 4.1% (95% CI, 2.1% to 6.2%) and the number needed to treat was 24 (**Table 2, Figure 2A**). The secondary thrombotic endpoint of cardiac death, non-fatal MI, stroke, readmission due to ACS, or definite or probable stent thrombosis, occurred in 196 patients (8.1%) in the clopidogrel group and 273

patients (11.9%) in the aspirin group (HR 0.66, 95% CI 0.55 to 0.79, p<0.001; **Figure 2B**). Any bleeding (BARC type ≥2) occurred in 110 patients (4.5%) in the clopidogrel group and 140 patients (6.1%) in the aspirin group (HR 0.74, 95% CI 0.57 to 0.94, p=0.016; **Figure 2C**). The incidence of all-cause death was similar (6.2% vs. 6.0%; HR 1.04, 95% CI 0.82 to 1.31), p=0.742) between the two groups (**Figure 2D**). The specific causes of mortality events are described in **Table S4**. Among other secondary endpoints, the risk of stroke, readmission due to ACS, major bleeding events and any revascularization was lower in the clopidogrel group (**Table 2**). The frequency of gastrointestinal bleeding (2.2% vs. 2.9%) and intracranial bleeding (0.5% vs. 1.0%) was higher in the aspirin group. The specific site and individual type of bleeding according to the BARC definition is presented in the **Table S5.**

In a landmark analysis at 2 years after randomization, the beneficial effect was consistent in the in-trial period (HR 0.69, 95% CI 0.56 to 0.86, p=0.001) and in the post-trial period (HR 0.78, 95% CI 0.63 to 0.97, p=0.022) in terms of the primary endpoint (**Figure S2**). This trend was also consistent for the secondary composite endpoints and all-cause death (**Figure S3, S4, S5, Table S6**).

**Subgroup Analyses and Intention to treat Analysis**

Regarding the primary endpoint, the beneficial effect of clopidogrel monotherapy as compared with aspirin monotherapy, was generally consistent across all subgroups (**Figure 3**). This was also consistent for the secondary thrombotic endpoints (**Figure S6**) and bleeding endpoint (**Figure S7**). The intention to treat analyses based on patients who were randomized in the HOST-EXAM trial, yielded similar results to the per protocol analyses for the primary study endpoint (HR 0.79, 95% CI 0.69 to 0.91, p=0.001), and the secondary endpoints (**Figure S8, S9, S10**). Detailed individual endpoints for the intention to treat analyses both at 2 years and at the final follow-up are provided in **Table S7**.

## Discussion

In this HOST-EXAM Extended study, we compared the long-term effects of clopidogrel and aspirin monotherapy during the chronic maintenance period in patients that received stenting with DES. During a median follow-up duration of 5.8 years after randomization, the incidence of the primary endpoint of all-cause death, nonfatal MI, stroke, readmission due to ACS, and major bleeding was lower in the clopidogrel group. Further, the secondary thrombotic endpoint and bleeding endpoint were also lower in the clopidogrel group, suggesting continuous benefit of clopidogrel beyond the initial trial study period. The incidence of all-cause death was similar between the two groups, indicating no difference in mortality risk. In a landmark analysis at 2-years after randomization, the beneficial effect was sustained in both the trial period and the post-trial extended follow-up period with continued divergence of the curves. Subgroup analyses showed consistent treatment effects of clopidogrel in various subgroups with no significant interaction. Collectively, the extended follow-up of the HOST-EXAM trial shows the persistent benefit of clopidogrel monotherapy over aspirin monotherapy in patients with coronary artery disease treated with DES.

The HOST-EXAM trial was the first randomized trial to compare clopidogrel and aspirin monotherapy head-to-head during the chronic maintenance phase in patients that received stenting with DES and had successfully completed 6-18 months of dual antiplatelet therapy without events. In that trial, clopidogrel was superior to aspirin in prevention of the net composite outcome of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding during 24 months of follow-up. Further, clopidogrel was associated with lower risk of both ischemic and bleeding events.[2] Previously, the CAPRIE trial also compared aspirin and clopidogrel monotherapy in 19,185 patients with atherosclerotic vascular disease for a mean duration of follow-up of 1.91 years. Clopidogrel was associated with a 8.7% relative risk reduction in the primary endpoint of ischemic stroke,

myocardial infraction or vascular death compared with aspirin. Aspirin was also related with higher rate of gastrointestinal discomfort and bleeding events.[9] However, the study participants were not a PCI population and this trial was performed in the early 1990s, before the era of high intensity statins. Therefore the results cannot be purely extrapolated to patients in the current era. Additionally, a recent meta-analysis of over 24,000 patients (PANTHER study, PROSPERO registration number: CRD42021290774) confirmed that $P2Y_{12}$ inhibitor monotherapy was associated with a lower risk of adverse clinical outcomes in patients with coronary artery disease.

Despite the positive results of the HOST-EXAM trial, we still need a longer term follow up for us to consider clopidogrel monotherapy lifelong instead of aspirin for a few reasons. First, because antiplatelet therapy for secondary prevention needs to be continued for the duration of the life expectancy of the patients that we treat, confirming the long-term beneficial effect of clopidogrel monotherapy is essential. Even for aspirin, however, the benefit for lifelong secondary prevention in the contemporary era of high intensity statins is controversial and sometimes not supported by previous trials.[10, 11] Moreover, long term data can be used to calculate the impact of clopidogrel on not only clinical outcomes, but also the cost-effectiveness of switching from aspirin to clopidogrel monotherapy. Second, although clopidogrel monotherapy showed benefit in reducing the incidence of the primary endpoint in the HOST-EXAM trial, there was a statistically insignificant but mild trend of higher mortality in the clopidogrel arm. This raised substantial concerns of the impact of antiplatelet monotherapy on mortality and caused confusion in translating the results of the HOST-EXAM trial. Longer term data could clarify whether the statistically insignificant trend was a chance finding or whether aspirin indeed had non-platelet related benefits regarding mortality. Third, despite the current guideline recommendations to continue aspirin lifelong for secondary prevention,[3] many patients do not adhere to aspirin due to various reasons

including but not limited to bruising, minor bleeding events, or gastrointestinal discomfort, especially in the elderly population.[12, 13] Therefore, longer term follow up can confirm whether adherence issues can be improved by using clopidogrel.

During the extended follow up period, clopidogrel monotherapy was associated with a 26% risk reduction of the primary endpoint, which was similar to the results during the in-trial period (HR 0.73, 95% CI 0.59–0.90) in the HOST-EXAM trial). The consistent divergence of the cumulative incidence curve suggests continuous benefit of clopidogrel throughout the extended follow-up period. An interesting finding that should be noted is that clopidogrel monotherapy was associated with a reduction in both thrombotic and bleeding endpoints. The reduction in bleeding events without an elevation of ischemic events, which at a glance seem to be counterintuitive, has been seen in recent trials. This can be explained by various mechanisms. First, both outcomes are closely related to the medication adherence. An even minor bleeding complication may impact the adherence of the antiplatelet medication leading to higher risk of ischemic events. Therefor an antiplatelet agent with lower bleeding risk has the potential to lower even the ischemic risk of the patient. Second, although the ischemic and bleeding events may have an opposite phenotype, patients at higher risk for these events share risk factors. Clinical risk factors such as old age, chronic kidney disease and diabetes are risk factors for ischemic and bleeding events, leaving these patients at higher risk for any adverse events, regardless of the antiplatelet regimen.[14]

Regarding all-cause death, when follow-up was extended to beyond 5 years, there was no difference between aspirin and clopidogrel. In particular, a landmark analysis from 2 years showed very similar curves with no differences (In-trial period: HR 1.27, 95% CI 0.85 to 1.92, post-trial follow up period: HR 1.04, 95% CI 0.71 to 1.25). Also, as shown in the supplementary appendix, the risk of cardiovascular death was numerically lower in the clopidogrel group in the post-trial follow-up period (4.0% vs. 4.3%, p=0.688). Even with

longer term follow up, the trial was not powered to detect mortality differences and therefore, we cannot confirm whether there is or is not a difference in mortality. However, the extended follow up suggests that the statistically insignificant trend toward higher mortality of the clopidogrel arm in the original trial was probably a play-of-chance finding.

Interestingly, we found that the medication discontinuation rate was significantly higher in the aspirin group, with a higher risk of gastrointestinal discomfort or bleeding events. Various previous trials have reported such side effects in aspirin users,[15, 16] which have raised concerns and resulted in a recent paradigm shift in the role of aspirin. The paradigm shift away from aspirin is attributed to not only the side effects but also the better antithrombotic efficacy of P2Y12 inhibitors compared with aspirin.[1, 17] As explained above, poor adherence to medication itself is a risk of adverse events. A previous study reported that discontinuation of medication was independently associated with higher mortality of 3- to 4-fold in coronary artery disease patients.[18, 19] The higher adherence to clopidogrel monotherapy also supports the benefit of clopidogrel as the lifelong antiplatelet agent in the chronic maintenance period after PCI.

There are several limitations of the current trial that should be considered. First, this was an extended follow-up of a randomized clinical trial. Therefore, the antiplatelet regimen was open-labeled, and a specific antiplatelet regimen was not obligatory. The physicians' discretion on antiplatelet selection could have been influenced by multiple factors, including the results of the original study. However, we performed a per-protocol analysis to reflect the actual antiplatelet agent, while all endpoints were specifically adjudicated by an independent committee that was unaware of the treatment group. Second, this trial was not powered to evaluate the impact of antiplatelet therapy on mortality. Nevertheless, we cross-checked data for mortality for 99.9% of the patients and found no mortality difference between the two groups. Along with the current study results, we are continuing follow-up of these patients for

up to 10 years. Third, phenotypic and genetic testing for clopidogrel was not performed and the study population was an East Asian population, therefore the generalizability of the study to other ethnicities may be limited. However, routine platelet function or genetic testing is not recommended in clinical practice.[20, 21]

## Conclusion

In the extended follow-up of patients who were event-free for 6~18 months post-PCI and successfully received the intended duration of DAPT, clopidogrel monotherapy as compared with aspirin monotherapy significantly reduced the risk of the composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to ACS, and BARC type ≥3 bleeding.

## Acknowledgments

None.

## Sources of Funding

The funding source of this study was grants of the Patient-Centered Clinical Research Coordinating Center (grant number: HI19C0481, HC19C0305) and Korea Health Technology R&D Project (grant number: HI17C2085) funded by the Ministry of Health & Welfare, Korea. This research was partially supported by a grant from Seoul National University Hospital (Research ID: 06-2011-2830, 06-2015-2150, 06-2015-2860). The study funder had no role in trial design; data collection, analysis, interpretation; or writing of the manuscript.

## Disclosure Statement

HSK has received research grants or speaker's fees from Daiichi Sankyo, Boston Scientific, Terumo, Biotronik and Dio, as well as Medtronic, Abbott Vascular, Edwards Life Science,

AmGen, and Behringer Ingelheim. KWP reports speaker's fees from Daiichi Sankyo, InnoN Pharmaceutical, DaeWoong Pharmaceutical, JW Pharmaceutical outside of the submitted work.

**Supplemental Materials**

1. Investigators and Collaborators
2. Data Sharing Statement
3. Inclusion and Exclusion Criteria of the HOST-EXAM trial
4. Definition of Subgroups and Clinical Outcomes
5. Study Design and Execution
6. Tables S1 – 7
7. Figures S1 – 10

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**Table 1. Baseline Characteristics of the Per-protocol Population**

| | Clopidogrel (N = 2431) | Aspirin (N = 2286) |
|---|---|---|
| **Demographics and Comorbidities** | | |
| Age (years) | 63.3 ± 10.8 | 63.3 ± 10.7 |
| Body Mass Index (kg/m$^2$) | 24.9 ± 3.1 | 24.8 ± 3.4 |
| Male | 1807 (74.3%) | 1723 (75.4%) |
| Diabetes mellitus | 818 (33.6%) | 775 (33.9%) |
| Insulin dependent Diabetes mellitus | 48 (2.0%) | 51 (2.2%) |
| Hypertension | 1493 (61.4%) | 1402 (61.3%) |
| Dyslipidemia | 1690 (69.5%) | 1613 (70.6%) |
| Current smoker | 479 (19.7%) | 500 (21.9%) |
| Chronic kidney disease | 314 (12.9%) | 273 (11.9%) |
| Previous MI | 406 (16.7%) | 362 (15.8%) |
| Previous CVA | 103 (4.2%) | 110 (4.8%) |
| Clinical Indication of PCI | | |
| Silent ischemia | 52 (2.1%) | 61 (2.7%) |
| Stable angina | 620 (25.5%) | 593 (26.0%) |
| Unstable angina | 871 (35.8%) | 773 (33.8%) |
| NSTEMI | 471 (19.4%) | 454 (19.9%) |
| STEMI | 417 (17.2%) | 404 (17.7%) |
| ***Laboratory results*** | | |
| White blood cells (/uL) | 6740 ± 1920 | 6810 ± 1890 |
| Hemoglobin (g/dL) | 13.7 ± 1.7 | 13.8 ± 1.6 |
| Creatinine (mg/dL) | 1.00 ± 0.67 | 0.99 ± 0.64 |
| Total cholesterol (mg/dL) | 137 ± 30 | 138 ± 30 |
| Triglyceride (mg/dL) | 126 ± 88 | 126 ± 73 |
| HDL-cholesterol (mg/dL) | 46 ± 12 | 46 ± 12 |
| LDL-cholesterol (mg/dL) | 70 ± 24 | 72 ± 23 |
| ***Angiographic Data per Patient*** | | |
| Extent of CAD | | |
| 1-vessel disease | 1229 (50.6%) | 1140 (49.9%) |
| 2-vessel disease | 763 (31.4%) | 716 (31.3%) |
| 3-vessel disease | 439 (18.1%) | 428 (18.7%) |
| Left main disease | 127 (5.2%) | 112 (4.9%) |
| PCI for bifurcation lesion | 261 (10.7%) | 232 (10.2%) |
| 2-stenting for bifurcation PCI | 39 (1.6%) | 33 (1.4%) |
| PCI for CTO lesion | 235 (9.3%) | 223 (9.8%) |
| Number of treated lesions | 1.32 ± 0.59 | 1.30 ± 0.57 |
| Mean diameter of implanted stents | 3.08 ± 0.43 | 3.08 ± 0.43 |
| Minimum diameter of implanted stents | 3.00 ± 0.46 | 3.01 ± 0.45 |
| Total length of implanted stents | 36.3 ± 24.3 | 35.3 ± 23.2 |
| Total number of implanted stents | 1.5 ± 0.8 | 1.5 ± 0.8 |

Abbreviations: CAD, coronary artery disease; CTO, chronic total occlusion; CVA, cerebrovascular accident; DES, drug-eluting stent; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

Data presented as mean ± standard deviation or as n (%). There were no significant differences between the two groups.

**Table 2. Clinical Outcomes of the Per-protocol Population**

| | Clopidogrel (N = 2431) | Aspirin (N = 2286) | Hazard Ratio (95% CI) | P |
|---|---|---|---|---|
| | *No. of patients (%)* | | | |
| Primary composite endpoint† | 311 (12.8%) | 387 (16.9%) | 0.74 (0.63-0.86) | <0.001 |
| Thrombotic composite endpoint‡ | 196 (8.1%) | 273 (11.9%) | 0.66 (0.55-0.79) | <0.001 |
| Any bleeding (BARC type ≥2)§ | 110 (4.5%) | 140 (6.1%) | 0.74 (0.57-0.94) | 0.016 |
| All-cause death‖ | 150 (6.2%) | 136 (6.0%) | 1.04 (0.82-1.31) | 0.742 |
| Cardiovascular death | 69 (2.8%) | 71 (3.1%) | 0.92 (0.66-1.28) | 0.602 |
| Non-cardiovascular death | 81 (3.3%) | 65 (2.8%) | 1.18 (0.85-1.63) | 0.332 |
| Non-fatal myocardial infarction | 40 (1.6%) | 53 (2.3%) | 0.71 (0.47-1.07) | 0.102 |
| Stroke | 37 (1.5%) | 66 (2.9%) | 0.53 (0.35-0.79) | 0.002 |
| Ischemic stroke | 27 (1.1%) | 42 (1.8%) | 0.61 (0.37-0.98) | 0.041 |
| Hemorrhagic stroke | 10 (0.4%) | 24 (1.1%) | 0.39 (0.19-0.82) | 0.013 |
| Readmission due to ACS ¶ | 111 (4.6%) | 176 (7.7%) | 0.59 (0.47-0.75) | <0.001 |
| Major bleeding (BARC type ≥3) | 62 (2.6%) | 90 (3.9%) | 0.65 (0.47-0.90) | 0.008 |
| Any revascularization | 129 (5.3%) | 157 (6.9%) | 0.77 (0.61-0.98) | 0.030 |
| Target lesion revascularization | 53 (2.2%) | 68 (3.0%) | 0.73 (0.51-1.05) | 0.089 |
| Target vessel revascularization | 76 (3.1%) | 98 (4.3%) | 0.73 (0.54-0.98) | 0.039 |
| Definite or probable stent thrombosis | 12 (0.5%) | 17 (0.7%) | 0.67 (0.32-1.39) | 0.280 |

Abbreviations: ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CI, confidence interval

† Primary composite endpoint is defined as a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome and major bleeding events (BARC type ≥3).

‡ Thrombotic composite endpoint is defined as cardiac death, non-fatal myocardial infarction, ischemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis.

§ Any bleeding events is defined as BARC type ≥2 bleeding events.

‖ The specific causes of mortality events are described in the Supplementary Appendix.

¶ Among the total 287 patients, 93 patients (32.4%) were diagnosed as myocardial infarction, and 194 (67.6%) were diagnosed as unstable angina. Among the 194 patients diagnosed as unstable angina, 122 (62.9%) received percutaneous coronary intervention, and 72 patients (37.1%) received medical treatment without additional intervention.

## Figure Legends

### Figure 1. Enrollment, Randomization, and Follow-up.

The follow-up duration of patients who were enrolled in the HOST-EXAM trial (those who underwent percutaneous coronary intervention with a drug-eluting stent and maintained dual antiplatelet therapy without any clinical events during 12 ± 6 months after the index procedure) was extended in the HOST-EXAM Extended study. The follow-up was comprised of the in-trial follow-up period and the post-trial follow-up period. The study end points were analyzed during the entire follow-up duration in the per-protocol population (patients that continued to receive the original allocated treatment).

### Figure 2. Cumulative Incidence of the Primary Endpoint, Secondary Endpoints, and All-cause death

Panel **A** shows the cumulative incidence of the primary endpoint, consisting of all-c ause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (Bleeding Academic Research Consortium type ≥3 bleeding) complications. Panel **B** shows the cumulative incidence of the secondary thrombotic endpoint, consisting of cardiac death, non-fatal myocardial infarction, ischemic stroke, readmission due to acute coronary syndrome, or definite or probable stent thrombosis. Panel **C** shows the cumulative incidence of the any bleeding events. Panel **D** shows the cumulative incidence of all-cause death. The hazard ratio shown is for clopidogrel monotherapy versus aspirin monotherapy.

**Figure 3. Subgroup Analysis.**

The hazard ratio for the primary endpoint (a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding complications) in the two groups are shown according to various subgroups.

†Complex PCI was defined as having at least 1 of the following features: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion.[7]

‡High bleeding risk was defined based on the Academic Research Consortium for High Bleeding Risk definition.[8]

**Figure 1**

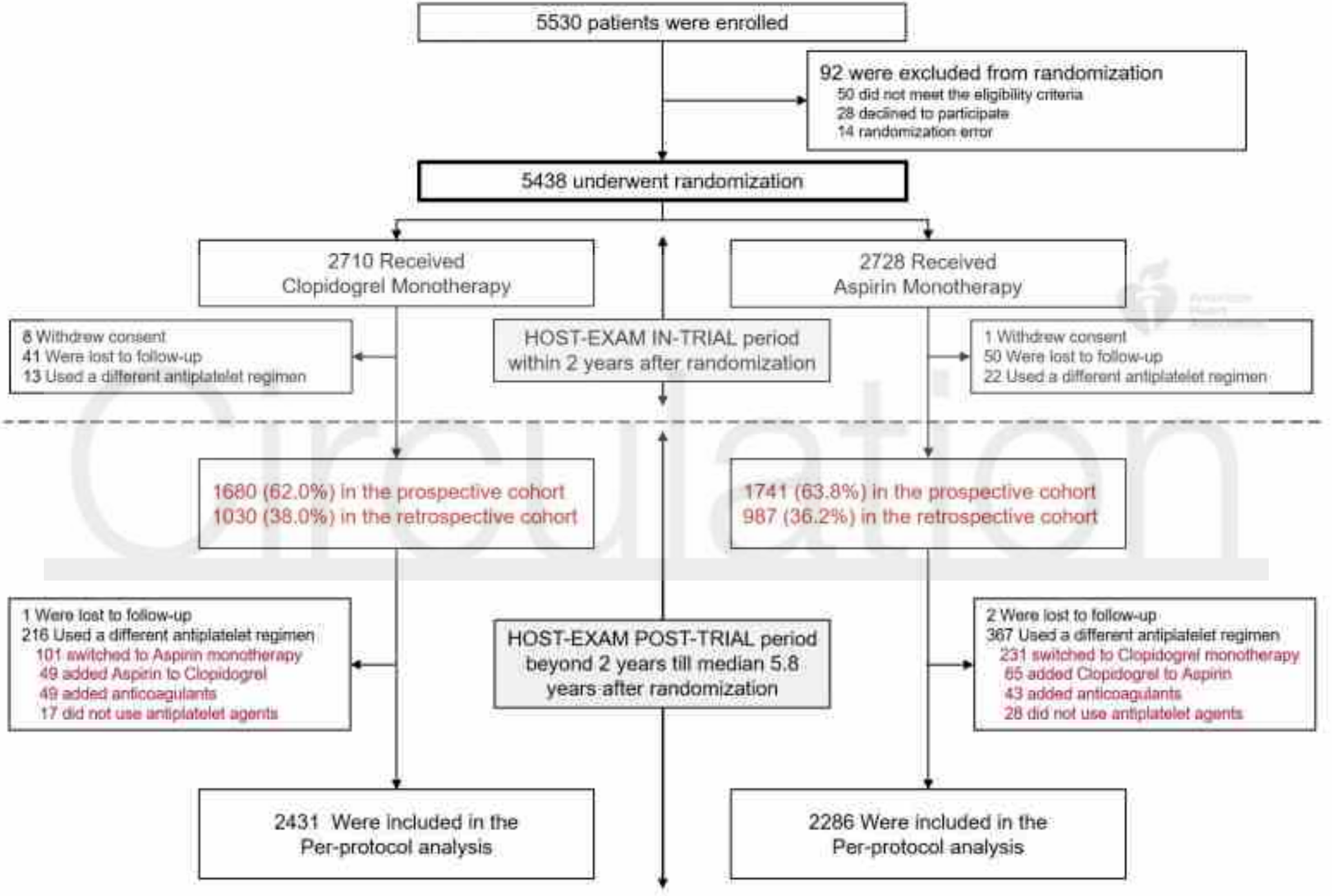
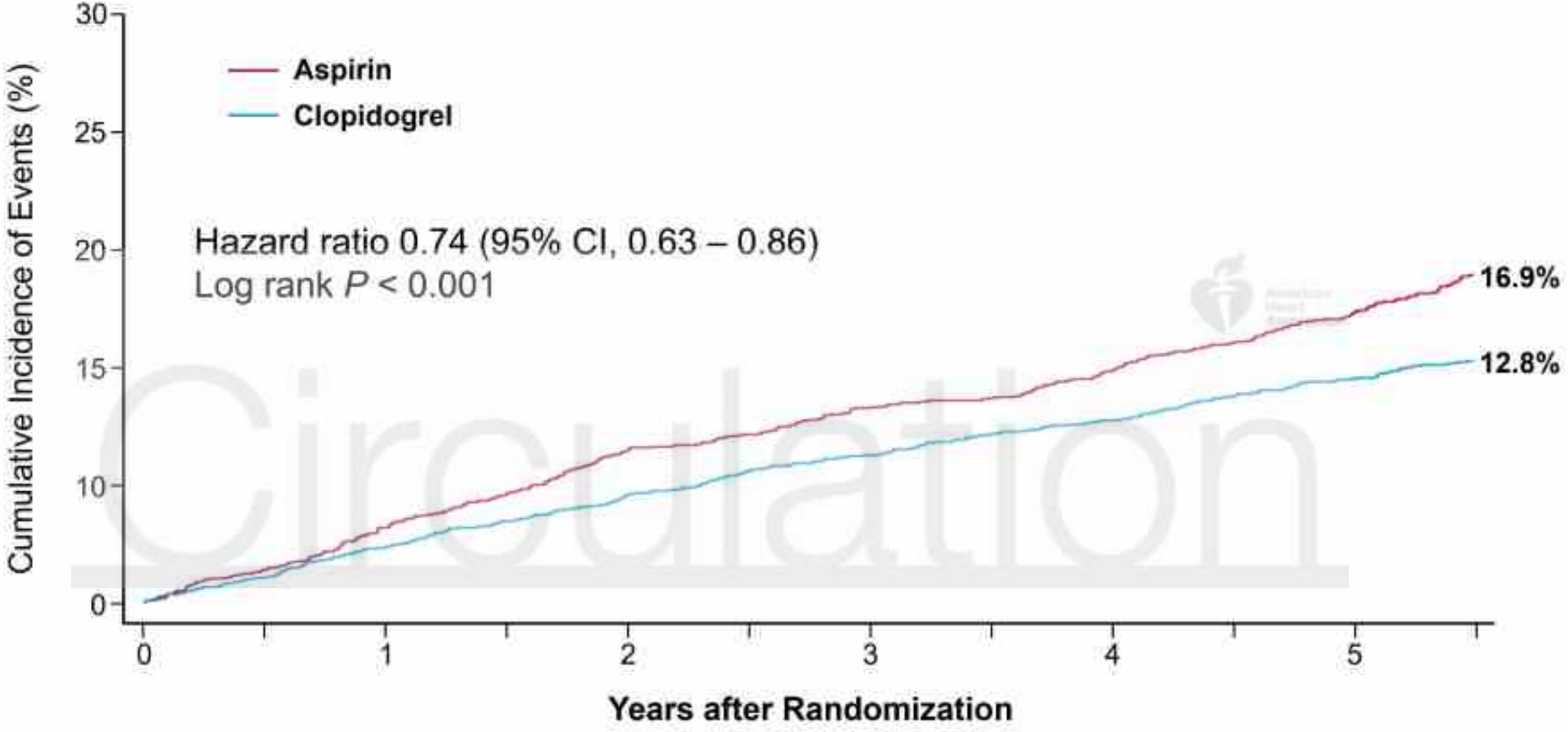


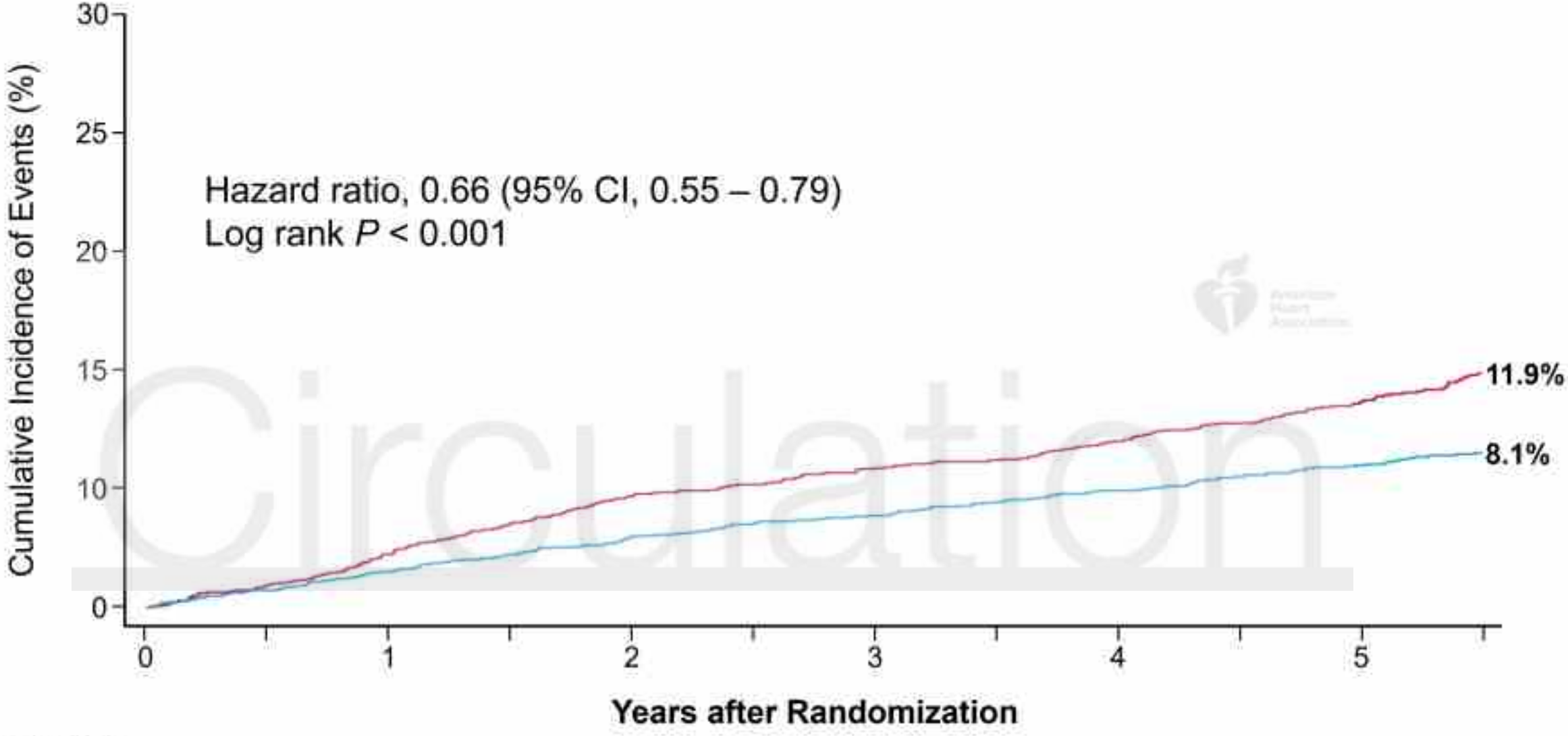
**Figure 2A**




**Number at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Aspirin | 2286 | 2189 | 2086 | 2014 | 1777 | 1287 | 1007 |
| Clopidogrel | 2431 | 2355 | 2280 | 2214 | 1964 | 1462 | 1181 |

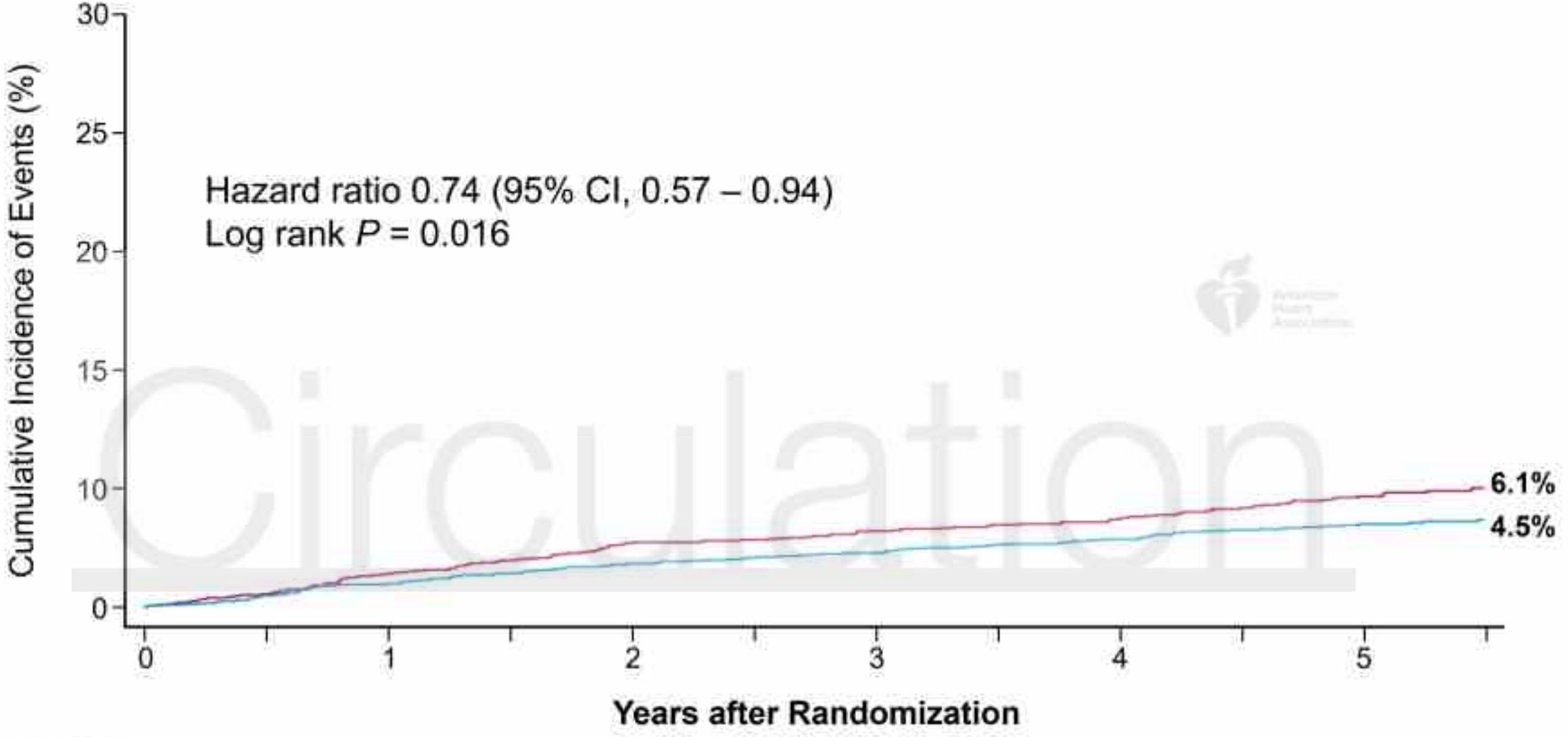
**Figure 2B**




**Number at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Aspirin | 2286 | 2208 | 2120 | 2053 | 1819 | 1322 | 1040 |
| Clopidogrel | 2431 | 2371 | 2304 | 2245 | 1992 | 1489 | 1202 |

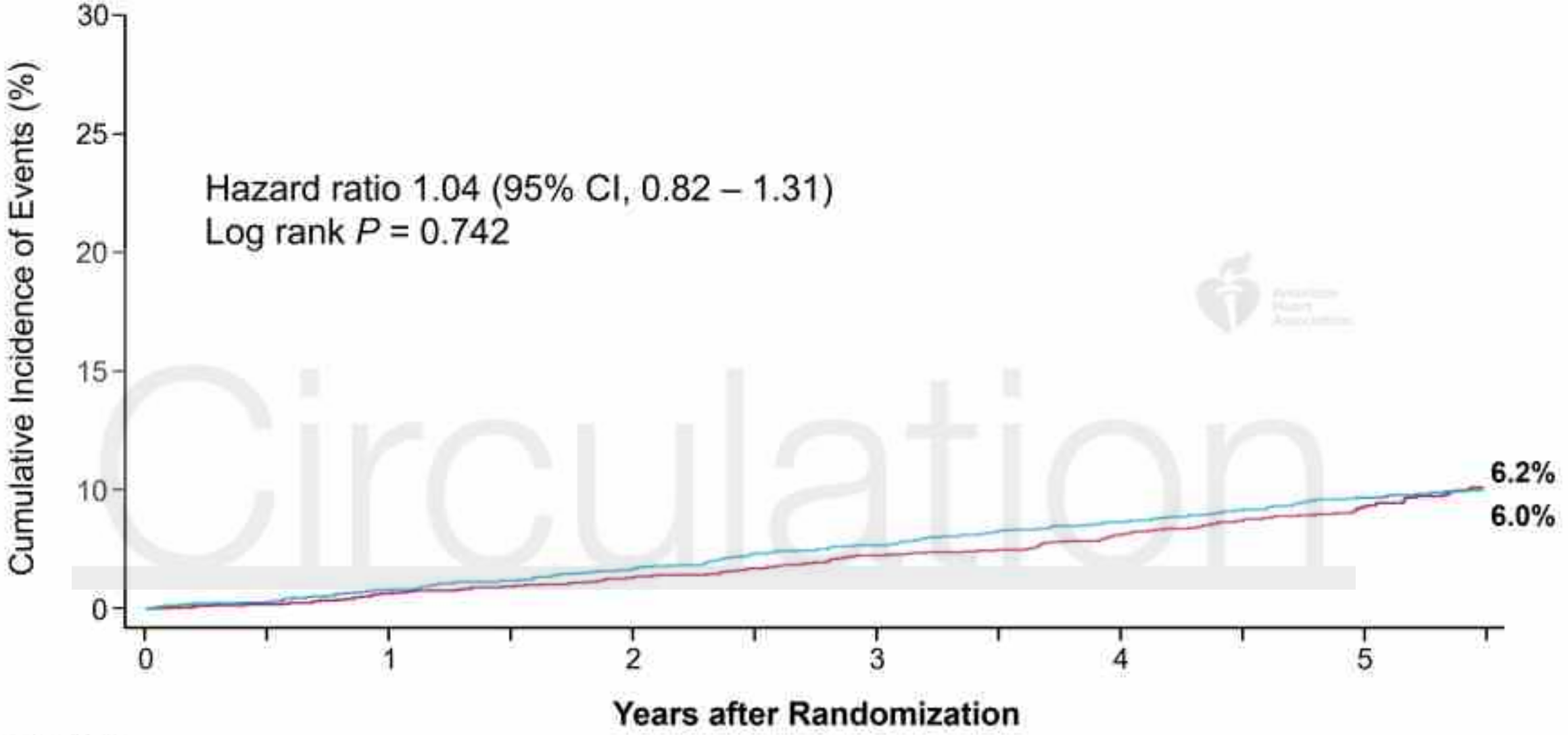
**Figure 2C**




**Number at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Aspirin | 2286 | 2229 | 2175 | 2123 | 1888 | 1395 | 1104 |
| Clopidogrel | 2431 | 2375 | 2323 | 2271 | 2028 | 1525 | 1238 |

**Figure 2D**




**Number at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Aspirin | 2286 | 2267 | 2244 | 2198 | 1971 | 1471 | 1165 |
| Clopidogrel | 2431 | 2405 | 2374 | 2330 | 2088 | 1579 | 1285 |

Figure 3

| | Clopidogrel group (events/patients) | Aspirin group (events/patients) | Hazard Ratio (95% CI) | P value | Interaction P |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| ≥65 | 200/1040 | 232/992 | 0.80 (0.66-0.96) | 0.019 | 0.176 |
| <65 | 110/1390 | 155/1294 | 0.65 (0.51-0.83) | <0.001 | |
| Sex | | | | | |
| Male | 222/1807 | 287/1723 | 0.72 (0.60-0.85) | <0.001 | 0.563 |
| Female | 89/624 | 100/563 | 0.79 (0.59-1.05) | 0.107 | |
| Body Mass Index ≥ 25 kg/m² | | | | | |
| Yes | 119/1103 | 140/976 | 0.74 (0.58-0.94) | 0.014 | 0.936 |
| No | 179/1244 | 231/1233 | 0.75 (0.61-0.91) | 0.003 | |
| Diabetes Mellitus | | | | | |
| Yes | 128/817 | 165/776 | 0.71 (0.57-0.90) | 0.004 | 0.764 |
| No | 182/1613 | 222/1510 | 0.75 (0.62-0.91) | 0.004 | |
| Chronic Kidney Disease | | | | | |
| Yes | 77/313 | 95/274 | 0.67 (0.50-0.90) | 0.009 | 0.614 |
| No | 233/2117 | 292/2012 | 0.74 (0.62-0.88) | 0.001 | |
| Multivessel Disease | | | | | |
| Yes | 170/1201 | 227/1145 | 0.69 (0.57-0.85) | 0.002 | 0.356 |
| No | 140/1229 | 159/1140 | 0.80 (0.64-1.00) | 0.054 | |
| Acute Myocardial Infarction | | | | | |
| Yes | 116/888 | 143/858 | 0.77 (0.60-0.98) | 0.036 | 0.756 |
| No | 194/1542 | 244/1428 | 0.72 (0.59-0.86) | <0.001 | |
| Acute Coronary Syndrome | | | | | |
| Yes | 219/1758 | 274/1631 | 0.72 (0.61-0.86) | <0.001 | 0.556 |
| No | 91/672 | 113/655 | 0.76 (0.58-1.00) | 0.053 | |
| Complex PCI | | | | | |
| Yes | 60/530 | 92/499 | 0.59 (0.43-0.82) | 0.002 | 0.138 |
| No | 249/1882 | 294/1769 | 0.78 (0.66-0.92) | 0.004 | |
| High Bleeding Risk | | | | | |
| Yes | 113/461 | 126/390 | 0.71 (0.55-0.92) | 0.009 | 0.860 |
| No | 161/1616 | 204/1538 | 0.74 (0.60-0.90) | 0.004 | |
| Proton Pump Inhibitor usage | | | | | |
| Yes | 39/251 | 56/266 | 0.72 (0.48-1.08) | 0.113 | 0.888 |
| No | 272/2160 | 331/2020 | 0.74 (0.63-0.87) | <0.001 | |