

THE LANCET

Supplementary appendix

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Detailed Statistical Analysis

The primary analysis was conducted on the intention-to-treat population. Outcomes at the longest available follow-up were primarily evaluated using semi-parametric shared log-normal frailty models including a random intercept (mixed-effects models) to account for differences in the baseline hazard across trials and a random slope to account for between-trial differences in treatment effects (one-stage analyses).^{1,2}

Treatment effects were expressed as hazard ratios (HRs) with 95% CIs. In the ASCET trial, the exact timing of outcomes was unavailable, and events were assumed to occur at the end of the follow-up period. Outcomes between treatment groups were described as counts, Kaplan-Meier estimates, and incidence rates per 100 person-years. Cumulative event distributions from the initiation of antithrombotic monotherapies to the longest available follow-up were illustrated by Kaplan-Meier curves after excluding patients from the ASCET trial and compared by the log-rank test. Median follow-up time was estimated with the reverse Kaplan-Meier method.³

The proportional hazards assumption was assessed using the Grambsch-Therneau test and Schoenfeld scaled residuals.² One-stage analyses were validated through multivariable mixed-effects models conducted across datasets (n=10) generated by chain equation multiple imputation accounting for the multilevel structure of data due to trial-level clustering.⁴ These models included the following variables along with the treatment strategy: age, haemoglobin (continuous variables), sex, body mass index, geographic region, index clinical presentation, treatment for CAD before randomisation, diabetes, hypertension, hypercholesterolemia, smoking status, prior myocardial infarction, prior stroke, prior bleeding, peripheral artery disease, chronic kidney disease, proton pump inhibitor use, and aspirin dose (categorical variables). The results across imputed datasets were pooled according to Rubin.⁴ We employed multivariate imputation by chained equations, which is a robust, informative procedure to handle missing values in relevant covariates through an iterative series of predictive models. Each variable with missing values is regressed on all the other values, restricted to subjects with the observed variable of interest. Missing values are replaced by simulated draws from the posterior predictive distribution of the variable of interest that reflects the correlation with observed data. The process operates on the subsequent variable with missing values, and so on. The process is repeated for a number of cycles, with the imputations being updated. Predictive mean matching, logistic regression, polytomous logistic regression, and ordinal regression were used for continuous, binomial, unordered categorical, and ordered categorical variables, respectively. Time-to-event outcomes were incorporated by the Nelson-Aalen estimator.

As recommended for individual patient data meta-analyses, outcomes were also assessed with two-stage analyses, according to which trial-level HRs and 95% CIs were computed by Cox proportional hazards regression and subsequently combined by random-effects models with inverse-variance weighting.⁵ In isolated cases of rare outcomes with monotonic likelihood and complete separation in smaller trials, a Firth's correction was applied.⁶ Between-trial heterogeneity was assessed by the Q test and quantified by the I^2 and τ^2 statistics.⁵ The restricted maximum likelihood estimator was used to compute τ^2 .⁵ Summary estimates from the two-stage analyses were further assessed after conservative adjustment of the 95% CI using the Hartung-Knapp

method.⁵ Frequentist random-effects estimates were complemented by prediction intervals and Bayesian random-effects models based on uninformative priors. We conducted a post-hoc trial sequential analysis to determine whether the results were conclusive for the primary efficacy outcome of MACCE based on the relative risk reduction observed at the one-stage analysis, a two-sided α of 0.050, and a β of 0.10.⁷ The trial sequential analysis integrates the cumulative sample size derived from the trials included in the individual patient data (IPD) meta-analysis with an adjusted threshold of statistical significance to account for repeated testing. According to this methodology, we computed monitoring boundaries based on the Lan-DeMets implementation of the O'Brien-Fleming α -spending function accounts for repeated statistical testing as each trial is added to the IPD meta-analysis on a chronological order. In parallel, we computed futility boundaries based on the Lan-DeMets implementation of the O'Brien-Fleming β -spending function to evaluate simultaneously whether non-significant summary effects would be unlikely to result in a statistical significance by adding future trials on the topic. Given an α of 0.05 and a β of 0.10, we also computed the heterogeneity-adjusted required information size required to conclusively demonstrate superiority or inferiority of clopidogrel monotherapy versus aspirin monotherapy in terms of MACCE for the observed 5-year relative risk reduction of 14%.

A prespecified sensitivity analysis was performed using a 1000-day landmark, given that 2000 days is the maximum available follow-up, to investigate possible temporal differences in event occurrence between the treatment groups. The co-primary efficacy and safety outcomes were assessed across prespecified subgroups. Treatment-by-subgroup interaction was assessed and the corresponding P value reported. If one or more interaction P values were significant, an additional analysis applying the Benjamini-Hochberg method was prespecified to account for multiplicity.

As prespecified, one-stage and two-stage analyses were replicated in the per-protocol population. The per-protocol population excluded (a) ineligible patients according to the study enrollment criteria, and/or (b) patients who never received the allocated treatment strategy. An additional prespecified analysis was conducted to evaluate whether the clinical factors of the ABCD-GENE score,⁸ which have been identified as independent predictors of impaired responsiveness to clopidogrel, influenced the comparative efficacy and safety of clopidogrel versus aspirin monotherapy. Based on the original derivation study, a score threshold of 10 was used to stratify patients into lower and higher risk categories.⁸

All analyses were performed using R 4.3.2.

Table S1. PRISMA-IPD Checklist.

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	3-4
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6

Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	5-6
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	6
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	6-8
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	6-8, Appendix
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	6-8
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	7-8, Appendix
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such	

		as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	Appendix
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	7-8, Appendix
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	7-8
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	7-8
Synthesis methods	14	<p>Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to):</p> <ul style="list-style-type: none"> • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable). 	8-10

Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	8-10
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	8
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	8-10
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	Appendix
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	Table 1, Appendix
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	10-11
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	10-11, Appendix
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	10-14, Table 2, Figures 1-

			3, Appendix
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	10-14, Table 2, Figures 1-3, Appendix
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	Appendix
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarize the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	13-14, Appendix
Discussion			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome.	14-19
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	14-19
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	14-19
Implications	A4	Consider relevance to key groups (such as policy makers, service providers, and service users). Consider implications for future research.	14-19

Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	10, Appendix

Table S2. Search Strategy.

Search String	Results
MedLine through PubMed ("aspirin"[Title/Abstract] OR "acetylsalicylic acid"[Title/Abstract]) AND ("p2y12 inhibitor"[Title/Abstract] OR "clopidogrel"[Title/Abstract] OR "prasugrel"[Title/Abstract] OR "ticagrelor"[Title/Abstract]) AND ("atherosclerosis"[Title/Abstract] OR "coronary artery disease"[Title/Abstract] OR "percutaneous coronary intervention"[Title/Abstract] OR "coronary artery bypass grafting"[Title/Abstract] OR "myocardial infarction"[Title/Abstract] OR "stroke"[Title/Abstract] OR "peripheral artery disease"[Title/Abstract])	5643
Scopus (TITLE-ABS ("aspirin") OR TITLE-ABS ("acetylsalicylic acid")) AND (TITLE-ABS ("P2Y12 inhibitor") OR TITLE-ABS ("clopidogrel") OR TITLE-ABS ("prasugrel") OR TITLE-ABS ("ticagrelor")) AND (TITLE-ABS ("atherosclerosis") OR TITLE-ABS ("coronary artery disease") OR TITLE-ABS ("percutaneous coronary intervention") OR TITLE-ABS ("coronary artery bypass grafting") OR TITLE-ABS ("myocardial infarction") OR TITLE-ABS ("stroke") OR TITLE-ABS ("peripheral artery disease"))	6319
Web of Science (aspirin OR acetylsalicylic acid>Title) or aspirin OR acetylsalicylic acid>Abstract)) AND (p2y12 inhibitor or clopidogrel or prasugrel or ticagrelor>Title) or p2y12 inhibitor or clopidogrel or prasugrel or ticagrelor>Abstract)) AND (atherosclerosis OR coronary artery disease OR percutaneous coronary intervention OR coronary artery bypass grafting OR myocardial infarction OR stroke OR peripheral artery disease>Title) or atherosclerosis OR coronary artery disease OR percutaneous coronary intervention OR coronary artery bypass grafting OR myocardial infarction OR stroke OR peripheral artery disease>Abstract))	5277
Embase through Ovid (aspirin or acetylsalicylic acid).ab,ti. AND (p2y12 inhibitor or clopidogrel or prasugrel or ticagrelor).ab,ti. AND (atherosclerosis or coronary artery disease or percutaneous coronary intervention or coronary artery bypass grafting or myocardial infarction or stroke or peripheral artery disease).ab,ti.	10787

Table S3. List of Studies Excluded After Full-Text Screening.

N	Authors	Title	Journal	Year
1	Fork F. T., Lafolie P., Tóth E., Lindgärde F.	Gastroduodenal tolerance of 75 mg clopidogrel versus 325 mg aspirin in healthy volunteers : A gastroscopic study	Scandinavian Journal of Gastroenterology	2000
2	Moshfegh K., Redondo M., Julmy F., Wuillemin W. A., Gebauer M. U., Haeberli A., Meyer B. J.	Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: Enhanced inhibitory effects of combination therapy	Journal of the American College of Cardiology	2000
3	Bhatt D. L., Chew D. P., Hirsch A. T., Ringleb P. A., Hacke W., Topol E. J.	Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery	Circulation	2001
4	Cannon C. P., Caprie Investigators	Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (CAPRIE trial)	American Journal of Cardiology	2002
5	Yusuf S., Mehta S. R., Zhao F., Gersh B. J., Commerford P. J., Blumenthal M., Budaj A., Wittlinger T., Fox K. A.	Early and late effects of clopidogrel in patients with acute coronary syndromes	Circulation	2003
6	Pettersen AÄR, Seljeflot I., Abdelnoor M., Arnesen H.	Unstable angina stroke myocardial infarction and death in aspirin non-responders.: A prospective randomized trial.: The ASCET (ASpirin non-responsiveness and Clopidogrel Endpoint Trial) design	Scandinavian Cardiovascular Journal	2004
7	Sanon S., Lee V. V., Elayda M., Wilson J. M.	Use of Aspirin Versus Clopidogrel Plus Aspirin After Coronary Artery Bypass Graft Surgery	Clinical and Applied Thrombosis-Hemostasis	2009
8	Muhlestein J. B., Pearson R. R., Horne B. D., May H. T., Kennedy P. K., Barnett T. J., Anderson J. L.	Does clopidogrel suppress vascular inflammation marked by C-reactive protein in patients with stable coronary artery disease? Primary results of a randomized double-blind prospective trial: CATER	Journal of the American College of Cardiology	2009
9	Pettersen A. A., Arnesen H., Opstad T. B., Akra S., Seljeflot I.	The influence of cyp 2c19*2 polymorphism on functional platelet testing in clopidogrel users	European Heart Journal	2010
10	Pettersen A. A. R., Seljeflot I., Bratseth V., Akra S., Arnesen H.	Residual platelet reactivity in patients with stable coronary artery disease on chronic single aspirin treatment	Pathophysiology of Haemostasis and Thrombosis	2010
11	Singer E., Imfeld S., Staub D., Hoffmann U., Buschmann I., Labs K. H., Jaeger K. A.	Effect of aspirin versus clopidogrel on walking exercise performance in intermittent claudication-a double-blind randomized multicenter trial	Journal of the American Heart Association	2012
12	Ferreiro J. L., Bhatt D. L., Ueno M., Bauer D., Angiolillo D. J.	Impact of Smoking on Long-Term Outcomes in Patients With Atherosclerotic Vascular Disease Treated With Aspirin or Clopidogrel	Journal of the American College of Cardiology	2014
13	Ting-Tse L., Liao M. T., Lai C. L.	Comparable Effectiveness Between Aspirin Clopidogrel and Dual Antiplatelet Therapy in Very Elderly Patients with Medically Managed Acute Myocardial Infarction	Journal of the American College of Cardiology	2016
14	Koh J. S., Park Y., Tantry U. S., Ahn J. H., Kang M. G., Kim K., Jang J. Y., Park H. W., Park J. R., Hwang S. J., Kwak C. H., Hwang J. Y., Gurbel P. A., Jeong Y. H.	Pharmacodynamic effects of a new fixed-dose clopidogrel-aspirin combination compared with separate administration of clopidogrel and aspirin in patients treated with coronary stents: The ACCEL-COMBO trial	Platelets	2017
15	Lee H., Koo B. K., Park K. W., Shin E. S., Lim S. W., Rha S. W., Bae J. W., Jeon D. W., Oh S. K., Hur S. H., Kim B. S., Lee J. H., Park T. H., Lee N. H., Kim H. S., Host-Exam Investigators	A randomized clinical trial comparing longterm clopidogrel vs aspirin monotherapy beyond dual antiplatelet therapy after drug eluting coronary stent implantation: Design and rationale of the Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy (HOST-EXAM) trial	American Heart Journal	2017
16	Hahn J. Y., Bin Song Y., Oh J. H., Chun W. J., Park Y. H., Jang W. J., Im E. S., Jeong J. O., Cho B. R., Oh S. K., Yun K. H., Cho D. K., Lee J. Y., Koh Y. Y., Bae J. W., Choi J., Lee W. S., Yoon H. J., Lee S. U., Cho J. H., Choi W. G., Rha S. W., Lee J. M., Park T. K., Yang J. H., Choi J. H., Choi	Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention The SMART-CHOICE Randomized Clinical Trial	Journal of the American Medical Association	2019

	S. H., Lee S. H., Gwon H. C., Kim D. B., Cho S. C., Hwang S. H., Jeon D. W., Choi J. W., Ryu J. K., Kim M. H., Chae I. H., Kim S. H., Kim H. L., Cho J. H., Jin D. K., Suh I. W., Park J. S., Shin E. S., Kim S. J., Cheong S. S., Ho K., Lee S. Y., Chae J. K., Koh Y. Y., Yang Y. M., Choi J. H., Yu C. W., Kim S. W., Choi S. Y., Kim H. J., Kim B. K., Park S. J., Smart-Choice Investigators			
17	Watanabe H., Domei T., Morimoto T., Natsuaki M., Shiomi H., Toyota T., Ohya M., Suwa S., Takagi K., Nanasato M., Hata Y., Yagi M., Suematsu N., Yokomatsu T., Takamisawa I., Doi M., Noda T., Okayama H., Seino Y., Tada T., Sakamoto H., Hibi K., Abe M., Kawai K., Nakao K., Ando K., Tanabe K., Ikari Y., Hanaoka K. I., Morino Y., Kozuma K., Kadota K., Furukawa Y., Nakagawa Y., Kimura T., Stopdapt- Investigators	Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI The STOPDAPT-2 Randomized Clinical Trial	Journal of the American Medical Association	2019
18	Natsuaki M., Morimoto T., Watanabe H., Abe M., Kawai K., Nakao K., Ando K., Tanabe K., Ikari Y., Hanaoka K. I., Morino Y., Kozuma K., Kadota K., Kimura T., Stopdapt- Trial Investigators, Stopdapt- Trial Investigators	Clopidogrel Monotherapy vs. Aspirin Monotherapy Following Short-Term Dual Antiplatelet Therapy in Patients Receiving Everolimus-Eluting Coronary Stent Implantation	Circulation Journal	2020
19	Sim D. S., Jeong M. H., Kim H. S., Gwon H. C., Seung K. B., Rha S. W., Chae S. C., Kim C. J., Cha K. S., Park J. S., Yoon J. H., Chae J. K., Joo S. J., Choi D. J., Hur S. H., Seong I. W., Cho M. C., Kim D. I., Oh S. K., Ahn T. H., Hwang J. Y., Kamar-Nih Registry Investigators	Clopidogrel versus Aspirin after Dual Antiplatelet Therapy in Acute Myocardial Infarction Patients Undergoing Drug-Eluting Stenting	Korean Circulation Journal	2020
20	Koo B. K., Kang J., Park K. W., Rhee T. M., Yang H. M., Won K. B., Rha S. W., Bae J. W., Lee N. H., Hur S. H., Yoon J., Park T. H., Kim B. S., Lim S. W., Cho Y. H., Jeon D. W., Kim S. H., Han J. K., Shin E. S., Kim H. S., Host-Exam Investigators	Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated prospective randomised open-label multicentre trial	Lancet	2021
21	Lee S. H., Lee S. Y., Chun W. J., Song Y. B., Choi S. H., Jeong J. O., Oh S. K., Yun K. H., Koh Y. Y., Bae J. W., Choi J. W., Gwon H. C., Hahn J. Y., Smart-Choice Investigators	Clopidogrel monotherapy in patients with and without on-treatment high platelet reactivity: a SMART-CHOICE substudy	Eurointervention	2021
22	Park H. W., Kang M. G., Ahn J. H., Bae J. S., Tantry U. S., Gurbel P. A., Jeong Y. H.	Effects of Monotherapy with Clopidogrel vs. Aspirin on Vascular Function and Hemostatic Measurements in Patients with Coronary Artery Disease: The Prospective Crossover I-LOVE-MONO Trial	Journal of Clinical Medicine	2021
23	Rhee T. M., Kang J., Park K. W., Yang H. M., Won K. B., Rha S. W., Bae J. W., Lee N. H., Hur S. H., Yoon J., Park T. H., Kim B. S., Lim S. W., Cho Y. H., Jeon D. W., Kim S. H., Han K. R., Moon K. W., Oh S. K., Kim U., Rhee M. Y., Kim D. I., Kim S. Y., Lee S., Lee S. U., Kim S. W., Kim S. Y., Jeon H. K., Cha K. S., Jo S. H., Ryu J. K., Suh I. W., Choi H. H., Woo S. I., Chae I. H., Shin W. Y., Kim D. K., Oh J. H., Jeong M. H., Kim Y. H., Han J. K., Shin E. S., Koo B. K., Kim H. S.	Impact of Diabetes Mellitus on the Effectiveness of Aspirin Versus Clopidogrel as a Chronic Maintenance Antiplatelet Monotherapy After Percutaneous Coronary Intervention: Results From the HOST-EXAM Trial	Journal of the American College of Cardiology	2021
24	Kang J., Hwang D., Han J. K., Yang H. M., Park K. W. W., Koo B. K., Rha S. W. W., Bae J. W., Shin E. S.	Long Term Follow-Up of Aspirin vs. Clopidogrel Monotherapy in the Chronic Maintenance Period After Percutaneous Coronary Intervention: The Host-Exam Extended Study	Circulation	2022
25	Kang J., Park K. W., Hwang D., Han J. K., Yang H. M., Kang H. J., Koo B. K., Kim H. S.	Clopidogrel Versus Aspirin in the Chronic Maintenance Period Following Percutaneous Coronary Intervention in Patients With Acute Coronary Syndrome: Subgroup Analysis of the HOSTEXAM Trial	Journal of the American College of Cardiology	2022
26	Obayashi Y., Watanabe H., Morimoto T., Yamamoto K., Natsuaki M., Domei T., Yamaji K., Suwa S., Isawa T., Watanabe H., Yoshida R., Sakamoto H., Akao M., Hata Y., Morishima I., Tokuyama H., Yagi M., Suzuki H., Wakabayashi K., Suematsu N., Inada T., Tamura T., Okayama H., Abe M., Kawai K., Nakao K., Ando K., Tanabe K., Ikari Y., Morino Y.,	Clopidogrel Monotherapy After 1-Month Dual Anti platelet Therapy in Percutaneous Coronary Intervention: From the STOPDAPT-2 Total Cohort	Circulation Cardiovascular Interventions	2022

	Kadota K., Furukawa Y., Nakagawa Y., Kimura T., Stopdapt, Stopdapt-Acs Investigators			
27	Watanabe H., Morimoto T., Natsuaki M., Yamamoto K., Obayashi Y., Ogita M., Suwa S., Isawa T., Domei T., Yamaji K., Tatsumi S., Watanabe H., Ohya M., Tokuyama H., Tada T., Sakamoto H., Mori H., Suzuki H., Nishikura T., Wakabayashi K., Hibi K., Abe M., Kawai K., Nakao K., Ando K., Tanabe K., Ikari Y., Morino Y., Kadota K., Furukawa Y., Nakagawa Y., Kimura T.	Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome: The STOPDAPT-2 ACS Randomized Clinical Trial	JAMA Cardiol	2022
28	Chung J., Kang J., Lee H., Hwang D., Park K. W., Yang H. M., Han J. K., Shin E. S., Koo B. K., Kim H. S.	Clopidogrel vs. aspirin in the chronic maintenance period following percutaneous coronary intervention in high thrombotic and high bleeding risk patients:sub-analysis of the HOST-EXAM Extended study	European Heart Journal	2023
29	Rhee T. M., Bae J. W., Park K. W., Rha S. W., Kang J., Lee H., Yang H. M., Kwak S. H., Chae I. H., Shin W. Y., Kim D. K., Oh J. H., Jeong M. H., Kim Y. H., Lee N. H., Hur S. H., Yoon J., Han J. K., Shin E. S., Koo B. K., Kim H. S.	Aspirin vs Clopidogrel for Long-term Maintenance After Coronary Stenting in Patients With Diabetes A Post Hoc Analysis of the HOST-EXAM Trial	JAMA Cardiology	2023
30	Shin E. S., Her A. Y., Kim B., Hahn J. Y., Bin Song Y., Lee J. M., Park T. K., Yang J. H., Choi J. H., Choi S. H., Lee S. H., Gwon H. C., Smart Choice Investigators	Sex-Based Outcomes of P2Y12 Inhibitor Monotherapy After Three Months of Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention	Journal of Korean Medical Science	2023
31	Shin E. S., Jun E. J., Kim B., Won K. B., Koo B. K., Kang J., Park K. W., Rhee T. M., Yang H. M., Han J. K., Kim H. S., Host Exam Investigators	Association of Clinical Outcomes With Sex in Patients Receiving Chronic Maintenance Antiplatelet Monotherapy After Percutaneous Coronary Intervention: A Post Hoc Gender Analysis of the HOST-EXAM Study	Journal of the American Heart Association	2023
32	Yamamoto K., Watanabe H., Morimoto T., Obayashi Y., Natsuaki M., Yamaji K., Domei T., Ogita M., Ohya M., Tatsumi S., Suzuki H., Tada T., Ishii M., Nikaido A., Watanabe N., Fujii S., Mori H., Nishikura T., Suematsu N., Hayashi F., Komiyama K., Shigematsu T., Isawa T., Suwa S., Ando K., Kimura T., Stopdapt-2 Stopdapt A. C. S.	Clopidogrel Monotherapy After 1-Month Dual Antiplatelet Therapy in Patients With Diabetes Undergoing Percutaneous Coronary Intervention	JACC Cardiovascular Interventions	2023
33	Yang S., Kang J., Park K. W., Hur S. H., Lee N. H., Hwang D., Yang H. M., Ahn H. S., Cha K. S., Jo S. H., Ryu J. K., Suh I. W., Choi H. H., Woo S. I., Han J. K., Shin E. S., Koo B. K., Kim H. S.	Comparison of Antiplatelet Monotherapies After Percutaneous Coronary Intervention According to Clinical Ischemic and Bleeding Risks	Journal of the American College of Cardiology	2023
34	Yamamoto K., Watanabe H., Morimoto T., Obayashi Y., Natsuaki M., Domei T., Yamaji K., Suwa S., Isawa T., Watanabe H., Yoshida R., Sakamoto H., Akao M., Hata Y., Morishima I., Tokuyama H., Yagi M., Suzuki H., Wakabayashi K., Suematsu N., Inada T., Tamura T., Okayama H., Abe M., Kawai K., Nakao K., Ando K., Tanabe K., Ikari Y., Morino Y., Kadota K., Furukawa Y., Nakagawa Y., Kimura T.	Clopidogrel Monotherapy After 1-Month DAPT in Patients With High Bleeding Risk or Complex PCI	JACC Asia	2023
35	Han M., Kang J., Kim B., Hwang D., Yang H. M., Park K. W., Han J. K., Koo B. K., Shin E. S., Kim H. S.	The Impact of Obesity on Antiplatelet Monotherapy for Secondary Prevention After Percutaneous Coronary Intervention: A Substudy of the HOST-EXAM Trial	Journal of the American College of Cardiology	2023
36	Kang J., Chung J., Park K. W., Bae J. W., Lee H. J., Hwang D., Yang H. M., Han K. R., Moon K. W., Kim U., Rhee M. Y., Kim D. I., Kim S. Y., Lee S. Y., Lee S. U., Kim S. W., Kim S. Y., Han J. K., Shin E. S., Koo B. K., Kim H. S.	Long-Term Aspirin vs Clopidogrel After Coronary Stenting by Bleeding Risk and Procedural Complexity	JAMA Cardiology	2024
37	Kang J., Hwang D., Han J. K., Yang H. M., Park K. W., Koo B. K., Kim H. S.	Long-Term Clopidogrel vs Aspirin Monotherapy in Stable Coronary Artery Disease Patients With High Ischemic Risk: A Post Hoc Analysis of the HOST-EXAM Extended Study	Journal of the American College of Cardiology	2024
38	Kang J., Park S. H., Park K. W., Koo B. K., Lee H., Han M., Hwang D., Yang H. M., Chae I. H., Shin W. Y., Oh J. H., Kim Y. H., Park T. H., Kim B. S., Han J. K., Shin E. S., Kim H. S.	Clopidogrel Versus Aspirin as Chronic Maintenance Antiplatelet Monotherapy in Patients After Percutaneous Coronary Intervention With Chronic Kidney Disease: A Post Hoc Analysis of the HOST-EXAM Trial	Journal of the American Heart Association	2024

39	Lee K. H., Kang J. H., Park K. W., Park T. H., Kim B. S., Lim S. W., Cho Y. H., Jeon D. W., Kim S. H., Yang H. M., Kang H. J., Han J. K., Shin E. S., Koo B. K., Kim H. S.	Impact of Age on Antiplatelet Monotherapy in the Chronic Maintenance Period After Percutaneous Coronary Intervention: A Post Hoc Analysis From the HOST-EXAM Extended Study	Canadian Journal of Cardiology	2024
40	Li Y., Li J., Wang B., Jing Q. M., Zeng Y. J., Hou A. J., Wang Z. F., Liu A. J., Zhang J. L., Zhang Y. J., Zhang P., Jiang D. M., Liu B., Fan J. M., Zhang J., Li L., Su G. H., Yang M., Jiang W. H., Qu P., Zeng H. S., Li L., Qiu M. H., Ru L. S., Chen S. L., Zhou Y. J., Qiao S. B., Stone G. W., Angiolillo D. J., Han Y. L., Opt Birisk Investigators	Extended Clopidogrel Monotherapy vs DAPT in Patients With Acute Coronary Syndromes at High Ischemic and Bleeding Risk The OPT-BIRISK Randomized Clinical Trial	JAMA Cardiology	2024
41	Min P. K., Kang T. S., Cho Y. H., Cheong S. S., Kim B. K., Kwon S. W., Park W. J., Lee J. H., Kim W., Lee W. S., Yoon Y. W., Lee B. K., Kwon H. M., Hong B. K., Share Investigators	P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy After Deployment of a Drug-Eluting Stent	JAMA Network Open	2024
42	Natsuaki M., Watanabe H., Morimoto T., Yamamoto K., Obayashi Y., Nishikawa R., Ando K., Domei T., Suwa S., Ogita M., Isawa T., Takenaka H., Yamamoto T., Ishikawa T., Hisauchi I., Wakabayashi K., Onishi Y., Hibi K., Kawai K., Yoshida R., Suzuki H., Nakazawa G., Kusuyama T., Morishima I., Ono K., Kimura T.	An Aspirin-Free Versus Dual Antiplatelet Strategy for Coronary Stenting: STOPDAPT-3 Randomized Trial	Circulation	2024
43	Natsuaki M., Watanabe H., Morimoto T., Yamamoto K., Obayashi Y., Nishikawa R., Ando K., Suwa S., Isawa T., Takenaka H., Ishikawa T., Yamada M., Wakatsuki T., Nozaki Y., Kitahara H., Kato R., Kawai R., Kobayashi Y., Ishii M., Goto Y., Ono K., Kimura T.	Aspirin-Free Strategy for Percutaneous Coronary Intervention in Patients With Oral Anticoagulation: Prespecified Subgroup Analysis From the STOPDAPT-3 Trial	Journal of the American Heart Association	2024
44	Vergallo R., Patrono C.	STOPDAPT-3 one-year results support similar efficacy and safety of aspirin and clopidogrel after percutaneous coronary intervention	European Heart Journal	2024
45	Yamamoto K., Natsuaki M., Watanabe H., Morimoto T., Obayashi Y., Nishikawa R., Ando K., Suwa S., Isawa T., Takenaka H., Ishikawa T., Ikari Y., Kurita T., Kaitani K., Sugimoto A., Ogata N., Ikuta A., Hashimoto K., Ishibashi Y., Masuda K., Miyabe T., Ono K., Kimura T., Stopdapt-Investigators	An aspirin-free strategy for percutaneous coronary intervention in patients with diabetes: a pre-specified subgroup analysis of the STOPDAPT-3 trial	European Heart Journal-Cardiovascular Pharmacotherapy	2024
46	Yamamoto K., Natsuaki M., Watanabe H., Morimoto T., Obayashi Y., Nishikawa R., Ando K., Suwa S., Isawa T., Takenaka H., Ishikawa T., Tamura T., Kawahatsu K., Hayashi F., Akao M., Serikawa T., Mori H., Kawamura T., Hagiwara A., Shibata N., Ono K., Kimura T., Stopdapt-Investigators	An Aspirin-Free Strategy for Immediate Treatment Following Complex Percutaneous Coronary Intervention	JACC Cardiovascular Interventions	2024
47	Domei T., Yamamoto K., Natsuaki M., Watanabe H., Morimoto T., Obayashi Y., Nishikawa R., Kimura T., Ando K., Suwa S., Isawa T., Takenaka H., Ishikawa T., Tamura T., Kawahatsu K., Hayashi F., Abe M., Serikawa T., Mori H., Kawamura T., Hagiwara A., Shibata N., Ono K., Kimura T.	Aspirin vs. clopidogrel monotherapy beyond 1 month after complex percutaneous coronary intervention: a pre-specified subgroup analysis of the STOPDAPT-3 trial	European Heart Journal-Cardiovascular Pharmacotherapy	2025

Table S4. Inclusion and Exclusion Criteria Across Trials.

Study	Major Inclusion Criteria	Major Exclusion Criteria
ASCET	<ul style="list-style-type: none">• Patients, male or female, aged 18-80 years• Stable coronary heart disease documented by coronary angiography, being treated with angioplasty/stent implantation or not	<ul style="list-style-type: none">• Indication for warfarin treatment• Acute coronary syndrome with an indication for long-term clopidogrel treatment• Indication for or contraindication to the study drugs• Pregnancy• Malignancy• Psychiatric disease, mental retardation, dementia, drug abuse, alcoholism, or conditions severely reducing compliance
CADET	<ul style="list-style-type: none">• Patients aged 21 years or more• Documented acute myocardial infarction (WHO criteria) within the last 3-7 days	<ul style="list-style-type: none">• Uncontrolled hypertension• Being scheduled for major surgery (including coronary artery bypass grafting)• Concomitant use of hormone replacement therapy
CAPRIE	<ul style="list-style-type: none">• Ischaemic stroke (including retinal origin and lacunar infarction): focal neurological deficit likely to be of atherothrombotic; onset ≥ 1 week and ≥ 6 months before randomisation; neurological signs persisting ≥ 1 week from stroke onset; computed tomography or magnetic resonance imaging ruling out haemorrhage or non-relevant disease	<ul style="list-style-type: none">• Age <21 years• Severe cerebral deficit likely resulting in the patient being bedridden or demented• Carotid endarterectomy after qualifying stroke• Qualifying stroke induced by carotid endarterectomy or angiography• Patient unlikely to be discharged alive after qualifying event• Severe co-morbidity likely to limit patient's life expectancy to less than 3 years• Uncontrolled hypertension

	<ul style="list-style-type: none"> • Myocardial infarction: onset ≤35 days before randomisation. Two characteristic ischaemic pain for ≥20 min; elevation of creatine kinase, creatine kinase-myocardial band, lactate dehydrogenase, or aspartate aminotransferase to 2x upper normal limit with no other explanation; development of new ≥40 Q waves in at least two adjacent electrocardiogram leads or new dominant R wave in V1 ($R \geq 1 \text{ mm} > S \text{ in V1}$) • Atherosclerotic peripheral arterial disease: Intermittent claudication (WHO: leg pain on walking, disappearing in <10 min on standing) of presumed atherosclerotic origin; and ankle/arm systolic blood pressure ratio ≤0.85 in either leg at rest (two assessments on separate days); or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty with no persisting complications from the intervention 	<ul style="list-style-type: none"> • Scheduled for major surgery • Contraindications to study drugs: severe renal or hepatic insufficiency; haemostatic disorder or systemic bleeding; history of haemostatic disorder or systemic bleeding; history of thrombocytopenia or neutropenia; history of drug-induced hematologic or hepatic abnormalities; known to have abnormal white blood cells, differential, or platelet count; anticipated requirement for long term anticoagulants, non-study antiplatelet drugs or non-steroidal anti-inflammatory drugs affecting platelet function; history of aspirin sensitivity • Women of childbearing age not using reliable contraception • Currently receiving investigation drug • Previously entered in other clopidogrel studies • Geographic or other factors making study participation impractical
HOST-EXAM	<ul style="list-style-type: none"> • Male and female aged ≥20 years • Maintenance of DAPT or triple antiplatelet therapy at least 12 ± 6 months after PCI with drug-eluting stent • No history of further clinical events after PCI with drug-eluting stent • Plan to change to antiplatelet monotherapy • Agreement to give written informed consent 	<ul style="list-style-type: none"> • History of hypersensitivity or contraindication to aspirin or clopidogrel • Active pathologic bleeding, such as peptic ulcer, tumour bleeding, or intracranial haemorrhage • History of major bleeding, BARC class ≥3, resulting in the interruption of antiplatelet agents within 3 months • Bleeding diathesis, known coagulopathy, or refusal of blood transfusion • Non-cardiac comorbidity with life expectancy <2 years from randomisation • Planned surgery or intervention requiring the interruption of antiplatelet agents ≥3 months • Females with childbearing potential or breast-feeding

SMART-CHOICE 3

- Male and female aged ≥ 20 years
- Maintenance of DAPT or triple antiplatelet therapy at least 12 ± 6 months after PCI with drug-eluting stent
- No history of further clinical events after PCI with drug-eluting stent
- Plan to change to antiplatelet monotherapy
- Agreement to give written informed consent

- Conditions potentially resulting in protocol non-compliance
- Co-administration of contraindicated medications: other P2Y₁₂ inhibitors (prasugrel or ticagrelor); anticoagulants (warfarin, new oral anticoagulants, or chronic therapy of heparin); cytochrome P450 2C19 inhibitors (fluoxetine, moclobemide, or voriconazole); probenecid; high dose of methotrexate (≥ 15 mg/week); lithium.

- History of hypersensitivity or contraindication to aspirin or clopidogrel
- Active pathologic bleeding, such as peptic ulcer, tumour bleeding, or intracranial haemorrhage
- History of major bleeding, BARC class ≥ 3 , resulting in the interruption of antiplatelet agents within 3 months
- Bleeding diathesis, known coagulopathy, or refusal of blood transfusion
- Non-cardiac comorbidity with life expectancy <2 years from randomisation
- Planned surgery or intervention requiring the interruption of antiplatelet agents ≥ 3 months
- Females with childbearing potential or breast-feeding
- Conditions potentially resulting in protocol non-compliance
- Co-administration of contraindicated medications: other P2Y₁₂ inhibitors (prasugrel or ticagrelor); anticoagulants (warfarin, new oral anticoagulants, or chronic therapy of heparin); cytochrome P450 2C19 inhibitors (fluoxetine, moclobemide, or voriconazole); probenecid; high dose of methotrexate (≥ 15 mg/week); lithium

STOPDAPT-2

- PCI with implantation of a cobalt-chromium everolimus-eluting stent
- Capability to assume oral DAPT consisting of aspirin and a P2Y₁₂ receptor antagonist

- Need for oral anticoagulation
- History of intracranial bleeding
- Need for antiplatelet therapy other than aspirin and P2Y₁₂ receptor blockers
- Known intolerance to clopidogrel
- Serious in-hospital complications (myocardial infarction, stroke, and major bleeding) after the index PCI
- Implantation of stents other than cobalt-chromium everolimus-eluting and bioresorbable vascular scaffolds

STOPDAPT-3

- Patients who are planned to have PCI with exclusive use of an everolimus-eluting stent
 - Patients with high bleeding risk defined by ARC or acute coronary syndrome
 - Patients who could take DAPT with aspirin and P2Y₁₂ inhibitors for 1-month
 - Patients who are judged to be unsuitable for participation by the principal investigator and co-investigator
 - Patients with a known allergy to the study drugs
 - Patients enrolled in the ongoing prospective interventional studies
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ARC=Academic Research Consortium; ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; BARC=Bleeding Academy Research Consortium; CADET=Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; CAPRIE=Clopidogrel versus aspirin in patients at risk of ischaemic events; DAPT=Dual Antiplatelet Therapy; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; PCI=Percutaneous Coronary Intervention; SMART-CHOICE 3=SMart Angioplasty Research Team: CHoice of Optimal Anti-Thrombotic Strategy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents 3; STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study; STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study; STOPDAPT-3=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-3 Study; WHO=World Health Organisation.

Table S5. Endpoint Definitions Across Trials.

Endpoint	ASCET	CADET	CAPRIE	HOST-EXAM	SMART-CHOICE 3	STOPDAPT-2	STOPDAPT-3
Original Primary Endpoint	The composite of acute coronary syndrome, myocardial infarction, non-haemorrhagic stroke, and death.	Reduction in Clauss fibrinogen.	Vascular death, myocardial infarction, or ischaemic stroke.	All-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding.	Death from any cause, myocardial infarction, or stroke.	Cardiovascular death, myocardial infarction, definite stent thrombosis, ischaemic or haemorrhagic stroke, or TIMI major or minor bleeding	BARC 3 or 5.
Cardiovascular or Vascular Death	Not collected.	Death due to vascular or cardiac causes.	Myocardial infarction or fatal ischaemic stroke based on either death within 28 days after the onset of signs or symptoms of the acute outcome event, in the absence of other clear causes, or on necropsy findings. Other vascular death: any deaths not clearly non-vascular and not	All deaths excluding those for which the underlying cause was solely documented as non-cardiovascular and all deaths for which a cardiovascular contributing cause was suspected.	Death from cardiovascular causes includes sudden cardiac death, death due to acute MI, heart failure or cardiogenic shock, other cardiovascular causes, or any unknown death without undisputed non-cardiac cause.	Any death due to proximate cardiac cause (e.g. myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment, and death due to non-coronary vascular	Any death due to proximate cardiac cause (e.g. myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment, and death due to non-coronary vascular

			defined as fatal stroke, fatal myocardial infarction, or fatal bleeding.		causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.	causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.	
Myocardial Infarction	First universal definition.	WHO criteria	<p>Myocardial infarction was defined as two of:</p> <ul style="list-style-type: none"> (i) Characteristic ischaemic pain for >20 min; (ii) elevation of creatine kinase, creatine kinase-myocardial band, lactate dehydrogenase, or aspartate aminotransferase to 2 x upper limit of laboratory normal with no other explanation; (iii) development of new Q waves (40 ms) in at least 2 adjacent 	Third universal definition.	Fourth universal definition.	ARC definitions.	ARC definitions.

			electrocardiogram leads or new dominant R wave in V1 ($R > 1$ mm or $> S$ in V1).				
Stroke	Non-haemorrhagic stroke.	Any stroke.	Focal neurological deficit (including retinal and lacunar infarction) likely to be of atherothrombotic origin. Neurological signs must have persisted ≥ 1 week from stroke onset; computed tomography or magnetic resonance imaging must have ruled out haemorrhage or non-relevant concomitant disease. Acute neurological vascular event with focal signs must have lasted for ≥ 24 h. If in a new location,	Any non-convulsive, focal or global neurological deficit of abrupt onset lasting for more than 24 hours or leading to death, caused by ischaemia or haemorrhage within the brain.	Acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture	Ischaemic lesion with symptoms lasting over 24 hours.	Ischaemic lesion with symptoms lasting over 24 hours.

		without evidence of intracranial haemorrhage. If worsening of previous event, must have lasted >1 week, or >24 h if accompanied by appropriate computed tomography or magnetic resonance imaging findings.			
Bleeding	Major bleeding: bleeding requiring transfusion of blood or surgical intervention or intracranial bleeding.	Defined as: (i) intracranial haemorrhage (intracerebral haemorrhage, including intracranial and haemorrhage subarachnoid, and subdural hematoma documented by appropriate neuroimaging investigations; traumatic intracranial haemorrhage was recorded but not	Adjudicated according to the BARC classification.	Adjudicated according to the BARC classification.	Adjudicated according to the TIMI, BARC, and GVSTO classification.
	Minor bleeding: bleeding not requiring transfusion or surgical intervention, including subcutaneous bruising, minor hematoma, and oozing from	Major bleeding: bleeding requiring transfusion of blood or surgical intervention or intracranial bleeding.	Adjudicated according to the BARC classification.	Adjudicated according to the TIMI, BARC, and GVSTO classification.	Adjudicated according to the TIMI, BARC, and GVSTO classification.
		Minor bleeding: not fulfilling major bleeding definition.			

puncture sites or gums.	counted as outcome event); (ii) gastrointestinal haemorrhage; (iii) fatal haemorrhage; (iv) any bleeding disorder.
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ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; BARC=Bleeding Academy Research Consortium; CADET=Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; DAPT=Dual Antiplatelet Therapy; GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; SCAI=Society for Cardiovascular Angiography and Interventions; SMART-CHOICE 3=SMart Angioplasty Research Team: CHoice of Optimal Anti-Thrombotic Strategy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents 3; STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2; STOPDAPT-3=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-3; TIMI=Thrombolysis in Myocardial Infarction; WHO=World Health Organisation.

Table S6. Sources of Funding Across Trials.

Study	Institutional Funding Source	Industry Funding Source
ASCET	Norwegian Council for Cardiovascular Diseases, "Ada og Hagbart Waages Humanitære og Veldedige stiftelse," "Alf og Aagot Helgesens Legat," and Stein Erik Hagen Foundation for Clinical Heart Research (Oslo, Norway)	—
CADET	—	Sanofi-Synthelabo
CAPRIE	—	Sanofi and Bristol-Myers Squibb
HOST-EXAM	South Korea Ministry of Health and Welfare	ChongKunDang, SamJin, HanMi, and DaeWoong
SMART-CHOICE 3	—	Dong-A ST
STOPDAPT-2	Kyoto University	Abbott
STOPDAPT-3	Kyoto University	Abbott

ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CADET=Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; CAPRIE=Clopidogrel versus aspirin in patients at risk of ischaemic events; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; SMART-CHOICE 3=SMart Angioplasty Research Team: Choice of Optimal Anti-Thrombotic Strategy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents 3; STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study; STOPDAPT-3=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-3 Study.

Table S7. Baseline Characteristics Across Trials.

	ASCET (n=1001)	CADET (n=184)	CAPRIE (n=8446)	HOST-EXAM (n=5438)	SMART-CHOICE 3 (n=5506)	STOPDAPT-2 (n=2882)	STOPDAPT-3 (n=5525)
Age (years)	62·3 [56·1-69·1]	62·6 [54·6-70·8]	58·0 [38·0-65·5]	64·0 [56·0-72·0]	65·0 [58·0-73·0]	69·9 [62·9-76·4]	73·0 [64·0-80·0]
Female	218 (21·8%)	35 (19·0%)	1662 (19·7%)	1384 (25·5%)	1002 (18·2%)	644 (22·3%)	1261 (22·8%)
Body mass index (kg/m ²)	27·1 [24·8-29·6]	26·4 [24·8-28·5]	—	24·6 [22·8-26·6]	24·9 [23·0-26·9]	24·2 [22·0-26·4]	23·6 [21·5-26·0]
Region							
Europe	1001 (100%)	184 (100%)	3865 (45·8%)	0	0	0	0
North America	0	0	4581 (54·2%)	0	0	0	0
Asia	0	0	0	5438 (100%)	5506 (100%)	2882 (100%)	5525 (100%)
Diabetes	159 (15·9%)	—	1545 (18·3%)	1860 (34·2%)	2247 (40·8%)	1098 (38·1%)	2471 (44·7%)
Hypertension	555 (55·4%)	6 (3·3%)	3754 (44·4%)	3338 (61·4%)	3446 (62·6%)	2123 (73·7%)	4242 (76·8%)
Hypercholesterolaemia	—	—	3666 (43·4%)	3767 (69·3%)	3230 (58·7%)	2149 (74·6%)	3723 (67·4%)
Current smoking	204 (20·4%)	65 (35·3%)	2417 (28·6%)	1126 (20·7%)	936 (17·0%)	678 (23·5%)	1313 (23·8%)
Prior myocardial infarction	437 (43·7%)	184 (100%)	8446 (100%)	2253 (41·4%)	2552 (46·3%)	383 (13·3%)	428 (7·7%)
Prior stroke	27 (2·7%)	—	1031 (12·2%)	253 (4·7%)	142 (2·6%)	174 (6·0%)	512 (9·3%)

Clinical presentation							
Chronic coronary syndrome	1001 (100%)	0	2144 (25·4%)	1517 (27·9%)	1334 (24·2%)	1744 (60·5%)	1416 (25·6%)
Acute coronary syndrome	0	184 (100%)	6302 (74·6%)	3921 (72·1%)	4172 (75·8%)	1138 (39·5%)	4109 (74·4%)
Myocardial ischaemia treatment							
Medical therapy alone	193 (19·3%)	—	7101 (84·1%)	0	0	0	0
Percutaneous coronary intervention	623 (62·2%)	—	597 (7·1%)	5364 (98·6%)	5506 (100%)	2882 (100%)	5525 (100%)
Coronary artery bypass grafting	77 (7·7%)	—	656 (7·8%)	0	0	0	0
Percutaneous coronary intervention and coronary artery bypass grafting	108 (10·8%)	—	92 (1·1%)	74 (1·4%)	0	0	0
Drug-eluting stent							
No	—	—	—	7 (0·1%)	172 (3·1%)	0	102 (1·8%)
First-generation	—	—	—	53 (1·0%)	152 (2·8%)	0	0
Second-generation	—	—	—	5324 (97·9%)	5182 (94·1%)	2882 (100%)	5423 (98·2%)
Unknown generation	—	—	—	54 (1·0%)	0	0	0
Peripheral artery disease	54 (5·4%)	—	1367 (16·2%)	68 (1·3%)	45 (0·8%)	308 (10·7%)	310 (5·6%)

Chronic kidney disease	128 (12·8%)	—	—	826 (15·2%)	931 (17·4%)	508 (17·7%)	1681 (30·5%)
Estimated glomerular filtration rate (mL/min/1·73 m ²)	81·6 [69·0-100·0]	—	—	81·1 [66·1-100·6]	80·5 [65·6-98·3]	85·1 [67·1-103·6]	75·6 [54·7-96·9]
Prior bleeding	5 (0·5%)	—	—	16 (0·3%)	36 (0·7%)	40 (1·4%)	143 (2·6%)
Haemoglobin (g/dL)	14·4 [13·6-15·1]	—	—	13·9 [12·7-14·9]	14·0 [12·9-15·0]	13·6 [12·3-14·7]	13·7 [12·2-15·1]
Aspirin dose							
Low	0	90 (48·9%)	0	2728 (50·2%)	2754 (50·0%)	1437 (49·9%)	2760 (50·0%)
High	502 (50·1%)	0	4204 (49·8%)	0	0	0	0
Proton pump inhibitor	110 (11·0%)	—	468 (5·5%)	621 (11·4)	1134 (20·6%)	2278 (94·5%)	4826 (87·6%)
Follow-up duration (clopidogrel vs. aspirin), median [IQR]	2·0 years [2·0-2·0]	0·5 years [0·5-0·5]	2·0 years [1·3-2·4]	5·5 years [4·7-5·5]	2·2 years [1·6-2·9]	4·0 years [4·0-4·0]	0·9 years [0·9-0·9]
Timing of antiplatelet monotherapy initiation	At randomisation (if PCI, after ≥1 month of DAPT)	At randomisation (recent MI, within 3-7 days)	At randomisation (prior MI, at any time)	At randomisation (6-18 months of DAPT after PCI)	At randomisation (≥12 months of DAPT after MI; ≥6 months of DAPT after elective PCI)	1 year after randomisation (e.g., 1 year after PCI with drug-eluting stent)	1 month after randomisation (e.g., 1 month after PCI with drug-eluting stent)

Continuous values are medians [interquartile ranges]. Categorical values are counts (proportions).

Drug-eluting stent type was not collected in the ASCET trial.

Table S8. GRADE assessment of the certainty of evidence across co-primary and secondary outcomes.

Trials Design Patients Primary Estimate Heterogeneity	Quality Assessment					Overall Quality
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	
MACCE						
7 Randomised 28,982 0·86 [0·77-0·96] 0%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ HIGH
Major Bleeding						
7 Randomised 28,982 0·94 [0·74-1·21] 50·7%	Mild	Moderate	Not serious	Not serious	Not serious	⊕⊕⊕○ MODERATE
NACCE						
7 Randomised 28,982 0·89 [0·81-0·98] 1·9%	Mild	Not serious	Not serious	Mild	Not serious	⊕⊕⊕⊕ HIGH
All-Cause Death						
7 Randomised 28,982 0·99 [0·89-1·09] 0%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ HIGH

Cardiovascular Death

7 Randomised 28,982 0·98 [0·84-1·13] 0%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ HIGH
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Myocardial Infarction

7 Randomised 28,982 0·76 [0·66-0·89] 0·7%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ HIGH
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Stroke

7 Randomised 28,982 0·79 [0·66-0·96] 0%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ HIGH
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Ischaemic Stroke

6 Randomised 27,981 0·80 [0·65-0·98] 0%	Mild	Not serious	Not serious	Mild	Not serious	⊕⊕⊕○ MODERATE
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Haemorrhagic Stroke

6 Randomised 27,981 0·77 [0·49-1·19] 0%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕○ MODERATE
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Definite or Probable Stent Thrombosis

4 Randomised 19,351 0·63 [0·36-1·11] 0%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕○ MODERATE
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Definite Stent Thrombosis

4 Randomised 19,351 0·77 [0·39-1·50] 0%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕○ MODERATE
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Probable Stent Thrombosis

4 Randomised 19,351 0·39 [0·13-1·16] 0%	Mild	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕○ MODERATE
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Any Bleeding

7 Randomised 28,982 1·04 [0·86-1·26] 67·2%	Mild	Serious	Not serious	Not serious	Not serious	⊕⊕⊕○ MODERATE
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Major Gastrointestinal Bleeding

6 Randomised 27,981 0·98 [0·58-1·64] 77·3%	Mild	Serious	Not serious	Not serious	Not serious	⊕⊕⊕○ MODERATE
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Any Gastrointestinal Bleeding



MACCE=Major adverse cardiovascular or cerebrovascular events; NACCE=Net adverse cardiac or cerebrovascular events.

Table S9. Missing outcomes and missing values across variables included in the multiple imputation process.

	Clopidogrel (N=14,507)	Aspirin (N=14,475)
Age	0 (0%)	0 (0%)
Sex	0 (0%)	0 (0%)
Body Mass Index	192 (1.3%)	205 (1.4%)
Region	0 (0%)	0 (0%)
Presentation	0 (0%)	0 (0%)
Myocardial Revascularisation	94 (0.6%)	90 (0.6%)
Diabetes	94 (0.6%)	90 (0.6%)
Hypertension	0 (0%)	0 (0%)
Hypercholesterolaemia	593 (4.1%)	592 (4.1%)
Smoking Status	0 (0%)	0 (0%)
Prior Myocardial Infarction	0 (0%)	0 (0%)
Prior Stroke	94 (0.6%)	90 (0.6%)
Prior Bleeding	4336 (29.9%)	4294 (29.7%)
Peripheral Artery Disease	100 (0.7%)	95 (0.7%)
Chronic Kidney Disease	4425 (30.5%)	4387 (30.3%)
Proton Pump Inhibitor	338 (2.3%)	332 (2.3%)
MACCE	0 (0%)	0 (0%)

Major Bleeding	0 (0%)	0 (0%)
NACCE	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)
Cardiovascular Death	0 (0%)	0 (0%)
Myocardial Infarction	0 (0%)	0 (0%)
Stroke	0 (0%)	0 (0%)
Ischaemic Stroke	499 (3.4%)	502 (3.5%)
Haemorrhagic Stroke	499 (3.4%)	502 (3.5%)
Definite or Probable Stent Thrombosis	698 (3.4%)	722 (3.5%)
Definite Stent Thrombosis	698 (3.4%)	722 (3.5%)
Probable Stent Thrombosis	698 (3.4%)	722 (3.5%)
Any Bleeding	0 (0%)	0 (0%)
Major Gastrointestinal Bleeding	499 (3.4%)	502 (3.5%)
Any Gastrointestinal Bleeding	499 (3.4%)	502 (3.5%)

The denominator of stent thrombosis is the number of patients who underwent prior percutaneous coronary intervention.

MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events.

Table S10. Clinical Outcomes by Two-Stage Analyses.

	Standard 95% CI		Adjusted 95% CI		I ² (%)	T ²	P _{Het}
	HR [95% CI]	P	HR [95% CI]	P			
MACCE	0·86 [0·77-0·95]	0·0040	0·86 [0·75-0·98]	0·028	0%	0·003	0·52
Major Bleeding	0·96 [0·72-1·26]	0·75	0·96 [0·68-1·35]	0·76	50·7%	0·063	0·058
NACCE	0·89 [0·80-0·98]	0·015	0·89 [0·78-1·00]	0·052	1·9%	0·003	0·41
Death	0·99 [0·86-1·13]	0·80	0·99 [0·87-1·12]	0·81	0%	0	0·54
Cardiovascular Death	0·99 [0·89-1·09]	0·85	0·99 [0·84-1·17]	0·86	0%	0	0·86
Myocardial Infarction	0·78 [0·68-0·90]	0·0044	0·78 [0·65-0·93]	0·013	0·7%	<0·001	0·42
Stroke	0·82 [0·67-1·00]	0·047	0·82 [0·63-1·06]	0·10	0%	0·012	0·42
Ischaemic Stroke	0·85 [0·70-1·03]	0·10	0·85 [0·65-1·12]	0·18	0%	0·003	0·61
Haemorrhagic Stroke	0·72 [0·45-1·13]	0·15	0·72 [0·38-1·36]	0·22	0%	0	0·46
Definite or Probable Stent Thrombosis	0·69 [0·40-1·20]	0·19	0·69 [0·28-1·69]	0·28	0%	0	0·66
Definite Stent Thrombosis	0·82 [0·43-1·57]	0·55	0·82 [0·28-2·36]	0·59	0%	0	0·60
Probable Stent Thrombosis	0·49 [0·17-1·40]	0·19	0·49 [0·00-431·37]	0·41	0%	0	0·81
Any Bleeding	1·06 [0·85-1·32]	0·61	1·06 [0·80-1·40]	0·63	67·2%	0·056	0·0055
Major Gastrointestinal Bleeding	1·00 [0·55-1·79]	0·99	1·00 [0·43-2·29]	0·99	77·3%	0·339	0·0015

Any Gastrointestinal Bleeding	0·94 [0·70-1·27]	0·69	0·94 [0·62-1·44]	0·71	58·8%	0·067	0·046
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CI=Confidence Interval; HR=Hazard Ratio; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; P_{Het} =P of heterogeneity.

Two-stage analyses were performed by random-effect models combining trial-level outcome measures estimated by Cox models. The 95% CI adjustment was based on the Hartung-Knapp method.

Table S11. Landmark Analysis.

	Monotherapy Initiation to 1,000 Days		1,000 Days to Maximum Follow-Up		P_{int}
	HR [95% CI]	P	HR [95% CI]	P	
MACCE	0·87 [0·78-0·98]	0·017	0·71 [0·54-0·93]	0·012	0·16
Major Bleeding	0·92 [0·72-1·17]	0·48	1·06 [0·65-1·72]	0·81	0·60
NACCE	0·90 [0·82-1·00]	0·040	0·80 [0·64-1·02]	0·067	0·38
Death	1·02 [0·91-1·15]	0·70	0·80 [0·61-1·06]	0·13	0·12
Cardiovascular Death	1·03 [0·89-1·19]	0·66	0·75 [0·53-1·07]	0·11	0·10
Myocardial Infarction	0·79 [0·68-0·91]	0·0018	0·43 [0·22-0·85]	0·015	0·090
Stroke	0·75 [0·60-0·94]	0·012	0·83 [0·52-1·31]	0·42	0·70
Ischaemic Stroke	0·77 [0·61-0·97]	0·026	0·76 [0·43-1·33]	0·34	0·98
Haemorrhagic Stroke	0·70 [0·36-1·37]	0·30	1·20 [0·57-2·51]	0·63	0·29
Definite or Probable Stent Thrombosis	0·67 [0·37-1·19]	0·17	0·34 [0·03-3·24]	0·35	0·57
Definite Stent Thrombosis	0·80 [0·41-1·58]	0·52	0·34 [0·00-31·13]	0·28	0·71
Probable Stent Thrombosis	0·37 [0·11-1·25]	0·11	0·50 [0·05-5·57]	0·58	0·82
Bleeding	1·02 [0·83-1·25]	0·87	1·09 [0·78-1·52]	0·63	0·74
Major Gastrointestinal Bleeding	1·01 [0·60-1·71]	0·98	0·89 [0·43-1·83]	0·74	0·78
Any Gastrointestinal Bleeding	0·94 [0·73-1·21]	0·62	0·90 [0·50-1·63]	0·74	0·91

CI=Confidence Interval; HR=Hazard Ratio; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; P_{int} =P of Interaction.

Table S12. Per-Protocol One-Stage and Two-Stage Analyses.

	Clopidogrel	Aspirin	One-Stage Analysis		Two-Stage Analysis	
	Events / Patients (KM%) [Events 100 PY]	Events / Patients (KM%) [Events 100 PY]	HR [95% CI]	P	HR [95% CI]	P
MACCE	856 / 13529 (10.4%) [2.59]	975 / 13313 (13.0%) [3.04]	0.82 [0.73-0.93]	0.0019	0.83 [0.73-0.96]	0.0083
Major Bleeding	235 / 13529 (3.3%) [0.70]	256 / 13313 (4.1%) [0.78]	0.91 [0.71-1.17]	0.45	0.93 [0.71-1.23]	0.62
NACCE	1033 / 13529 (12.7%) [3.15]	1144 / 13313 (15.4%) [3.60]	0.86 [0.77-0.96]	0.0062	0.88 [0.78-0.99]	0.030
Death	642 / 13529 (8.8%) [1.91]	667 / 13313 (10.2%) [2.02]	0.94 [0.85-1.05]	0.30	0.95 [0.85-1.06]	0.34
Cardiovascular Death	388 / 13529 (4.9%) [1.15]	401 / 13313 (5.9%) [1.22]	0.91 [0.78-1.06]	0.22	0.95 [0.83-1.10]	0.50
Myocardial Infarction	341 / 13529 (3.9%) [1.02]	415 / 13313 (5.0%) [1.28]	0.76 [0.65-0.90]	0.0016	0.81 [0.70-0.94]	0.0044
Stroke	236 / 13529 (3.2%) [0.71]	295 / 13313 (4.1%) [0.91]	0.74 [0.60-0.92]	0.0075	0.76 [0.59-0.97]	0.028
Ischaemic Stroke	195 / 13076 (2.6%) [0.60]	235 / 12860 (3.2%) [0.74]	0.75 [0.59-0.94]	0.014	0.79 [0.62-1.00]	0.050
Haemorrhagic Stroke	31 / 13076 (0.6%) [0.09]	44 / 12860 (0.9%) [0.14]	0.69 [0.43-1.09]	0.11	0.67 [0.39-1.16]	0.15
Definite or Probable Stent Thrombosis	20 / 9220 (0.3%) [0.08]	31 / 9055 (0.5%) [0.13]	0.58 [0.32-1.06]	0.075	0.64 [0.36-1.14]	0.13
Definite Stent Thrombosis	15 / 9220 (0.2%) [0.06]	22 / 9055 (0.3%) [0.09]	0.66 [0.33-1.31]	0.23	0.70 [0.36-1.37]	0.30
Probable Stent Thrombosis	5 / 9220 (0.1%) [0.02]	9 / 9055 (0.2%) [0.04]	0.44 [0.14-1.35]	0.15	0.57 [0.19-1.69]	0.31
Any Bleeding	709 / 13529 (8.5%) [2.16]	704 / 13313 (9.0%) [2.20]	1.00 [0.83-1.21]	0.98	0.94 [0.50-1.74]	0.83
Major Gastrointestinal Bleeding	104 / 13076 (1.6%) [0.32]	108 / 12860 (1.9%) [0.34]	0.92 [0.53-1.61]	0.77	1.02 [0.82-1.26]	0.87
Any Gastrointestinal Bleeding	206 / 13076 (2.8%) [0.64]	233 / 12860 (3.4%) [0.74]	0.88 [0.65-1.17]	0.38	0.89 [0.65-1.22]	0.47

CI=Confidence Interval; HR=Hazard Ratio; KM%= Estimates; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; HR=Hazard Ratio; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; P_{int} =P of Interaction; PY=Person-Years.

Table S13. Bayesian and Frequentist Random-Effects Estimates with 95% Credible and Prediction Intervals for Primary and Secondary Outcomes.

Outcomes	Frequentist	Bayesian
	95% Prediction Interval	HR [95% Credible Interval]
MACCE	[0·71-1·04]	0·85 [0·73-0·98]
Major Bleeding	[0·47-1·93]	0·95 [0·69-1·38]
NACCE	[0·73-1·07]	0·89 [0·77-1·01]
Death	[0·87-1·12]	0·98 [0·82-1·16]
Cardiovascular Death	[0·84-1·17]	0·98 [0·80-1·19]
Myocardial Infarction	[0·66-0·93]	0·76 [0·60-0·94]
Stroke	[0·56-1·20]	0·82 [0·63-1·05]
Ischaemic Stroke	[0·62-1·17]	0·84 [0·62-1·10]
Haemorrhagic Stroke	[0·38-1·36]	0·75 [0·42-1·38]
Definite or Probable Stent Thrombosis	[0·28-1·69]	0·68 [0·34-1·38]
Definite Stent Thrombosis	[0·28-2·36]	0·80 [0·36-1·74]
Probable Stent Thrombosis	[0·00-431·37]	0·49 [0·12-1·92]
Any Bleeding	[0·56-2·01]	1·06 [0·80-1·42]
Major Gastrointestinal Bleeding	[0·16-6·13]	0·99 [0·54-1·84]
Gastrointestinal Any Bleeding	[0·41-2·16]	0·93 [0·65-1·38]

Table S14. Clinical Outcomes in the Study Population After Excluding Patients Treated with Oral Anticoagulation.

	Clopidogrel	Aspirin	One-Stage Analysis	
	Events / Patients (KM%) [Events 100 PY%]	Events / Patients (KM) [Events 100 PY]	HR [95% CI]	P
MACCE	917 / 14158 (10·7%) [2·60]	1047 / 14102 (12·9%) [2·98]	0·86 [0·77-0·96]	0·0086
Major Bleeding	239 / 14158 (3·3%) [0·67]	267 / 14102 (3·9%) [0·75]	0·92 [0·71-1·20]	0·54
NACCE	1091 / 14158 (12·8%) [3·11]	1222 / 14102 (15·2%) [3·50]	0·89 [0·81-0·98]	0·019
Death	697 / 14158 (9·3%) [1·94]	703 / 14102 (10·0%) [1·94]	0·99 [0·89-1·10]	0·85
Cardiovascular Death	421 / 14158 (5·1%) [1·17]	426 / 14102 (5·8%) [1·18]	0·98 [0·84-1·13]	0·74
Myocardial Infarction	356 / 14158 (3·9%) [1·00]	453 / 14102 (5·2%) [1·27]	0·77 [0·66-0·89]	0·00062
Stroke	260 / 14158 (3·4%) [0·73]	312 / 14102 (4·0%) [0·87]	0·79 [0·65-0·96]	0·016
Ischaemic Stroke	215 / 13659 (2·7%) [0·62]	249 / 13600 (3·1%) [0·72]	0·80 [0·65-0·98]	0·033
Haemorrhagic Stroke	34 / 13659 (0·7%) [0·10]	46 / 13600 (0·8%) [0·13]	0·74 [0·48-1·16]	0·19
Definite or Probable Stent Thrombosis	22 / 9323 (0·3%) [0·08]	33 / 9306 (0·5%) [0·12]	0·63 [0·36-1·11]	0·11
Definite Stent Thrombosis	17 / 9323 (0·2%) [0·06]	22 / 9306 (0·3%) [0·08]	0·77 [0·39-1·51]	0·44
Probable Stent Thrombosis	5 / 9323 (0·1%) [0·02]	11 / 9306 (0·2%) [0·04]	0·40 [0·14-1·17]	0·095
Any Bleeding	748 / 14158 (8·6%) [2·13]	727 / 14102 (8·7%) [2·07]	1·04 [0·85-1·27]	0·73
Major Gastrointestinal Bleeding	101 / 13659 (1·5%) [0·29]	106 / 13600 (1·6%) [0·30]	0·92 [0·53-1·60]	0·76

Any Gastrointestinal Bleeding	207 / 13659 (2·7%) [0·60]	232 / 13600 (3·0%) [0·67]	0·91 [0·69-1·21]	0·51
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CI=Confidence Interval; HR=Hazard Ratio; KM%=Kaplan-Meier Estimate; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; HR=Hazard Ratio; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; P_{int} =P of Interaction; PY=Person-Years.

Table S15. Clinical Outcomes After Stratifying Trials Based on the Design of the Initial DAPT Phase.

	Group of Trials	Clopidogrel			Aspirin			HR [95% CI]	P_{int}
		Events / Patients	KM%	Events 100 PY	Events / Patients	KM%	Events 100 PY		
MACCE	Unspecified DAPT	466 / 4336	15·0%	6·42	494 / 4294	16·2%	5·98	0·93 [0·82-1·06]	0·27
	Post-randomisation DAPT	194 / 4210	8·0%	2·89	223 / 4197	9·6%	2·50	0·87 [0·69-1·09]	
	Pre-randomisation DAPT	269 / 5961	7·1%	1·72	345 / 5984	9·1%	1·34	0·79 [0·67-0·92]	
Major Bleeding	Unspecified DAPT	44 / 4336	1·8%	0·67	54 / 4294	2·0%	0·54	0·81 [0·54-1·21]	0·34
	Post-randomisation DAPT	114 / 4210	5·2%	1·22	95 / 4197	4·1%	1·46	1·19 [0·83-1·69]	
	Pre-randomisation DAPT	98 / 5961	2·6%	0·64	130 / 5984	3·5%	0·49	0·90 [0·60-1·35]	
NACCE	Unspecified DAPT	494 / 4336	16·1%	6·87	526 / 4294	17·3%	6·37	0·92 [0·82-1·05]	0·22
	Post-randomisation DAPT	280 / 4210	11·8%	3·74	286 / 4197	12·1%	3·66	0·98 [0·83-1·15]	
	Pre-randomisation DAPT	342 / 5961	8·8%	2·19	435 / 5984	11·4%	1·72	0·81 [0·69-0·94]	
Death	Unspecified DAPT	277 / 4336	10·0%	3·32	268 / 4294	10·2%	3·41	1·03 [0·87-1·22]	0·74
	Post-randomisation DAPT	206 / 4210	9·1%	2·79	220 / 4197	9·6%	2·60	0·93 [0·77-1·13]	
	Pre-randomisation DAPT	230 / 5961	6·6%	1·15	235 / 5984	7·0%	1·13	0·96 [0·74-1·26]	
Cardiovascular Death	Unspecified DAPT	221 / 4336	7·9%	2·62	211 / 4294	7·5%	2·72	1·04 [0·86-1·26]	0·72
	Post-randomisation DAPT	90 / 4210	3·6%	1·19	94 / 4197	3·9%	1·14	0·95 [0·69-1·31]	
	Pre-randomisation DAPT	119 / 5961	3·2%	0·63	130 / 5984	3·9%	0·59	0·93 [0·72-1·19]	
Myocardial Infarction	Unspecified DAPT	201 / 4336	6·6%	3·11	243 / 4294	7·9%	2·54	0·81 [0·67-0·98]	0·83

Stroke	Post-randomisation DAPT	69 / 4210	2·8%	1·18	92 / 4197	4·3%	0·88	0·75 [0·54-1·06]
	Pre-randomisation DAPT	86 / 5961	2·2%	0·60	122 / 5984	3·1%	0·43	0·74 [0·54-0·99]
	Unspecified DAPT	131 / 4336	4·4%	1·72	136 / 4294	5·1%	1·64	0·95 [0·75-1·21]
	Post-randomisation DAPT	53 / 4210	2·5%	0·77	60 / 4197	2·8%	0·67	0·89 [0·60-1·34]
	Pre-randomisation DAPT	80 / 5961	2·2%	0·59	120 / 5984	3·0%	0·40	0·67 [0·50-0·89]
	Unspecified DAPT	125 / 4336	4·3%	1·61	128 / 4294	4·6%	1·56	0·97 [0·76-1·24]
Ischemic Stroke	Post-randomisation DAPT	40 / 4210	1·8%	0·65	51 / 4197	2·3%	0·51	0·79 [0·51-1·21]
	Pre-randomisation DAPT	53 / 5462	1·6%	0·38	74 / 5482	2·0%	0·28	0·72 [0·51-1·03]
	Unspecified DAPT	6 / 4336	0·2%	0·10	8 / 4294	0·4%	0·07	0·74 [0·26-2·15]
Hemorrhagic Stroke	Post-randomisation DAPT	13 / 4210	0·9%	0·11	9 / 4197	0·7%	0·16	1·60 [0·60-4·23]
	Pre-randomisation DAPT	16 / 5462	0·5%	0·15	29 / 5482	0·8%	0·08	0·57 [0·31-1·07]
	Unspecified DAPT	8 / 4210	0·4%	0·11	9 / 4197	0·3%	0·10	0·89 [0·34-2·30]
Stent Thrombosis	Post-randomisation DAPT	8 / 4210	0·4%	0·11	9 / 4197	0·3%	0·10	0·89 [0·34-2·30]
	Pre-randomisation DAPT	14 / 5462	0·3%	0·12	24 / 5482	0·6%	0·07	0·50 [0·22-1·13]
Definite Stent Thrombosis	Post-randomisation DAPT	8 / 4210	0·4%	0·10	8 / 4197	0·3%	0·10	1·00 [0·37-2·66]
	Pre-randomisation DAPT	9 / 5462	0·2%	0·07	14 / 5482	0·3%	0·05	0·57 [0·21-1·59]
Probable Stent Thrombosis	Post-randomisation DAPT	0 / 4210	0·0%	0·01	1 / 4197	0·0%	0·00	—
	Pre-randomisation DAPT	5 / 5462	0·1%	0·05	10 / 5482	0·3%	0·03	0·50 [0·17-1·46]
Bleeding	Unspecified DAPT	331 / 4336	10·4%	4·15	317 / 4294	10·4%	4·30	1·03 [0·89-1·21]
	Post-randomisation DAPT	196 / 4210	8·5%	2·30	178 / 4197	7·1%	2·55	1·11 [0·77-1·62]
	Pre-randomisation DAPT	253 / 5961	6·2%	1·32	265 / 5984	6·6%	1·27	1·01 [0·70-1·46]

Gastrointestinal Major Bleeding	Unspecified DAPT	12 / 4336	0·5%	0·34	27 / 4294	1·0%	0·15	0·44 [0·22-0·87]	0·0033
	Post-randomisation DAPT	57 / 4210	2·8%	0·43	34 / 4197	1·5%	0·73	1·68 [1·10-2·57]	
	Pre-randomisation DAPT	41 / 5462	1·1%	0·26	50 / 5482	1·5%	0·21	0·89 [0·54-1·47]	
Gastrointestinal Bleeding	Unspecified DAPT	61 / 4336	2·0%	1·08	86 / 4294	2·8%	0·76	0·70 [0·50-0·97]	0·10
	Post-randomisation DAPT	86 / 4210	4·1%	0·86	67 / 4197	3·0%	1·11	1·26 [0·82-1·94]	
	Pre-randomisation DAPT	73 / 5462	1·9%	0·46	89 / 5482	2·4%	0·38	0·84 [0·61-1·14]	

Trials were stratified based on the timing and definition of the initial DAPT phase as follows: (i) “unspecified DAPT”, when an initial DAPT phase was not defined in the original trial protocol (e.g., CADET, CAPRIE); (ii) “post-randomisation DAPT”, when an initial DAPT phase following PCI was initiated after randomisation as part of the trial design (e.g., STOPDAPT-2, STOPDAPT-3); and (iii) “pre-randomisation DAPT”, when patients completed an initial DAPT phase following PCI prior to randomisation (e.g., ASCET, HOST-EXAM, SMART-CHOICE 3).

CI=Confidence Interval; HR=Hazard Ratio; KM%=Kaplan-Meier Estimate; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; HR=Hazard Ratio; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; P_{int}=P of Interaction; PY=Person-Years.

Table S16. Clinical Outcomes After Stratifying Trials Based on Geographic Region (Asian Versus Non-Asian Countries).

	Group of Trials	Clopidogrel	Aspirin	HR [95% CI]	P	P_{int}
		Events / Patients (KM%) [Events 100 PY]	Events / Patients (KM%) [Events 100 PY]			
MACCE	Non-Asian	500 / 4835 (15·0%) [6·13]	533 / 4796 (16·3%) [5·69]	0·93 [0·82-1·05]	0·23	0·20
	Asian	429 / 9672 (7·8%) [1·97]	529 / 9679 (10·0%) [1·60]	0·82 [0·70-0·95]	0·0076	
Major Bleeding	Non-Asian	49 / 4835 (1·9%) [0·62]	56 / 4796 (2·0%) [0·54]	0·89 [0·58-1·35]	0·57	0·77
	Asian	207 / 9672 (3·6%) [0·82]	223 / 9679 (4·2%) [0·77]	0·96 [0·71-1·30]	0·79	
NACCE	Non-Asian	533 / 4835 (16·2%) [6·54]	567 / 4796 (17·3%) [6·09]	0·93 [0·82-1·04]	0·21	0·45
	Asian	583 / 9672 (10·2%) [2·56]	680 / 9679 (12·6%) [2·19]	0·86 [0·75-1·00]	0·045	
All-Cause Death	Non-Asian	282 / 4835 (9·4%) [3·00]	272 / 4796 (9·6%) [3·09]	1·03 [0·87-1·21]	0·75	0·53
	Asian	431 / 9672 (8·1%) [1·65]	451 / 9679 (8·9%) [1·58]	0·96 [0·84-1·10]	0·54	
Cardiovascular Death	Non-Asian	226 / 4835 (7·5%) [2·37]	215 / 4796 (7·0%) [2·48]	1·04 [0·86-1·26]	0·67	0·44
	Asian	204 / 9672 (3·7%) [0·80]	220 / 9679 (4·5%) [0·75]	0·94 [0·77-1·14]	0·52	
Myocardial Infarction	Non-Asian	219 / 4835 (6·7%) [2·96]	261 / 4796 (7·9%) [2·46]	0·82 [0·67-1·01]	0·064	0·31
	Asian	137 / 9672 (2·4%) [0·72]	196 / 9679 (3·5%) [0·51]	0·70 [0·56-0·88]	0·0024	
Stroke	Non-Asian	142 / 4835 (4·5%) [1·71]	153 / 4796 (5·3%) [1·58]	0·90 [0·70-1·14]	0·37	0·41
	Asian	122 / 9672 (2·5%) [0·60]	163 / 9679 (3·1%) [0·45]	0·77 [0·59-1·01]	0·059	
Ischaemic Stroke	Non-Asian	125 / 4336 (4·3%) [1·61]	128 / 4294 (4·6%) [1·56]	0·97 [0·76-1·24]	0·79	0·19
	Asian	93 / 9672 (1·8%) [0·46]	125 / 9679 (2·3%) [0·34]	0·76 [0·57-1·00]	0·047	

Haemorrhagic Stroke	Non-Asian	6 / 4336 (0·2%) [0·10]	8 / 4294 (0·4%) [0·07]	0·74 [0·26-2·15]	0·59	0·96
	Asian	29 / 9672 (0·7%) [0·14]	38 / 9679 (0·8%) [0·11]	0·77 [0·47-1·25]	0·29	
Any Bleeding	Non-Asian	410 / 4835 (12·6%) [4·26]	368 / 4796 (11·5%) [4·72]	1·16 [0·88-1·54]	0·30	0·34
	Asian	370 / 9672 (6·3%) [1·46]	392 / 9679 (6·9%) [1·39]	0·97 [0·76-1·23]	0·80	
Major Gastrointestinal Bleeding	Non-Asian	12 / 4336 (0·5%) [0·34]	27 / 4294 (1·0%) [0·15]	0·44 [0·22-0·87]	0·018	0·020
	Asian	98 / 9672 (1·7%) [0·31]	84 / 9679 (1·6%) [0·36]	1·20 [0·72-1·99]	0·48	
Any Gastrointestinal Bleeding	Non-Asian	61 / 4336 (2·0%) [1·08]	86 / 4294 (2·8%) [0·76]	0·70 [0·50-0·97]	0·033	0·086
	Asian	159 / 9672 (2·8%) [0·58]	156 / 9679 (2·8%) [0·59]	1·03 [0·77-1·37]	0·85	

CI=Confidence Interval; HR=Hazard Ratio; KM%=Kaplan-Meier Estimate; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; HR=Hazard Ratio; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; P_{int}=P of Interaction; PY=Person-Years.

Table S17. Clinical Outcomes After the Exclusion of the ASCET Trial due to the Unavailability of the Timing of Clinical Events.

	Clopidogrel	Aspirin	One-Stage Analysis	
	Events / Patients (KM%) [Events 100 PY]	Events / Patients (KM%) [Events 100 PY]	HR [95% CI]	P
MACCE	895 / 14008 (10·6%) [2·59]	1023 / 13973 (12·7%) [2·96]	0·86 [0·77-0·97]	0·012
Major Bleeding	251 / 14008 (3·4%) [0·72]	277 / 13973 (4·0%) [0·79]	0·93 [0·72-1·20]	0·59
NACCE	1077 / 14008 (12·7%) [3·14]	1206 / 13973 (15·1%) [3·53]	0·89 [0·80-0·99]	0·029
Death	708 / 14008 (9·5%) [2·00]	719 / 13973 (10·2%) [2·03]	0·99 [0·89-1·09]	0·79
Cardiovascular Death	425 / 14008 (5·2%) [1·20]	431 / 13973 (5·9%) [1·22]	0·98 [0·85-1·14]	0·83
Myocardial Infarction	338 / 14008 (3·8%) [0·97]	439 / 13973 (5·0%) [1·26]	0·75 [0·64-0·88]	0·00034
Stroke	253 / 14008 (3·3%) [0·72]	299 / 13973 (3·9%) [0·85]	0·79 [0·65-0·96]	0·020
Ischaemic Stroke	218 / 14008 (2·7%) [0·62]	253 / 13973 (3·1%) [0·72]	0·80 [0·65-0·98]	0·032
Haemorrhagic Stroke	35 / 14008 (0·7%) [0·10]	46 / 13973 (0·8%) [0·13]	0·77 [0·49-1·19]	0·23
Definite/Probable Stent Thrombosis	22 / 9672 (0·3%) [0·08]	33 / 9679 (0·5%) [0·12]	0·63 [0·36-1·11]	0·11
Definite Stent Thrombosis	17 / 9672 (0·2%) [0·06]	22 / 9679 (0·3%) [0·08]	0·77 [0·39-1·50]	0·44
Probable Stent Thrombosis	5 / 9672 (0·1%) [0·02]	11 / 9679 (0·2%) [0·04]	0·39 [0·13-1·16]	0·090
Any Bleeding	701 / 14008 (8·0%) [2·04]	709 / 13973 (8·4%) [2·06]	0·98 [0·82-1·16]	0·79

Major Gastrointestinal Bleeding	110 / 14008 (1·5%) [0·31]	111 / 13973 (1·7%) [0·31]	0·98 [0·58-1·64]	0·93
Any Gastrointestinal Bleeding	220 / 14008 (2·8%) [0·63]	242 / 13973 (3·1%) [0·69]	0·93 [0·71-1·22]	0·60

CI=Confidence Interval; HR=Hazard Ratio; KM%=Kaplan-Meier Estimate; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; HR=Hazard Ratio; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; PY=Person-Years.

Table S18. Clinical outcomes after stratifying trials based on DAPT status before antiplatelet monotherapy initiation.

		Clopidogrel	Aspirin	HR [95% CI]	P	P_{int}
		Events / Patients (KM%) [Events 100 PY]	Events / Patients (KM%) [Events 100 PY]			
MACCE	Unspecified DAPT	466 / 4336 (15·0%) [6·42]	494 / 4294 (16·2%) [5·98]	0·93 [0·82-1·06]	0·26	0·23
	Prior DAPT	463 / 10171 (8·1%) [2·04]	568 / 10181 (10·3%) [1·66]	0·83 [0·72-0·95]	0·0084	
Major Bleeding	Unspecified DAPT	44 / 4336 (1·8%) [0·67]	54 / 4294 (2·0%) [0·54]	0·81 [0·54-1·21]	0·30	0·43
	Prior DAPT	212 / 10171 (3·6%) [0·80]	225 / 10181 (4·1%) [0·76]	0·99 [0·73-1·34]	0·95	
NACCE	Unspecified DAPT	494 / 4336 (16·1%) [6·87]	526 / 4294 (17·3%) [6·37]	0·92 [0·82-1·05]	0·21	0·55
	Prior DAPT	622 / 10171 (10·5%) [2·62]	721 / 10181 (12·9%) [2·26]	0·88 [0·77-1·00]	0·049	
All-Cause Death	Unspecified DAPT	277 / 4336 (10·0%) [3·32]	268 / 4294 (10·2%) [3·41]	1·03 [0·87-1·22]	0·73	0·57
	Prior DAPT	436 / 10171 (8·0%) [1·60]	455 / 10181 (8·8%) [1·55]	0·97 [0·85-1·11]	0·63	
Cardiovascular Death	Unspecified DAPT	221 / 4336 (7·9%) [2·62]	211 / 4294 (7·5%) [2·72]	1·04 [0·86-1·26]	0·65	0·42
	Prior DAPT	209 / 10171 (3·7%) [0·79]	224 / 10181 (4·5%) [0·74]	0·93 [0·77-1·14]	0·50	
Myocardial Infarction	Unspecified DAPT	201 / 4336 (6·6%) [3·11]	243 / 4294 (7·9%) [2·54]	0·81 [0·67-0·98]	0·031	0·54
	Prior DAPT	155 / 10171 (2·6%) [0·76]	214 / 10181 (3·7%) [0·55]	0·74 [0·59-0·93]	0·0094	
Stroke	Unspecified DAPT	131 / 4336 (4·4%) [1·72]	136 / 4294 (5·1%) [1·64]	0·95 [0·75-1·21]	0·71	0·21
	Prior DAPT	133 / 10171 (2·6%) [0·64]	180 / 10181 (3·3%) [0·47]	0·77 [0·60-0·98]	0·031	
Ischaemic Stroke	Unspecified DAPT	125 / 4336 (4·3%) [1·61]	128 / 4294 (4·6%) [1·56]	0·97 [0·76-1·24]	0·79	0·19
	Prior DAPT	93 / 9672 (1·8%) [0·46]	125 / 9679 (2·3%) [0·34]	0·76 [0·57-1·00]	0·047	

Haemorrhagic Stroke	Unspecified DAPT	6 / 4336 (0·2%) [0·10]	8 / 4294 (0·4%) [0·07]	0·74 [0·26-2·15]	0·59	0·96
	Prior DAPT	29 / 9672 (0·7%) [0·14]	38 / 9679 (0·8%) [0·11]	0·77 [0·47-1·25]	0·29	
Any Bleeding	Unspecified DAPT	331 / 4336 (10·4%) [4·15]	317 / 4294 (10·4%) [4·30]	1·03 [0·89-1·21]	0·67	0·86
	Prior DAPT	449 / 10171 (7·4%) [1·59]	443 / 10181 (7·5%) [1·62]	1·06 [0·82-1·37]	0·64	
Major Gastrointestinal Bleeding	Unspecified DAPT	12 / 4336 (0·5%) [0·34]	27 / 4294 (1·0%) [0·15]	0·44 [0·22-0·87]	0·018	0·020
	Prior DAPT	98 / 9672 (1·7%) [0·31]	84 / 9679 (1·6%) [0·36]	1·20 [0·72-1·99]	0·48	
Any Gastrointestinal Bleeding	Unspecified DAPT	61 / 4336 (2·0%) [1·08]	86 / 4294 (2·8%) [0·76]	0·70 [0·50-0·97]	0·033	0·086
	Prior DAPT	159 / 9672 (2·8%) [0·58]	156 / 9679 (2·8%) [0·59]	1·03 [0·77-1·37]	0·85	

Trials were stratified based on DAPT status before antiplatelet monotherapy initiation as follows: (i) “unspecified DAPT”, when an initial DAPT phase was not defined in the original trial protocol (e.g., CADET, CAPRIE); (ii) “prior DAPT”, when patients received DAPT after PCI as part of the trial design before antiplatelet monotherapy (e.g., STOPDAPT-2, STOPDAPT-3, ASCET, HOST-EXAM, SMART-CHOICE 3).

CI=Confidence Interval; HR=Hazard Ratio; KM%=Kaplan-Meier Estimate; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; HR=Hazard Ratio; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; P_{int} =P of Interaction; PY=Person-Years.

Figure S1. Risk of Bias.

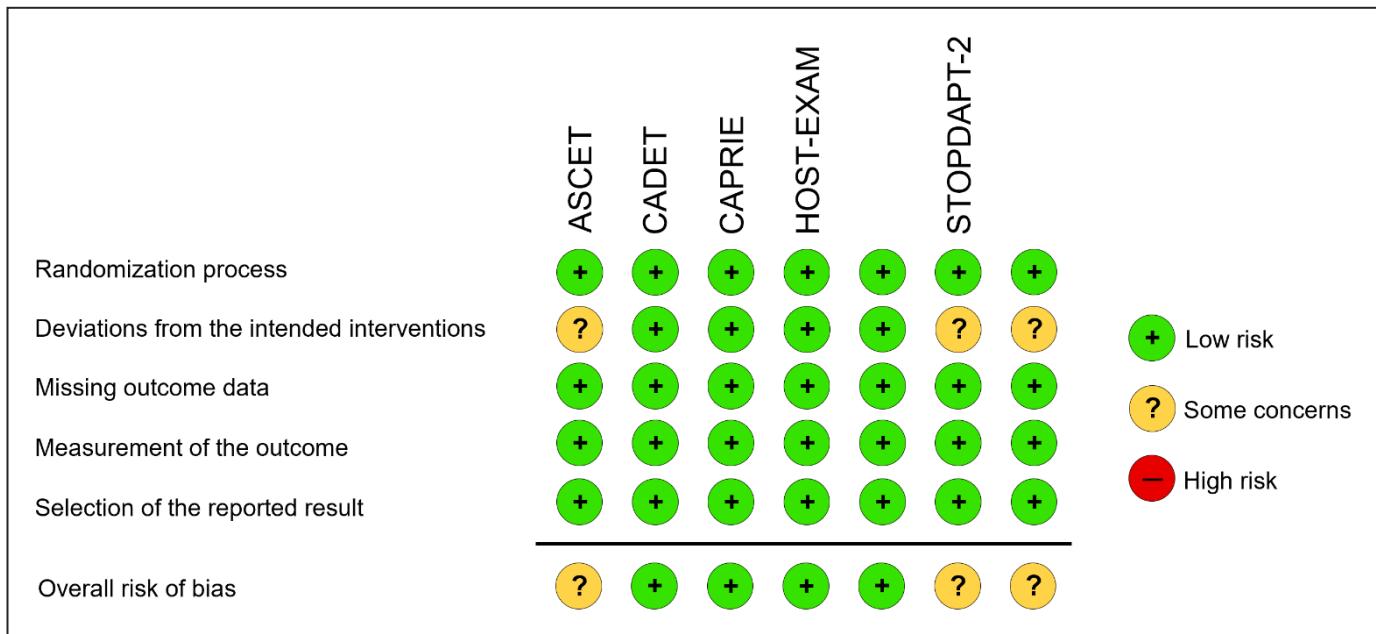
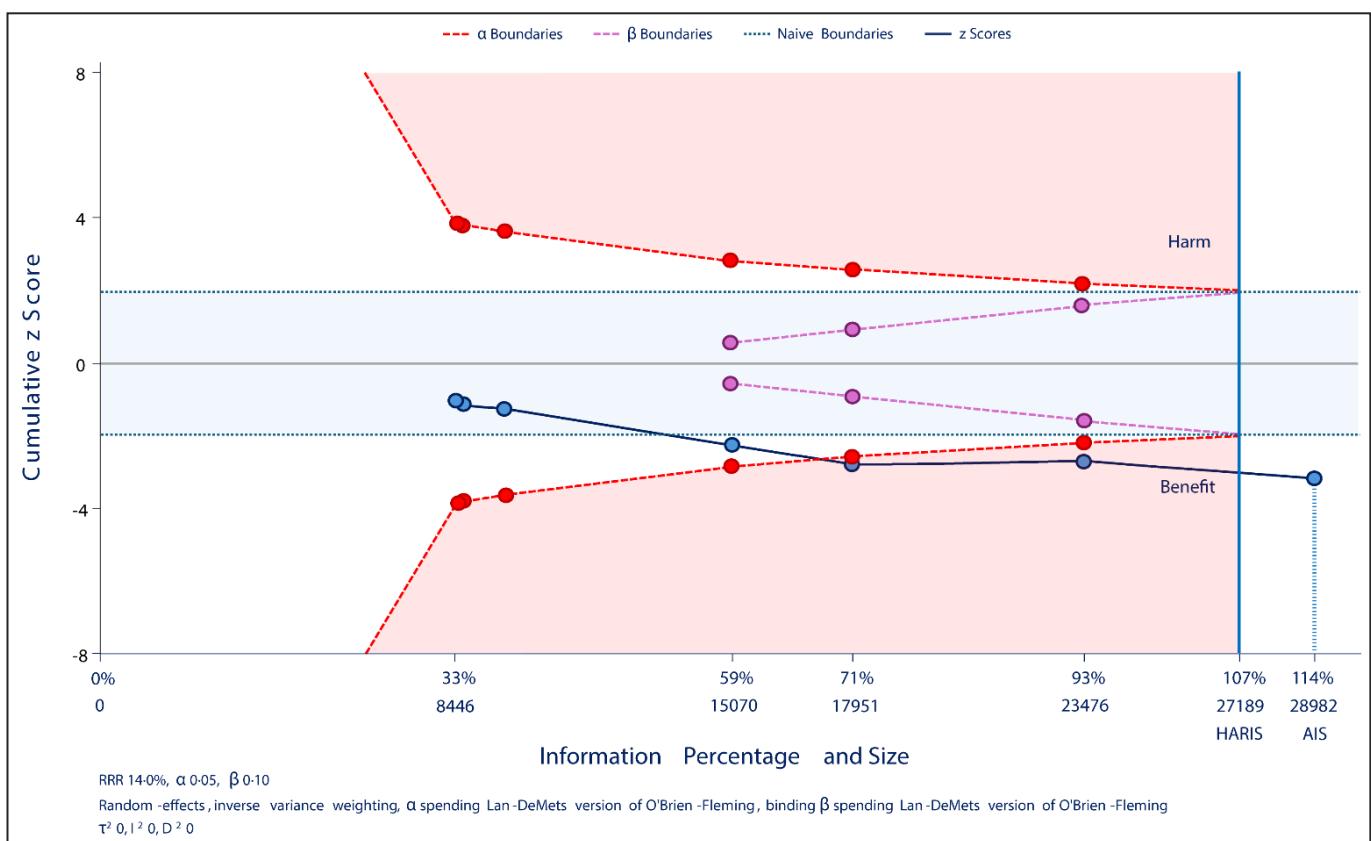


Figure S2. Trial Sequential Analysis for the Primary Efficacy Endpoint of MACCE.

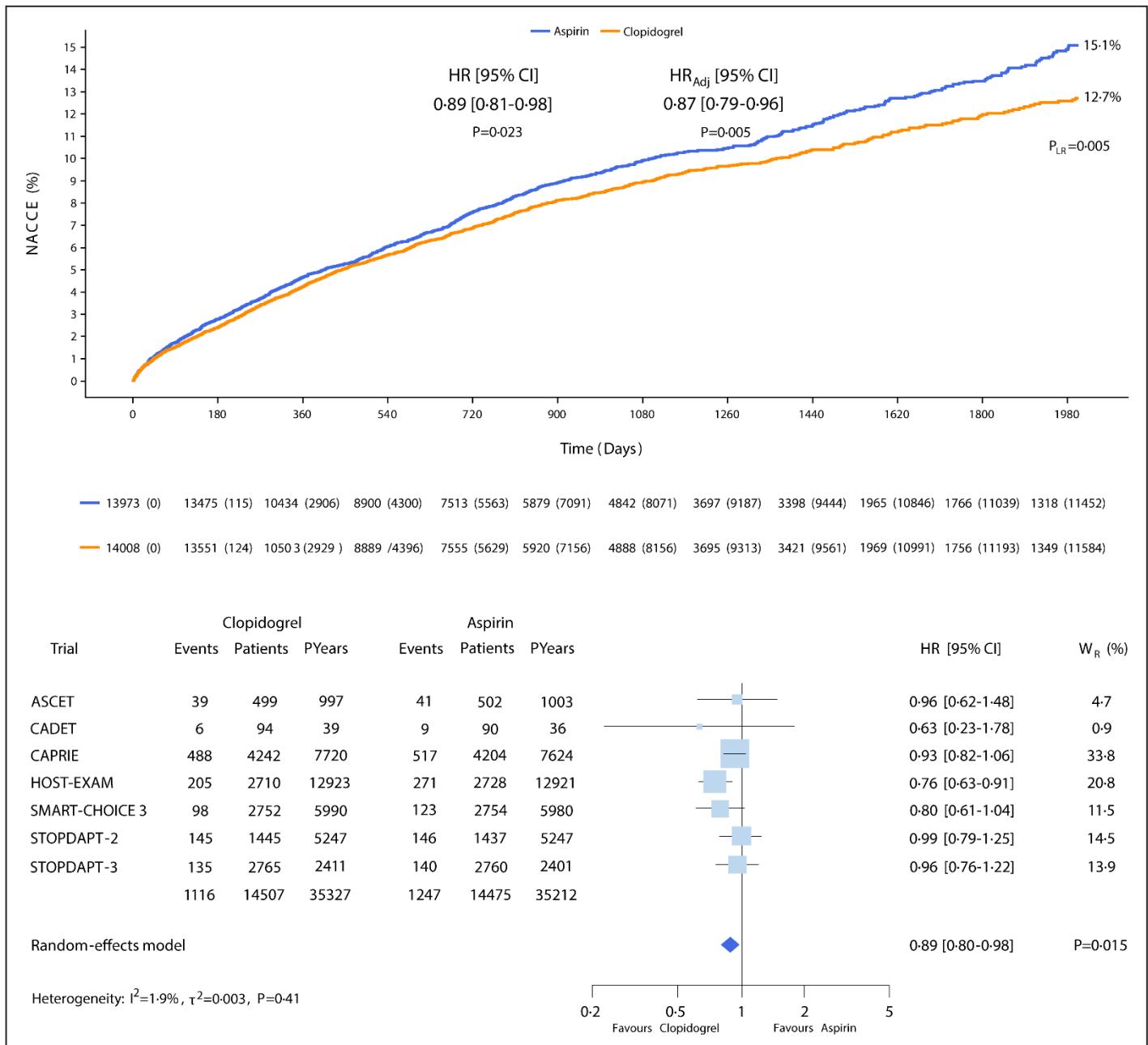


The trial sequential analysis integrates the cumulative sample size derived from the trials included in the individual patient data meta-analysis with an adjusted threshold of statistical significance to account for repeated testing.

The horizontal axis represents the number of patients included in the meta-analysis on a linear scale. The vertical axis represents the cumulative z score. The solid blue line represents the cumulative z curve, reflecting the evolving cumulative summary estimate after the addition of a trial to the individual patient data meta-analysis according to a chronological order (CAPRIE, CADET, ASCET, HOST-EXAM, STOPDAPT-2, STOPDAPT-3, and SMART-CHOICE 3). Red, blue, and violet dots represent the inclusion of each trial to the analysis. The blue horizontal dotted lines represent conventional significance thresholds (two tailed $\alpha = 0\cdot05$, $z = \pm 1\cdot96$), which do not account for repeated statistical testing. The red dotted lines (sloping inward) represent the monitoring boundaries based on the Lan-DeMets implementation of the O'Brien-Fleming α -spending function, which accounts for repeated statistical testing as each trial is added to the individual patient data meta-analysis. The violet dotted lines (inner outward sloping) represent the futility boundaries based on the Lan-DeMets implementation of the O'Brien-Fleming β -spending function. The futility area indicates that the effect is not statistically significant and that further trials are unlikely to result in statistical significance. The vertical blue solid line represents the heterogeneity-adjusted required information size to conclusively demonstrate superiority (benefit area) or inferiority (harm area) of clopidogrel monotherapy compared with aspirin monotherapy ($\alpha = 0\cdot05$, $\beta = 0\cdot10$). If the Z-curve reaches the heterogeneity-adjusted required information line, the accumulated information across trials (acquired information size) confers sufficient statistical power to the analysis.

In this individual patient data meta-analysis, the cumulative z score crossed the conventional significance threshold ($z = -1\cdot96$) after inclusion of HOST-EXAM, totaling 15,070 patients. The cumulative z score crossed the benefit monitoring boundary, after inclusion of STOPDAPT-2, totaling 17,951 patients. This indicated a significant reduction in MACCE associated with clopidogrel monotherapy compared with aspirin monotherapy after adjustment for repeated statistical testing. The 14% relative risk reduction observed at the maximum available follow-up relies on an acquired information size (28,982 patients), exceeding the heterogeneity-adjusted required information size (27,189 patients). This indicated sufficient statistical power to conclusively demonstrate the superiority of clopidogrel monotherapy over aspirin monotherapy in terms of MACCE. This achievement was made possible with the recent completion of the SMART-CHOICE 3 trial.

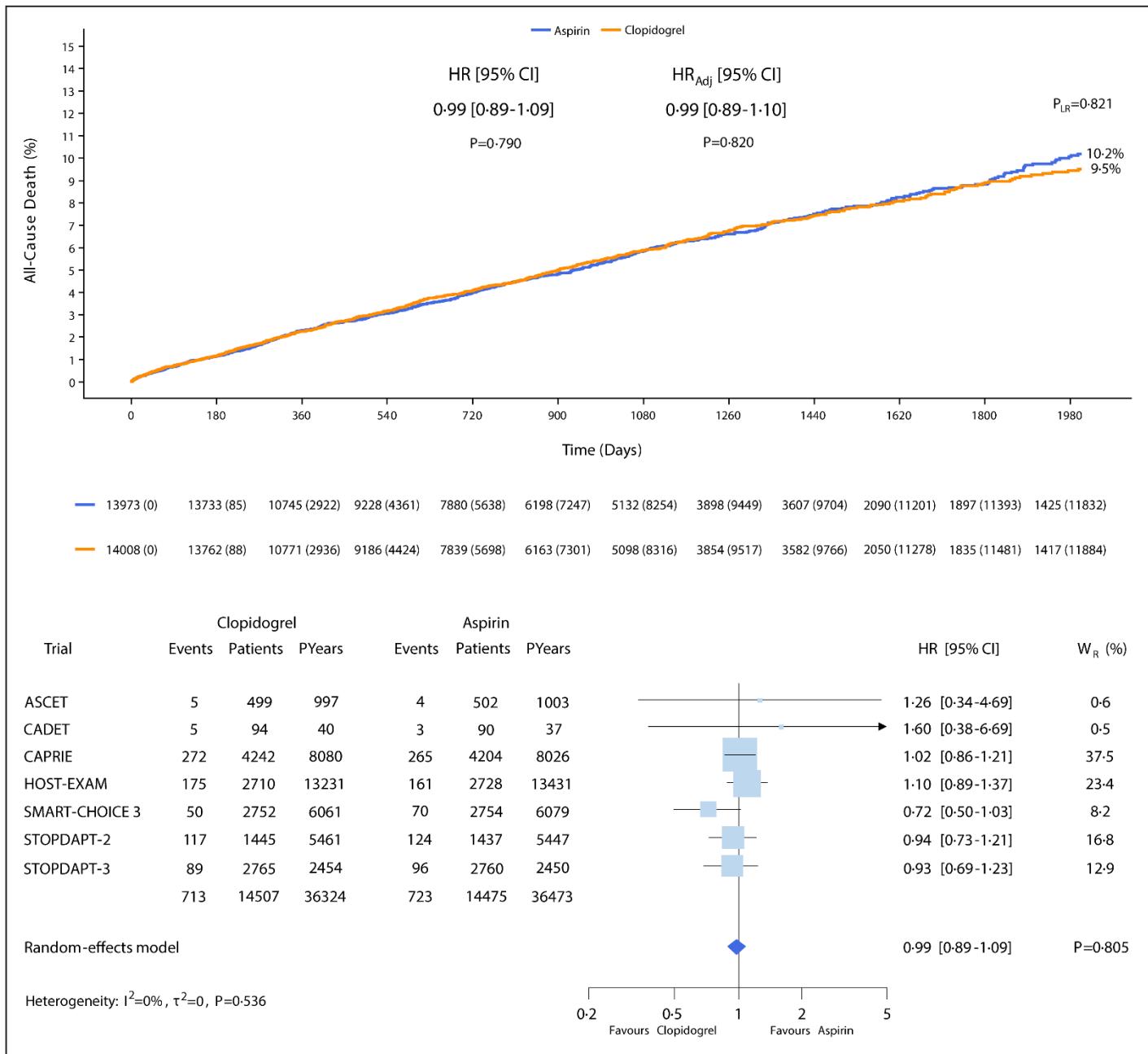
Figure S3. NACCE.



The upper panel illustrates the cumulative distribution of the key secondary outcome of NACCE, defined as a composite of cardiovascular death, myocardial infarction, stroke, or major bleeding. Patients enrolled in the ASCET trial were excluded from the graphical representation. The incidences were computed by the Kaplan-Meier method and compared by the log-rank test (P_{LR}). HR and 95% CI were computed by mixed-effects models (one-stage analysis). HR_{Adj} and 95% CI were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting.

CI=Confidence Interval; HR=Hazard Ratio; HR_{Adj} =Adjusted Hazard Ratio; P_{LR} =Log-Rank Test P Value; W_R =Weights by Random-Effects Model.

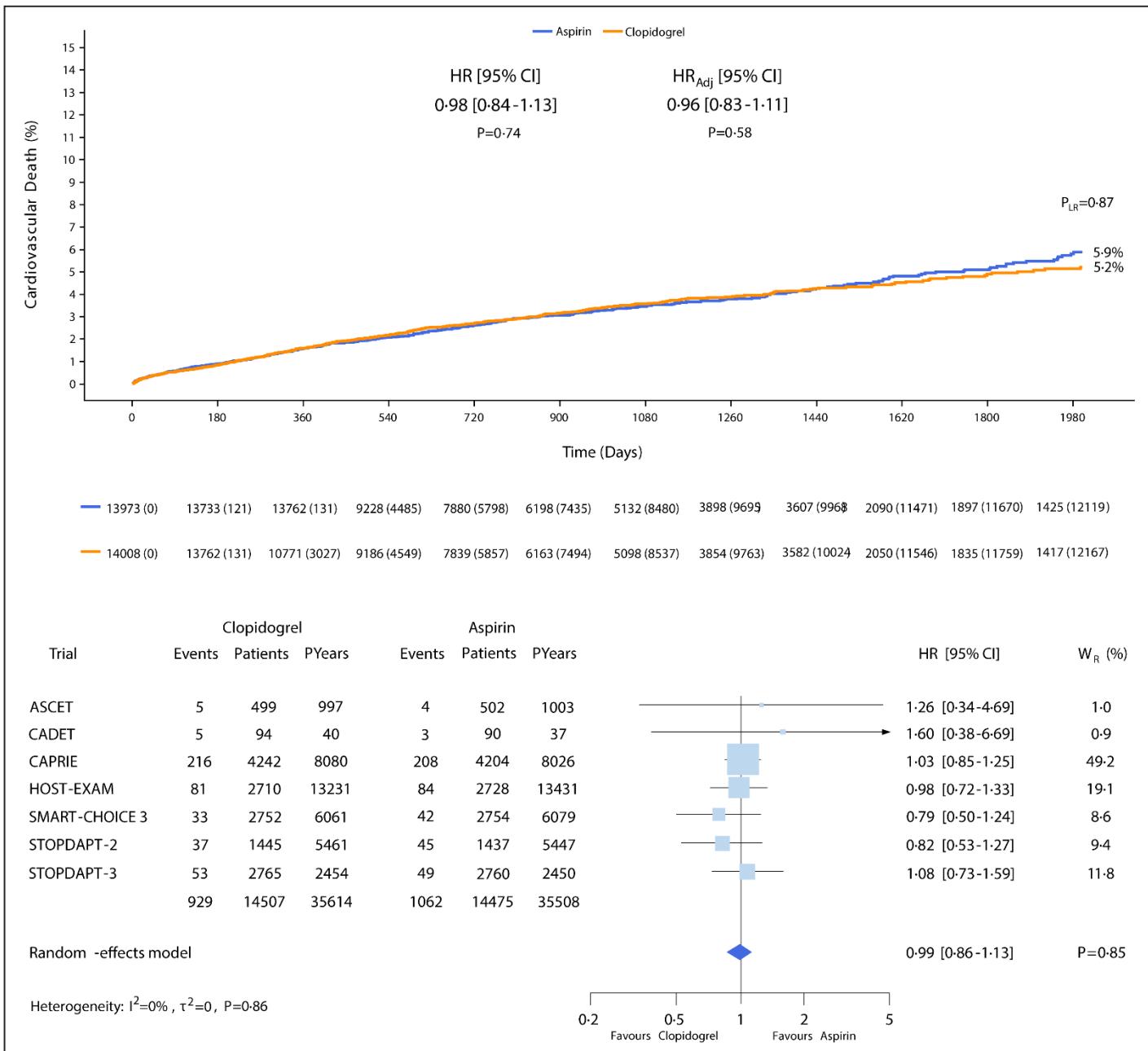
Figure S4. Cardiovascular Death.



The upper panel illustrates the cumulative distribution of all-cause death. Patients enrolled in the ASCET trial were excluded from the graphical representation. The rates between treatment groups were computed by the Kaplan-Meier method and compared by the log-rank test (P_{LR}). HR and 95% CI were computed by mixed-effects models accounting for the trial of origin (one-stage analysis). HR_{Adj} and 95% CI were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by inverse-variance weighting.

CI=Confidence Interval; HR=Hazard Ratio; HR_{Adj} =Adjusted Hazard Ratio; P_{LR} =Log-Rank Test P Value; W_R =Weights by Random-Effects Model.

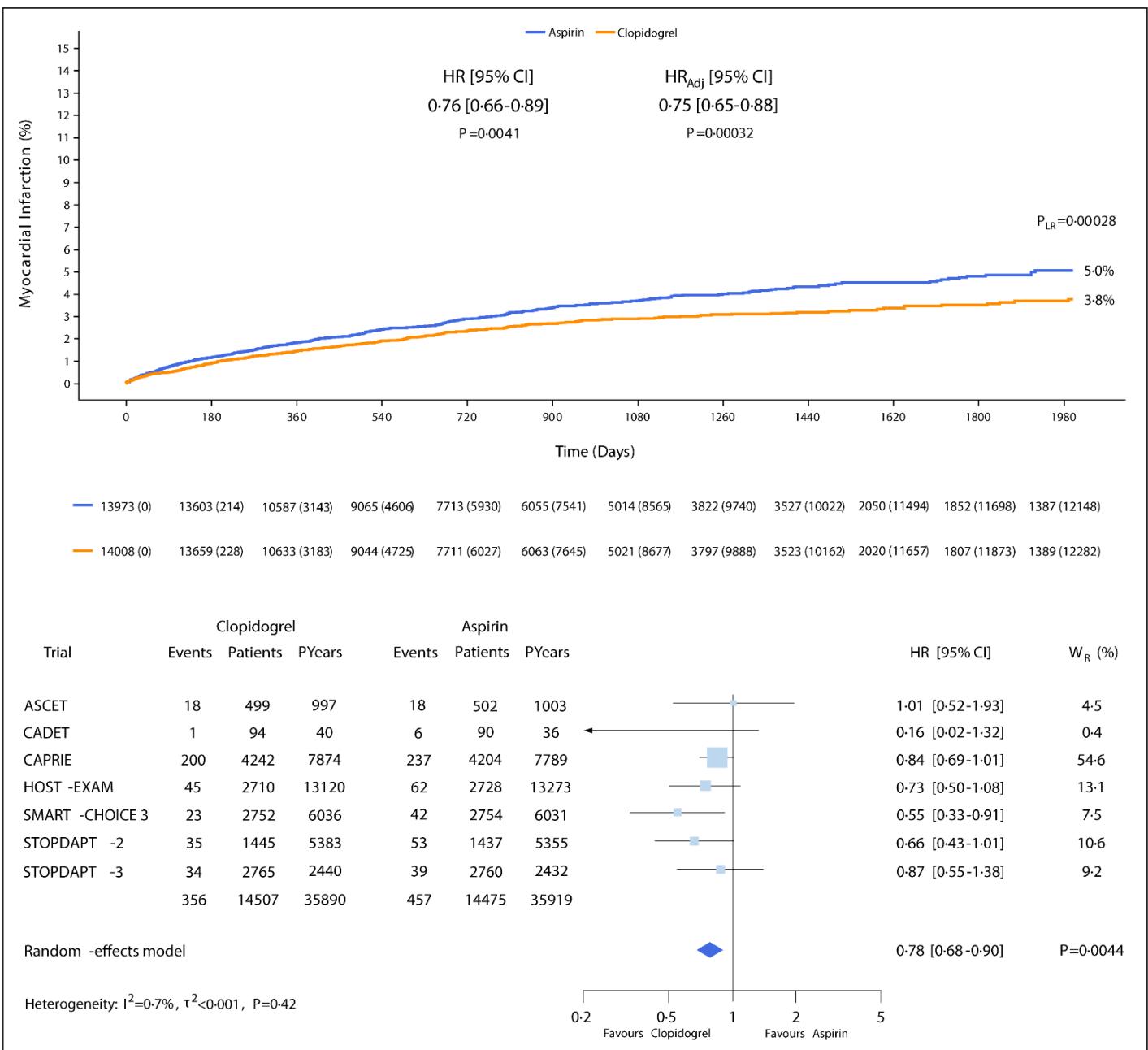
Figure S5. All-cause Death.



The upper panel illustrates the cumulative distribution of all-cause death. Patients enrolled in the ASCET trial were excluded from the graphical representation. The rates were between groups computed by the Kaplan-Meier method and compared by the log-rank test (P_{LR}). HR and 95% CI were computed by mixed-effects models accounting for the trial of origin (one-stage analysis). HR_{Adj} and 95% CI were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting.

CI=Confidence Interval; HR=Hazard Ratio; HR_{Adj} =Adjusted Hazard Ratio; P_{LR} =Log-Rank Test P Value; W_R =Weights by Random-Effects Model.

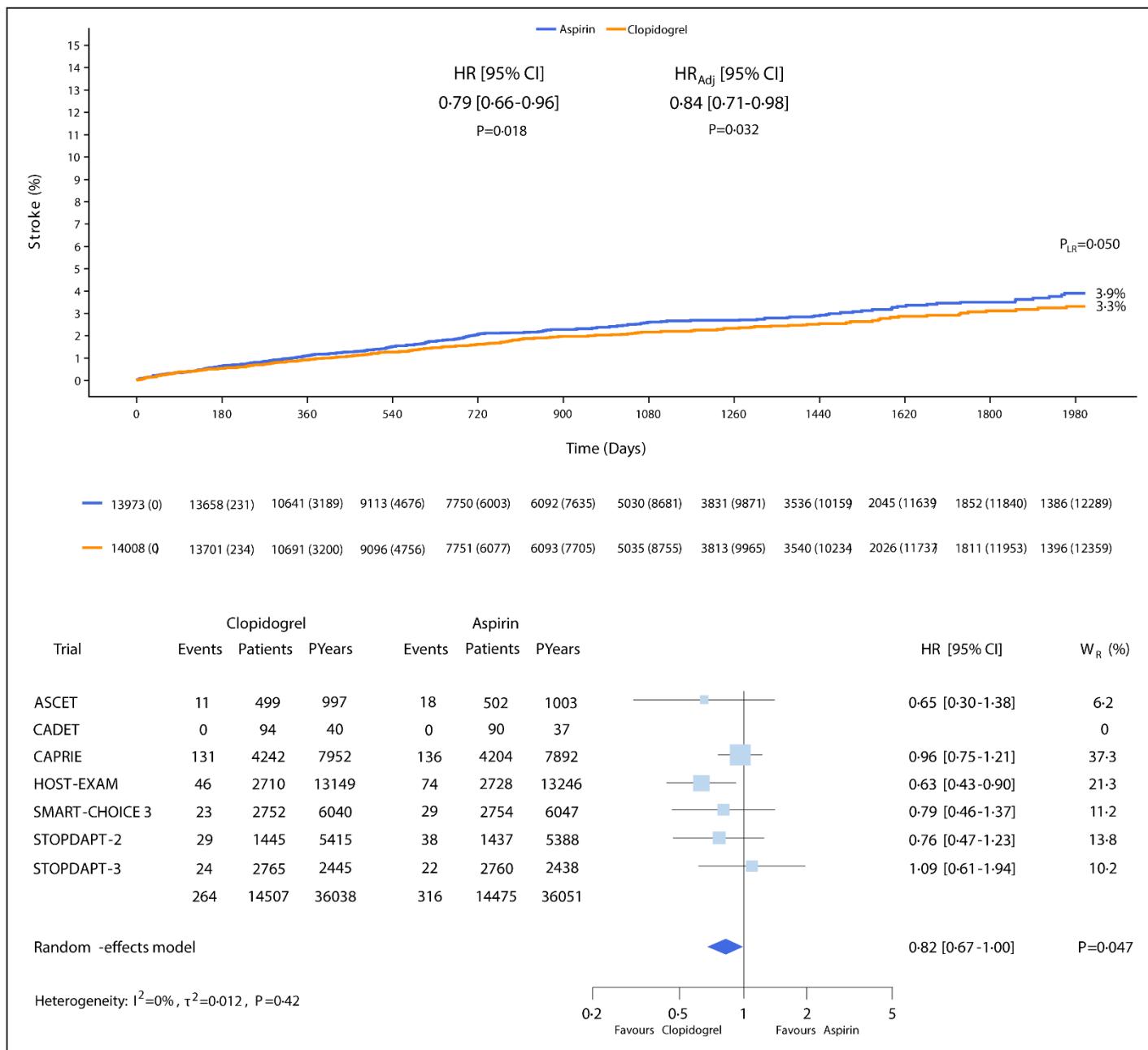
Figure S6. Myocardial Infarction.



The upper panel illustrates the cumulative distribution of myocardial infarction. Patients enrolled in the ASCET trial were excluded from the graphical representation. The rates between treatment groups were computed by the Kaplan-Meier method and compared by the log-rank test (P_{LR}). HR and 95% CI were computed by mixed-effects models accounting for the trial of origin (one-stage analysis). HR_{Adj} and 95% CI were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting.

CI=Confidence Interval; HR=Hazard Ratio; HR_{Adj} =Adjusted Hazard Ratio; P_{LR} =Log-Rank Test P Value; W_R =Weights by Random-Effects Model.

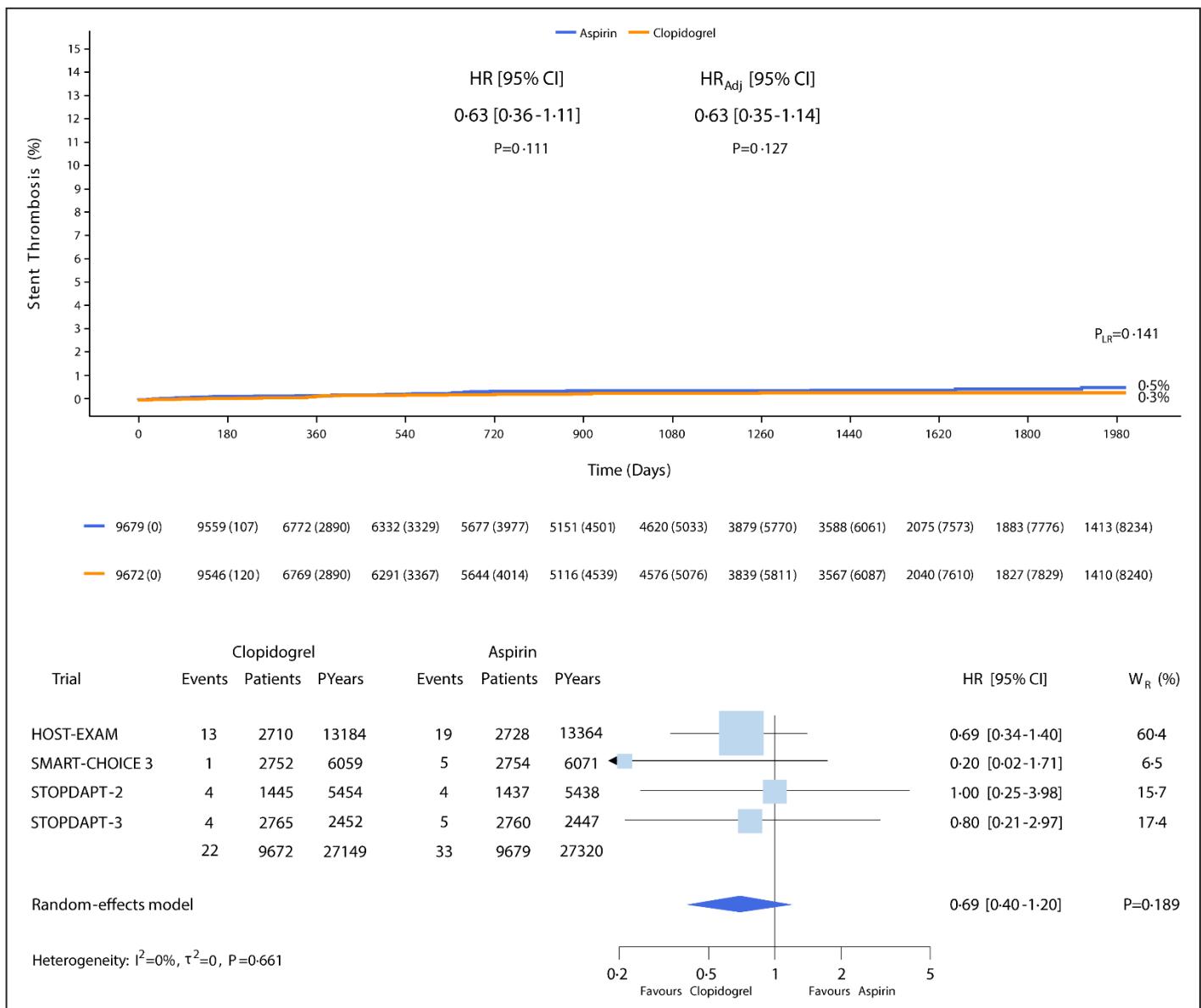
Figure S7. Stroke.



The upper panel illustrates the cumulative distribution of stroke. Patients enrolled in the ASCET trial were excluded from the graphical representation. The rates between treatment groups were computed by the Kaplan-Meier method and compared by the log-rank test (P_{LR}). HR and 95% CI were computed by mixed-effects models accounting for the trial of origin (one-stage analysis). HR_{Adj} and 95% CI were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting.

CI=Confidence Interval; HR=Hazard Ratio; HR_{Adj}=Adjusted Hazard Ratio; P_{LR}=Log-Rank Test P Value; W_R=Weights by Random-Effects Model.

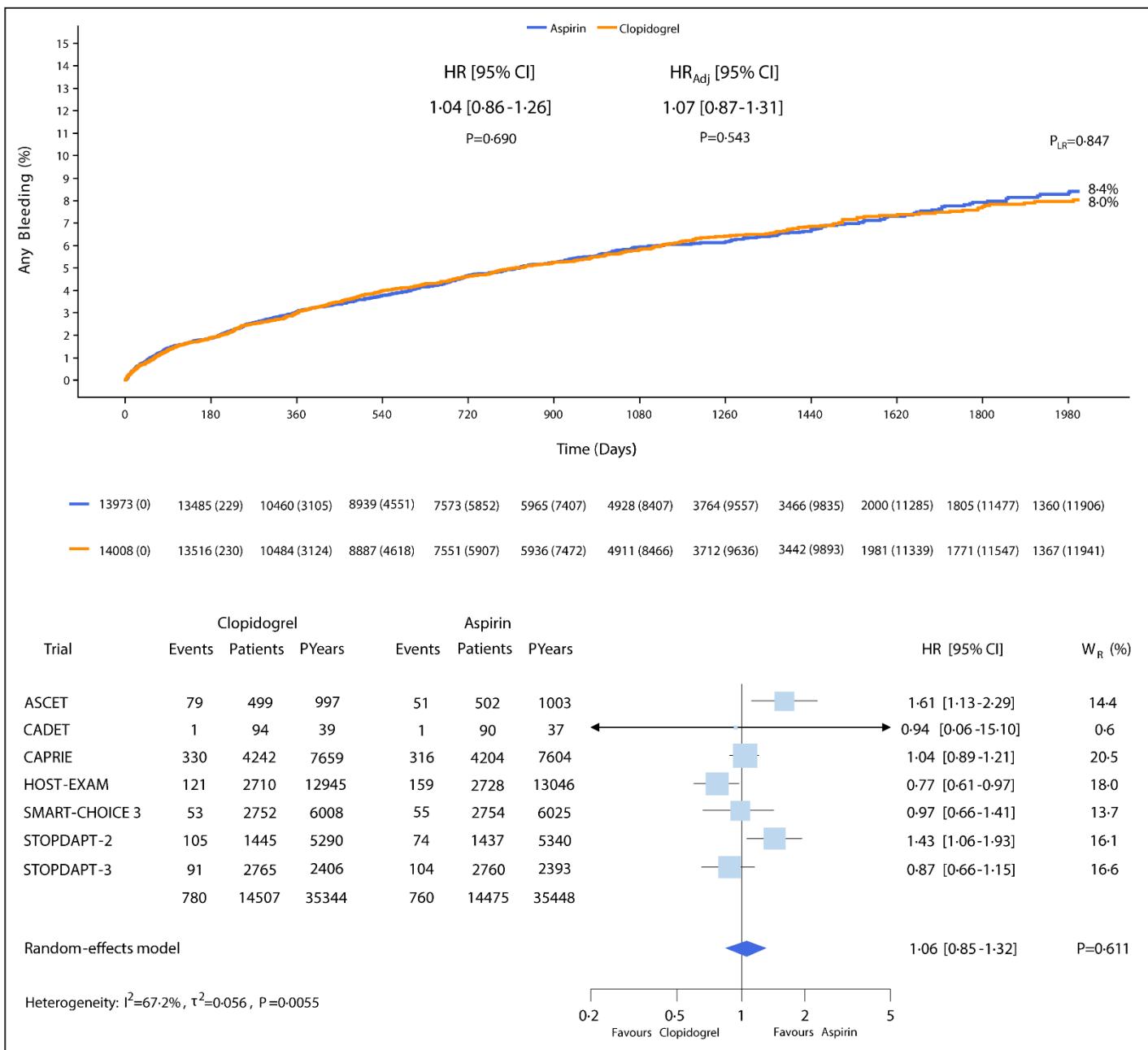
Figure S8. Definite or Probable Stent Thrombosis.



The upper panel illustrates the cumulative distribution of definite or probable stent thrombosis. Patients enrolled in the ASCET trial were excluded from the graphical representation. The rates between treatment groups were computed by the Kaplan-Meier method and compared by the log-rank test (P_{LR}). HR and 95% CI were computed by mixed-effects models accounting for the trial of origin (one-stage analysis). HR_{Adj} and 95% CI were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting.

CI=Confidence Interval; HR=Hazard Ratio; HR_{Adj} =Adjusted Hazard Ratio; P_{LR} =Log-Rank Test P Value; W_R =Weights by Random-Effects Model.

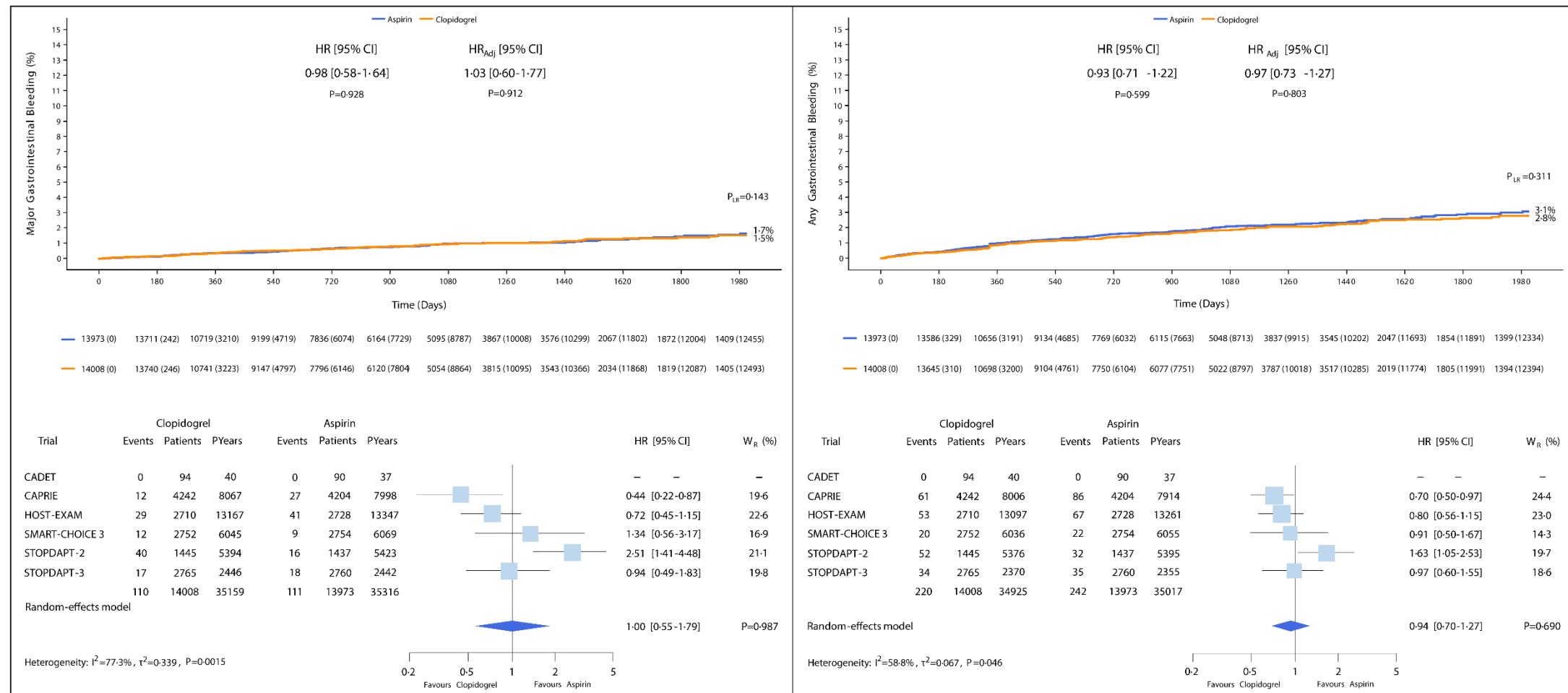
Figure S9. Any Bleeding.



The upper panel illustrates the cumulative distribution of any bleeding. Patients enrolled in the ASCET trial were excluded from the graphical representation. The rates between treatment groups were computed by the Kaplan-Meier method and compared by the log-rank test (P_{LR}). HR and 95% CI were computed by mixed-effects models accounting for the trial of origin (one-stage analysis). HR_{Adj} and 95% CI were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting.

CI=Confidence Interval; HR=Hazard Ratio; HR_{Adj} =Adjusted Hazard Ratio; P_{LR} =Log-Rank Test P Value; W_R =Weights by Random-Effects Model.

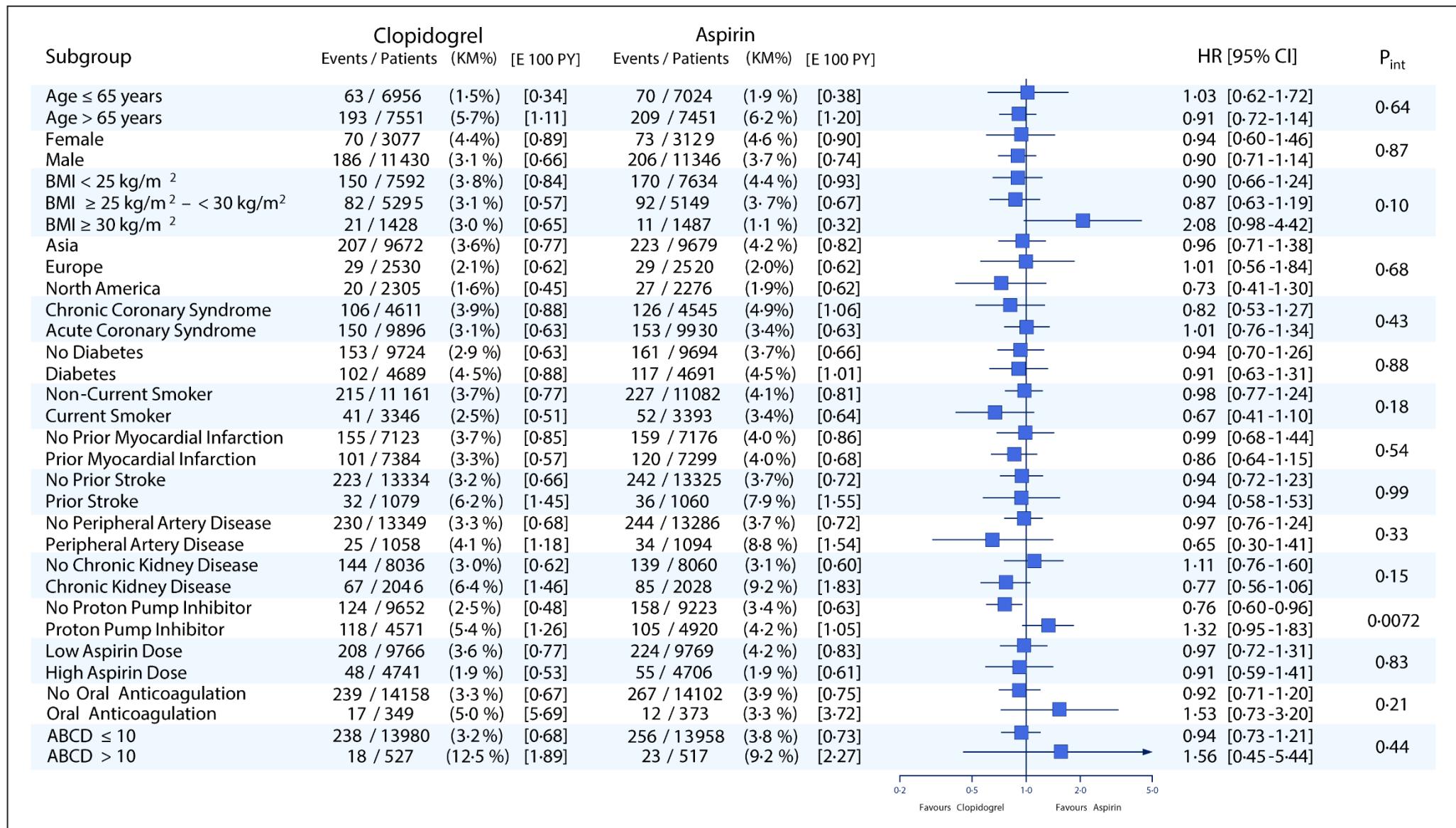
Figure S10. Major Gastrointestinal Bleeding or Any Gastrointestinal bleeding.



The upper panels illustrate the cumulative distribution of major gastrointestinal (left panel) or any gastrointestinal (right panel) bleeding. Patients enrolled in the ASCET trial were excluded from the graphical representation. The rates between treatment groups were computed by the Kaplan-Meier method and compared by the log-rank test (P_{LR}). HRs and 95% CIs were computed by mixed-effects models accounting for the trial of origin (one-stage analysis). HRs_{Adj} and 95% CIs were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panels show the results of the two-stage analysis for major gastrointestinal bleeding (left) and any gastrointestinal bleeding (right) by random-effects models with inverse-variance weighting.

CI=Confidence Interval; HR=Hazard Ratio; HR_{Adj}=Adjusted Hazard Ratio; P_{LR}=Log-Rank Test P Value; W_R=Weights by Random-Effects Model.

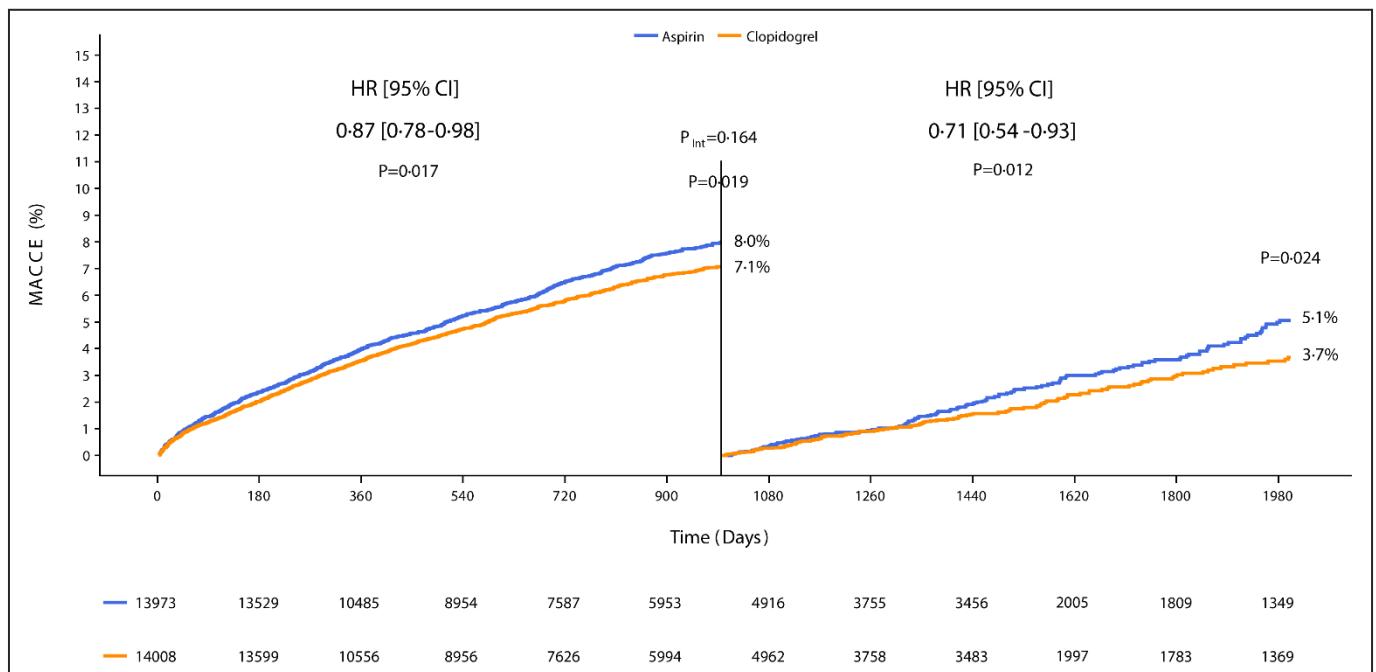
Figure S11. Subgroup Analysis for Major Bleeding.



Major bleeding across prespecified subgroups. The numbers of patients and events, the Kaplan-Meier estimates, and the incidences per 100 patient-years of follow-up between treatments by subgroups are reported. HRs and 95% CIs were computed by mixed-effects models (one-stage analysis). Unadjusted interaction P values (P_{int}) formally describe the heterogeneity of treatment effects between or across subgroups. The multiplicity-adjusted P value for proton pump inhibitor use was 0.11.

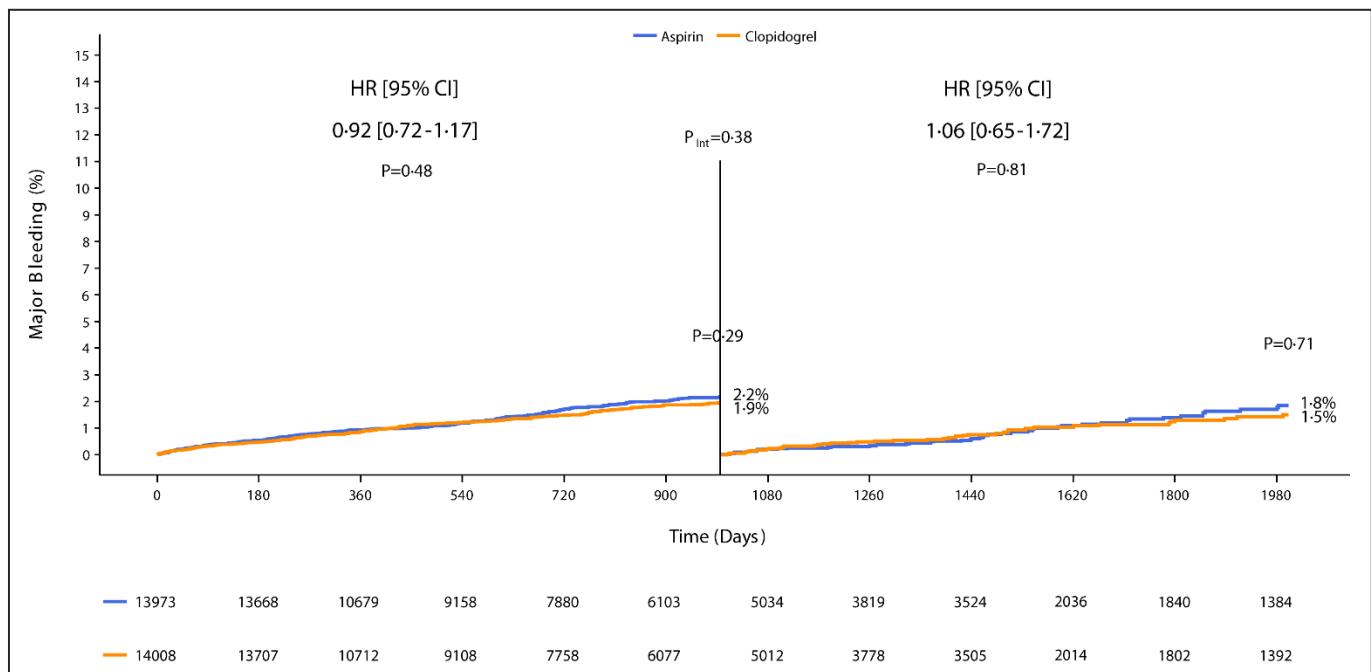
E 100 PY=Incidence Rate per 100 Person-Years; CI=Confidence Interval; HR=Hazard Ratio; P_{int} =P value of the interaction testing.

Figure S12. Landmark Analysis for MACCE.



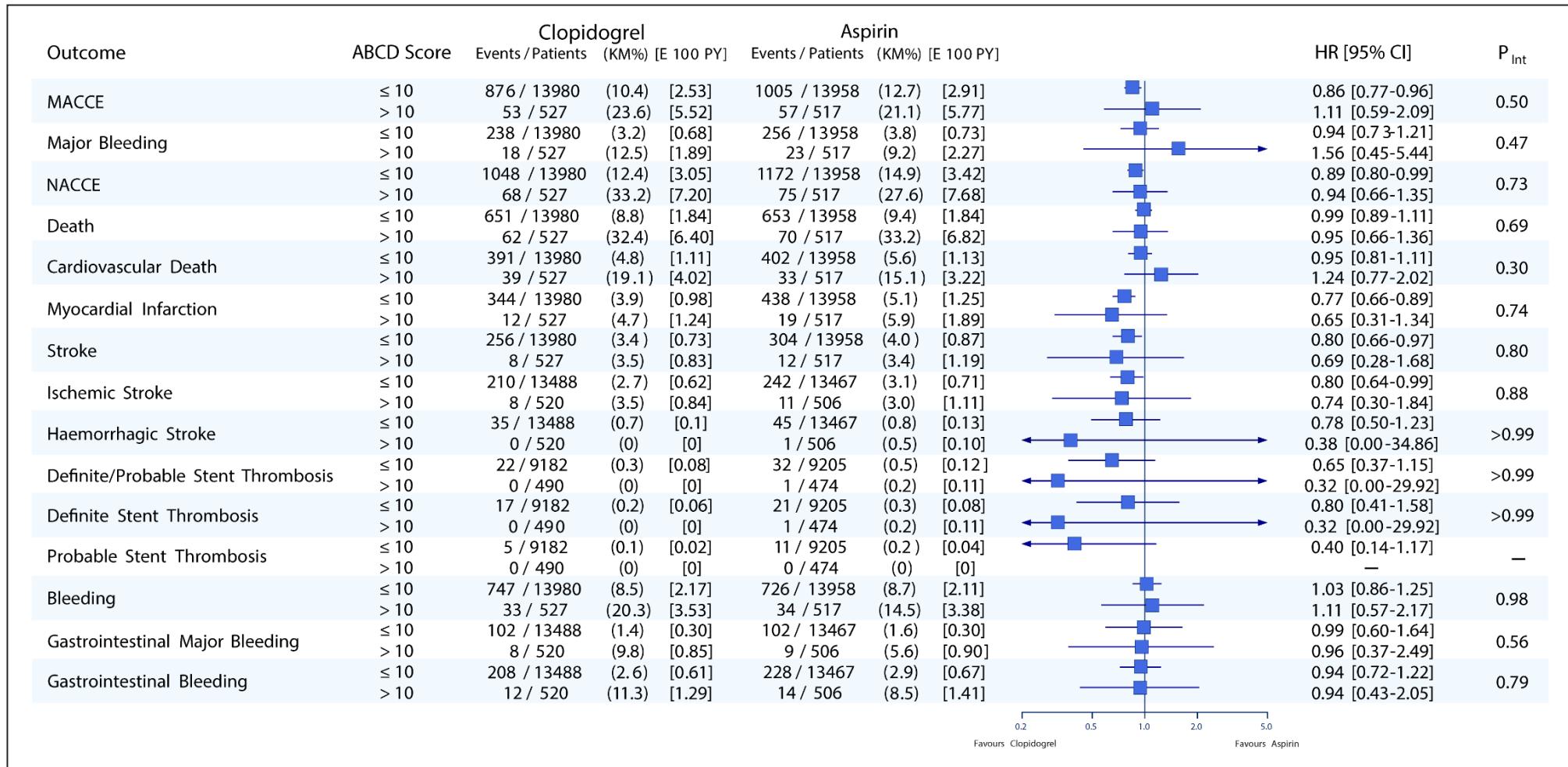
CI=Confidence Interval; HR=Hazard Ratio.

Figure S13. Landmark Analysis for Major Bleeding.



CI=Confidence Interval; HR=Hazard Ratio.

Figure S14. Analysis Stratified by ABCD-GENE Score of ≤10 or >10 Based on Clinical Factors.



E 100 PY=Incidence Rate per 100 Person-Years; CI=Confidence Interval; HR=Hazard Ratio; KM%=Kaplan-Meier Estimate; MACCE=Major Adverse Cardiovascular or Cerebrovascular Events; HR=Hazard Ratio; NACCE=Net Adverse Cardiovascular or Cerebrovascular Events; P_{Int} =P of Interaction.

Supplementary References

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