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Indobufen versus aspirin after percutaneous coronary intervention in elderly patients with acute coronary syndrome

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Abstract

Background Antiplatelet therapy is pivotal in managing elderly patients with Acute Coronary Syndrome (ACS) following Percutaneous Coronary Intervention (PCI). While aspirin remains a cornerstone of this therapy, its use is sometimes limited by the risk of gastrointestinal (GI) complications or allergic reactions in certain patients.

Purpose This study aims to assess the safety and efficacy of Indobufen as an alternative to aspirin when used in combination with clopidogrel in elderly ACS patients post-PCI.

Methods This is a single-center, retrospective study employing propensity score matching. Elderly ACS patients who underwent PCI between January 2019 and May 2022 were enrolled. Participant were categorized into two groups based on their medication regimen: the aspirin DAPT group and the indobufen DAPT group. The primary endpoint was the Net Adverse Clinical Event (NACE) at 1 year, which included all-cause mortality, stroke, myocardial infarction (MI), target lesion revascularisation, and bleeding events classified under the Bleeding Academic Research Consortium (BARC) criteria type 2, 3, or 5.

Results A total of 2087 patients were enrolled in this study. Based on their medication regimen, 348 patients were assigned to indobufen DAPT group, while 1739 individuals were assigned to aspirin DAPT group. After applying 1:1 propensity score matching, 306 patients were included in each group. During the 1-year follow-up, the NACE occurred in 59 patients (19.9%) of the Indobufen DAPT group and 58 patients (18.6%) in the aspirin DAPT group, with no significant difference between the groups (HR 1.029, 95% CI 0.714–1.484, $P=0.876$). Additionally, there were no significant difference in Patient-Oriented Composite Endpoint (POCE) and BARC 2, 3, or 5 bleeding events between

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the groups at 1, 3, or 6 months of follow-up. However, the indobufen DAPT group experienced a lower incidence of upper GI symptoms compared to the aspirin DAPT group.

Conclusion Indobufen, as an alternative to aspirin, demonstrates comparable efficacy and safety in elderly ACS patients after PCI, with a potential reduction in gastrointestinal symptoms. These findings support the use of indobufen as a viable alternative for elderly ACS patients who are intolerant to aspirin.

Clinical trial number Not applicable.

Plain Language Summary

What is the context?

• Antiplatelet therapy plays a crucial role in managing elderly patients with Acute Coronary Syndrome (ACS) following Percutaneous Coronary Intervention (PCI).

• However, these patients face heightened risks of both ischemic and bleeding events, making the selection of optimal antiplatelet therapy particularly challenging in clinical practice.

• Existing research has predominantly focused on the choice of P2Y12 inhibitors, often overlooking alternative options to aspirin, especially in elderly patients where aspirin intolerance is a frequent concern.

What is new?

• This study is the first to evaluate the use of indobufen in patients with ACS, specifically exploring its efficacy and safety in elderly patients.

• Over a 1-year observational period, the study found no significant differences between the indobufen and aspirin groups in terms of the cumulative incidence of Net Adverse Clinical Events (NACE), Patient-Oriented Composite Endpoint (POCE), and BARC 2, 3, or 5 bleeding events. This suggests that indobufen may be as effective and safe as aspirin for elderly ACS patients post-PCI.

• Of note, this study included gastrointestinal reactions as a safety outcome, revealing that the indobufen group experienced significantly fewer gastrointestinal events compared to the aspirin group.

What is the impact?

• We propose indobufen as a viable alternative for individuals intolerant to aspirin.

• The findings of this study have the potential to influence clinical practice by guiding the selection of antiplatelet therapy in elderly ACS patients undergoing PCI, particularly for those at risk of aspirin-related gastrointestinal issues.

Keywords Indobufen, Aspirin, Percutaneous coronary intervention, Acute coronary syndrome, Elderly patients

Introduction

Antiplatelet therapy is a cornerstone in the management of Acute Coronary Syndrome (ACS) patients, especially following Percutaneous Coronary Intervention (PCI). It plays a critical role in preventing thrombotic complications by inhibiting platelet aggregation. Current guidelines recommend dual antiplatelet therapy (DAPT) with aspirin as a key treatment for ACS patients after PCI[1, 2]. Aspirin, an irreversible inhibitor of platelet cyclooxygenase-1, has long been central to antiplatelet therapy. However, its side effects, particularly gastrointestinal (GI) issues and allergic reactions, present significant challenges. In a Japanese multicenter study involving 947 patients, up to 30% reported aspirin intolerance, primarily due to severe Gastrointestinal (GI) issues or allergies[3]. Similarly, a single-center study in China found that among 11,470 patients who underwent coronary angiography, 1139 (9.9%) were treated with cilostazol instead of aspirin due to intolerance though this proportion was likely underestimated[4]. The search for more effective and safer alternatives has led to the development of other antiplatelet drugs, including indobufen. This novel agent reversibly inhibits platelet aggregation by interfering with the formation of thromboxane A2, the release of various platelet factors, and the metabolism of arachidonic acid and adenosine-diphosphate (ADP), thereby preventing thrombosis[5, 6, 7].

There have been studies showed that in patients with chronic coronary syndrome (CCS), indobufen, as an alternative to aspirin, can reduce the risk of bleeding without increasing ischemic events[8, 9], which is especially important for patients with aspirin intolerance. However, a subgroup analysis from these studies suggested a potential increase in MACCE rates associated with indobufen in the ACS population, indicating the need for further investigation.

Elderly patients with coronary artery disease, who often have multiple comorbidities, face an increased risk of bleeding complications with antiplatelet therapies[10]. Managing these patients is particularly challenging, and

the existing research has primarily focused on the selection of P2Y12 inhibitors[11, 12], with less attention given to indobufen.

This study aims to evaluate the safety and efficacy of indobufen in combination with clopidogrel compared to asprin in elderly ACS patients post-PCI, with the goal of identifying a suitable alternative for those who are intolerant to aspirin.

Methods

Study design and participants

This was a single-center, retrospective study conducted in accordance with the Declaration of Helsinki. The study protocol received approval from the Clinical Research Ethics Committee of the Second Hospital of Tianjin Medical University (approved number: KY2023K078). Informed consent was waived due to the study's retrospective design.

This study enrolled patients with ACS treated at the Second Hospital of Tianjin Medical University between January 10, 2019, and May 31, 2022. The ACS cohort comprised individuals diagnosed with Unstable Angina (UA), ST-segment Elevation Myocardial Infarction (STEMI), and Non-ST-segment Elevation Myocardial Infarction (NSTEMI), based on the latest guidelines from the European Society of Cardiology (ESC) and the Fourth Universal Definition of Myocardial Infarction[13, 14].

Participants met the following criteria: (1) aged 65 or above, (2) presenting symptoms or signs indicative of myocardial ischemia, with or without electrocardiogram (ECG) changes, or elevated cardiac troponin (cTn) levels, and (3) having successfully undergone PCI with contemporary Drug-Eluting Stent (DES) or drug-eluting balloon angioplasty.

Exclusion criteria were as follows: (1) use of antiplatelet drugs other than aspirin, indobufen and clopidogrel; (2) treated with single or triple antiplatelet therapy; (3) non-standardized dual antiplatelet therapy dosage; (4) withdrawal or change of treatment regimen during follow-up; (5) failure to complete the 1-year follow-up.

Data collection

Data collection included patient demographics, medication, medical history, and laboratory results (such as cardiac enzymes and blood lipids), and clinical observations during hospitalization. Interventional characteristics, including the number and location of vascular lesions, stent implantation details, and SYNTAX score were also analyzed. The patients were divided into two groups based on their medication regimen: the aspirin DAPT group and the indobufen DAPT group. The indobufen DAPT group received indobufen 100 mg twice daily plus clopidogrel 75 mg daily for 12 months, while the aspirin DAPT group was treated with aspirin 100 mg daily plus clopidogrel 75 mg daily for the same duration. The follow-up time points at 1, 3, and 6 months were primarily used to retrieve records from the hospital database, while telephone follow-up was performed at 12 months post-PCI as a supplementary measure. Data from patients who were re-admitted to the hospital were also included in the follow-up records. Clinical data collected during follow-up included the clinical status of patients, medication adherence, thrombotic events, and adverse reactions. Patients who did not take their medications as prescribed after discharge were excluded from the study.

Endpoints

The primary endpoint event was net adverse clinical event (NACE), a composite of all-cause death, stroke, myocardial infarction (MI), revascularization, Bleeding Academic Research Consortium (BARC) criteria type 2, 3, or 5 bleeding at 1-year. The efficacy endpoint was defined as Patient-oriented composite endpoint (POCE), which included all-cause mortality, any stroke, any MI or target lesion revascularisation (TVR), according to the Academic Research Consortium-2 (ARC-2) consensus[15]. Additional efficacy endpoints included the individual components of POCE. The safety endpoint was defined as BARC criteria type 2, 3 or 5 bleeding. The additional safety endpoints focusing on BARC type 2 and BARC type 3 or 5. Upper GI adverse reactions, including gastric burning, nausea and vomiting, dyspepsia and peptic ulcer, were also analyzed as endpoint events.

Statistical analysis

Data were processed using R version 4.0.4 software. Categorical variables were presented as percentage, with group comparisons using the chi-square test. Continuous variable data were expressed as mean ± standard deviation, and comparisons between the two groups were conducted using the independent sample t-test. To address missing data (16,147 out of 280,207 data points, 5.448%), multiple imputation was employed. The imputation process created five complete datasets, based on observed data and probabilistic methods, with results pooled to estimate study parameters. To minimize bias inherent in observational studies, propensity score matching (PSM) was utilized at a 1:1 ratio between the two groups, using the nearest neighbor approach based on Mahalanobis distance with a caliper of 0.02. Propensity scores were calculated from a logistic regression model incorporating 23 clinically relevant covariates affecting patient's prognosis, including sex, age, ACS types (UA, NSTEMI, STEMI), hypertension, diabetes, Chronic Kidney Disease (CKD), atrial fibrillation, previous PCI, previous MI, previous ischemic stroke, prior cerebral hemorrhage, previous gastrointestinal bleeding, Academic Research Consortium - High Bleeding Risk (ARC-HBR), anemia

(Hb < 90 g/L), dyslipidemia, smoking history, drinking history, proton pump inhibitor (PPI) use, left ventricular ejection fraction (LVEF), SYNTAX score, and left anterior descending artery lesion treatment. Following PSM, curves to survival curves for NACE, POCE, and BARC 2, 3, or 5 bleeding events at the 12-month intervals were illustrated using Kaplan-Meier curve and compared using the Log-rank test. The p-values reported for comparisons of Kaplan-Meier curves are obtained from the log-rank test, and the hazard ratios and their corresponding confidence intervals are derived from the Cox regression analysis. Sensitivity analyses included 1-, 3-, 6-month outcomes for complete follow-up cohort and ischemic event assessments and baseline comparison for the incomplete follow-up cohort. To ensure the robustness, a multivariate Cox proportional hazards regression analysis was conducted on the 1-year follow-up data, adjusting for potential confounding covariates. All tests were two-tailed, with a significance level of $p < 0.05$.

Results

Patient disposition

This study examined 4365 elderly ACS patients who underwent PCI between January 10, 2019 and May 31, 2023, at the Second Hospital of Tianjin Medical University. Of these, 2087 patients were ultimately included in the cohort after applying exclusion criteria (e.g., non-standard treatment, treatment changes, and incomplete follow-up). The patients were divided into two groups: 348 patients in the indobufen DAPT group and 1739 patients in the aspirin DAPT group. After performing 1:1 propensity score matching, 306 patients remained in each group (Fig. 1).

Baseline characteristics before/after propensity score matching

The baseline characteristics of patients in the two groups, before and after matching, are summarized in Table 1. Before matching, the Indobufen DAPT group exhibited a higher average age, greater prevalence of CKD and previous gastrointestinal bleeding, higher SYNTAX scores, and a higher incidence of STEMI, along with increased use of PPIs. Meanwhile, the Indobufen DAPT group had a lower left ventricular ejection fraction (LVEF), and lower rates of ACEI/ARB use and anterior descending artery lesions (all $p < 0.05$).

After matching, baseline characteristics of the two groups were comparable (Figure S1). The median duration of follow-up was 771 days. The average patient age was 75.7 years, with 299 (48.9%) patients being male. Among them, 237 (38.7%) were diagnosed with unstable angina, 268 (43.8%) with NSTEMI, and 107 (17.5%) with STEMI. Left main coronary artery disease was observed in 50 cases (8.17%), left anterior descending artery disease in 574 cases (93.8%), and multivessel disease in 568 cases (92.8%). On average, each patient had 2.82 target lesions, and 1.36 stents were implanted per patient (Table 1).

Primary endpoints

The primary endpoint of net adverse cardiovascular events (NACE) occurred in 58 (19.9%) patients in the Indobufen DAPT group and 57 (17.6%) patients in the Aspirin DAPT group at 1 year. The Log-rank test showed no significant difference in NACE risk (HR 1.029, 95% CI 0.714–1.484, $p = 0.876$) (Table 2; Fig. 2).

Efficacy endpoints

The occurrence of POCE was observed in 45 patients (14.7%) in the Indobufen DAPT group and 47 patients (15.4%) in the Aspirin DAPT group. The HR indicated no significant difference in risk between the groups (HR 0.959, 95% CI 0.637–1.443, $p = 0.841$) (Table 2; Fig. 2). Rates of individual components and cardiac death were also comparable between the two groups (all p-values > 0.05).

Bleeding events

Both groups reported an identical rate of BARC 2, 3, or 5 type bleeding events, with 19 cases (6.2%) each group, and the risk ratio reamained non-significant (HR 1.009 95% CI 0.534–1.905, $p = 0.979$). BARC 2 type bleeding was observed in 14 (4.6%) patients in the Indobufen group and 12 (4.0%) patients in the Aspirin group ($p = 0.679$), and the incidence of BARC 3 or 5 type bleeding was 2.3% and 1.6%, respectively ($p = 0.575$), indicating no significant difference between the groups (Table 2; Fig. 2).

Gastrointestinal events

Patients on aspirin DAPT demonstrated a higher prevalence of upper GI symptoms (14.4%) compared to those on indobufen (7.5%), with statistical significance ($p = 0.010$)(Fig. 3). However, there was no significant difference between the two groups for individual symptom, such as, gastric burning, nausea, vomiting, diarrhea, constipation, dyspepsia, or peptic ulcer.

Sensitivity analysis

To rigorously assess the robustness of our findings, we performed three complementary analyses:

Multivariable cox regression for 1-year endpoints

Adjusted for a variety of covariates (see Supplementary Table S1), the Cox model confirmed consistent results between groups (aHR for NACE: 1.06, 95% CI 0.74–1.52, $P = 0.75$; aHR for POCE: 0.99, 95% CI 0.66–1.48, $P = 0.95$;

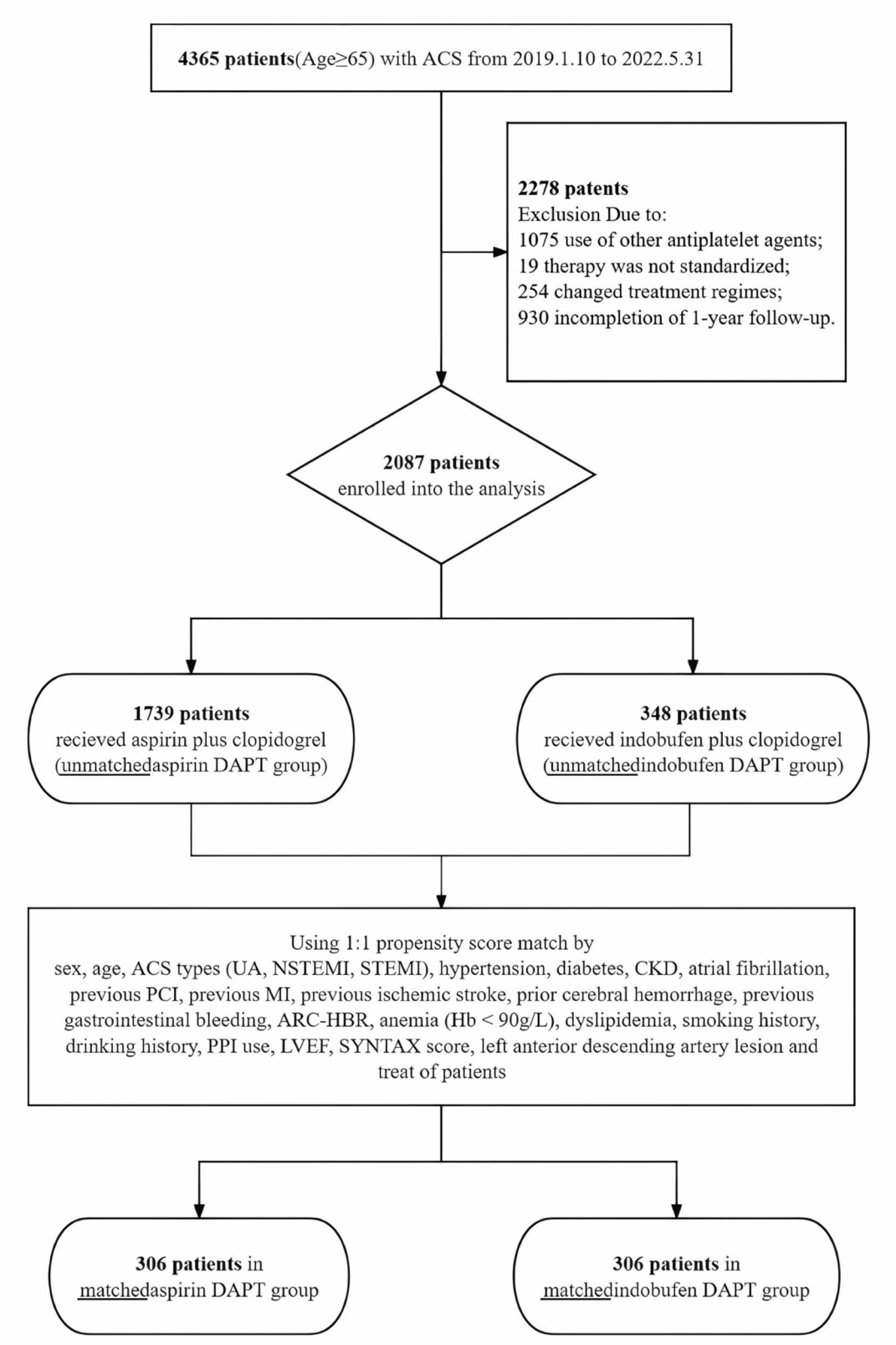

Fig. 1 Patient Disposition. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; UA, Unstable Angina. NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; ARC-HBR, the Academic Research Consortium-High Bleeding Risk; PPI, proton pump inhibitor; LVEF, left ventricular ejection fraction

Table 1 Clinical characteristics of patients

Parameter	Unmatched patients			Propensity-Score Matched patients		
	Aspirin (*n* = 1739)	Indobufen (*n* = 348)	*P*	Aspirin (*n* = 306)	Indobufen (*n* = 306)	*P*
Baseline characteristic						
Age (years)	73 ± 6	76 ± 7	**0.001**	75.8 ± 6.54	75.7 ± 7.05	0.731
Male, n(%)	944 (54.3%)	170 (48.9%)	0.073	149 (48.7%)	150 (49.0%)	1.000
Previous MI, n(%)	231 (13.3%)	40 (11.5%)	0.413	35 (11.4%)	35 (11.4%)	1.000
Previous PCI, n(%)	421 (24.2%)	83 (23.9%)	0.941	80 (26.1%)	73 (23.9%)	0.575
Hypertension, n(%)	1353 (77.8%)	270 (77.6%)	0.985	239 (78.1%)	236 (77.1%)	0.846
Diabetes, n(%)	627 (36.1%)	125 (35.9%)	1.000	111 (36.3%)	107 (35.0%)	0.800
Atrial fibrillation, n(%)	95 (5.46%)	26 (7.47%)	0.181	23 (7.52%)	25 (8.17%)	0.880
Chronic kidney disease, n(%)	266 (15.3%)	111 (31.9%)	**0.001**	87 (28.4%)	85 (27.8%)	0.928
Previous ischemic stroke, n(%)	307 (17.7%)	63 (18.1%)	0.902	58 (19.0%)	52 (17.0%)	0.599
Previous Gastrointestinal bleeding, n(%)	9 (0.52%)	18 (5.17%)	**0.001**	4 (1.31%)	5 (1.63%)	1.000
Previous cerebral hemorrhage, n(%)	14 (0.81%)	9 (2.59%)	0.008	7 (2.29%)	5 (1.63%)	0.771
Smoke history, n(%)	502 (28.9%)	97 (27.9%)	**0.001**	83 (27.1%)	87 (28.4%)	0.787
Drink history, n(%)	354 (20.4%)	73 (21.0%)	0.793	65 (21.2%)	59 (19.3%)	0.546
HBR, n(%)	801 (46.1%)	254 (73.0%)	< 0.001	220 (71.9%)	212 (69.3%)	0.535
SYNTAX score	12.6 (6.84)	13.6 (7.66)	**0.021**	13.2 (7.17)	13.4 (7.70)	0.745
Clinical Indication of PCI						
UA, n(%)	863 (49.6%)	121 (34.8%)	**0.001**	121 (39.5%)	116 (37.9%)	0.740
NSTEMI, n(%)	593 (34.1%)	160 (46.0%)	**0.001**	134 (43.8%)	134 (43.8%)	1.000
STEMI, n(%)	283 (16.3%)	67 (19.3%)	0.201	51 (16.7%)	56 (18.3%)	0.670
Medications						
β-blockers, n(%)	934 (53.7%)	175 (50.3%)	0.268	159 (52.0%)	152 (49.7%)	0.628
ACEI or ARB, n(%)	461 (26.5%)	55 (15.8%)	**0.001**	57 (18.6%)	54 (17.6%)	0.834
PPI, n(%)	1298 (74.6%)	302 (86.8%)	**0.001**	257 (84.0%)	260 (85.0%)	0.823
Statins, n(%)	1636 (94.1%)	320 (92.0%)	0.171	281 (91.8%)	281 (91.8%)	1.000
Laboratory results						
LVEF (%)	58.2 ± 9.67	56.1 ± 10.9	**0.001**	56.1 ± 11.1	56.7 ± 10.7	0.553
LDLc (mmol/L)	2.87 ± 0.95	2.86 ± 0.94	0.972	2.88 (0.94)	2.83 ± 0.88	0.533
CK-MB (ng/ml)	26.7 ± 45.7	33.0 ± 58.4	0.058	28.9 ± 52.4	31.4 ± 54.8	0.557
Interventional characteristics						
Target lesion location						
LM, n(%)	102 (5.87%)	30 (8.62%)	0.071	24 (7.84%)	26 (8.50%)	0.883
LAD, n(%)	1675 (96.3%)	322 (92.5%)	**0.002**	287 (93.8%)	287 (93.8%)	1.000
LCX, n(%)	1413 (81.3%)	288 (82.8%)	0.559	257 (84.0%)	251 (82.0%)	0.590
RCA, n(%)	1562 (89.8%)	317 (91.1%)	0.533	270 (88.2%)	280 (91.5%)	0.228
Ramus, n(%)	71 (4.08%)	13 (3.74%)	0.880	12 (3.92%)	11 (3.59%)	1.000
Multi-vessel disease, n(%)	1622 (93.3%)	324 (93.1%)	0.909	282 (92.2%)	286 (93.5%)	0.531
No. of diseased vessels, mean (SD)	2.79 ± (0.68)	2.84 ± 0.68	0.137	2.80 ± 0.72	2.83 ± 0.69	0.606
Implanted stents location						
LM, n(%)	6 (0.35%)	4 (1.15%)	0.069	1 (0.33%)	3 (0.98%)	0.624
LAD, n(%)	709 (40.8%)	113 (32.5%)	**0.005**	109 (35.6%)	97 (31.7%)	0.347
LCX, n(%)	364 (20.9%)	67 (19.3%)	0.526	69 (22.5%)	60 (19.6%)	0.428
RCA, n(%)	568 (32.7%)	125 (35.9%)	0.265	109 (35.6%)	114 (37.3%)	0.737

Table 1 (continued)

Parameter	Unmatched patients			Propensity-Score Matched patients		
	Aspirin (*n* = 1739)	Indobufen (*n* = 348)	*P*	Aspirin (*n* = 306)	Indobufen (*n* = 306)	*P*
Ramus, n(%)	16 (0.92%)	1 (0.29%)	0.336	2 (0.65%)	1 (0.33%)	1.000
No. of implanted stents, mean (SD)	1.38 (0.80)	1.32 (0.89)	0.292	1.39 (0.83)	1.34 (0.89)	0.424

previous MI, previous myocardial infarction; PCI, percutaneous coronary intervention; HBR, high bleeding risk; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PPI, proton pump inhibitor; LDLc, low-density lipoprotein cholesterol; CK-MB, creatine kinase-MB Isoenzyme; LM, left main coronary artery; LAD, left anterior desending artery; LCX, left circumflex artery; RCA, right coronary artery

Table 2 One-year clinical endpoints in the elderly ACS patients (Based on Log-Rank). Data are expressed as number of patients (percentage)

	Aspirin (*n* = 306)	Indobufen (*n* = 306)	HR (95%CI)	*P* value
Primary endpoint				
NACE (all-cause death, stroke, MI, TLR, BARC 2, 3 or 5 bleeding)	57(18.6%)	58(19.9%)	1.029 (0.714–1.484)	0.876
Ischemic events				
POCE (all-cause death, stroke, MI or TLR)	47(15.4%)	45(14.7%)	0.959 (0.637–1.443)	0.841
All-cause Death	25(8.2%)23(7.5%)	25(8.2%)23(7.5%)	0.919 (0.522–1.618)	0.769
Cardiac Death	11(3.6%)	13(4.2%)	1.180 (0.530–2.626)	0.686
Nonfatal MI	6(2.0%)	8(2.6%)	1.343 (0.471–3.829)	0.584
Stroke	17(5.6%)	10(3.3%)	0.581 (0.273–1.236)	0.168
TLR	7(2.3%)	6(2.0%)	0.841 (0.284–2.494)	0.755
Bleeding events				
BARC type 2, 3, or 5 bleeding	19(6.2%)	19(6.2%)	1.009 (0.534–1.905)	0.979
BARC type 2 bleeding	12(4.0%)	14(4.6%)	1.176 (0.545–2.537)	0.679
BARC type 3 or 5 bleeding	7(2.3%)	5(1.6%)	0.721 (0.233–2.235)	0.575

BARC, Bleeding Academic Research Consortium;

MI, myocardial infarction;

NACE, net adverse clinical event;

POCE, patient-oriented composite endpoint;

TLR, Target Lesion Revascularisation

aHR for BARC type 2, 3, or 5 bleeding: 1.06, 95% CI 0.58–1.92, $P = 0.86$).

Short-term outcome reanalysis

Analyses at 1, 3, and 6 months revealed no significant divergence from the 1-year results. NACE, POCE, and BARC 2, 3, or 5 bleeding rates remained comparable between groups across all intervals ($P \geq 0.05$; Supplementary Figures S2–S4).

Inclusion of incompletely followed patients

Patients with < 1-year follow-up were censored at their last recorded ischemic event or contact date. Baseline characteristics between these patients remained well-balanced after PSM (all $P > 0.05$; see Supplementary Table S2), confirming maintained comparability between treatment arms. Even after incorporating these cases ($n = 902$), the 1-year ischemic event rates (POCE and components) showed no significant intergroup differences (POCE HR: 1.02, 95% CI 0.71–1.45, $P = 0.93$; Supplementary Table S3), further supporting the primary conclusions.

All sensitivity analyses consistently aligned with the main findings, underscoring the reliability of the efficacy and safety of indobufen in elderly ACS patients.

Discussions

Indobufen is commonly used as a substitute for aspirin in clinical practice, particularly for patients who exhibit aspirin intolerance. However, the efficacy and safety between indobufen and aspirin in elderly patients with ACS after PCI had not been previously explored. Our research was the first to directly compare these two antiplatelet therapies in this specific patient population. Over a 1-year observational period, we found no significant differences in the cumulative incidence of NACE, POCE, and BARC 2, 3, or 5 between the indobufen based and aspirin based DAPT groups. Importantly, indobufen was associated with a lower risk of gastrointestinal symptoms compared to aspirin.

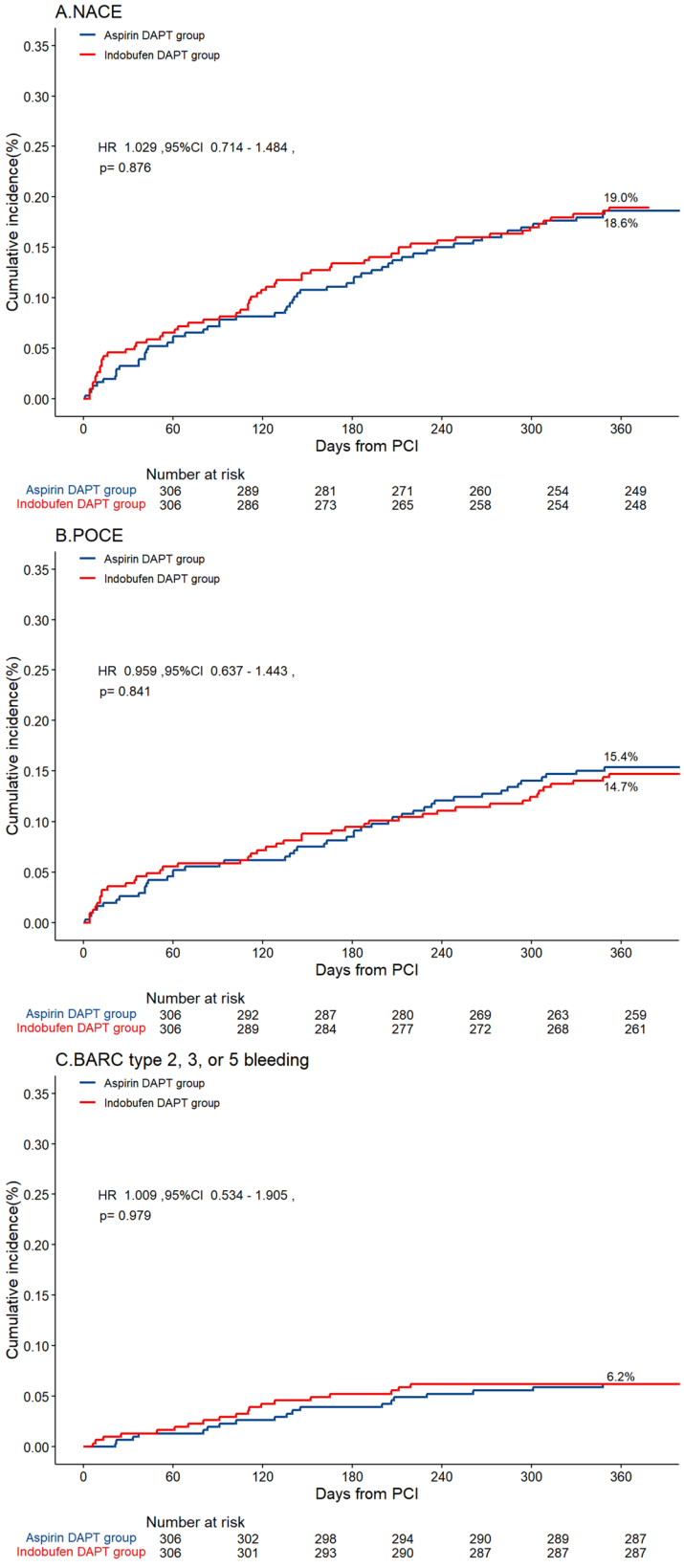

Fig. 2 Cumulative Kaplan-Meier curve estimates of NACE (**A**), POCE (**B**), and BARC 2, 3, or 5 (**C**) at 1 year in elderly patients with ACS. NACE, net adverse clinical event; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoint; BARC, bleeding academic research consortium; HR, hazard ratio; CI, confidence interval

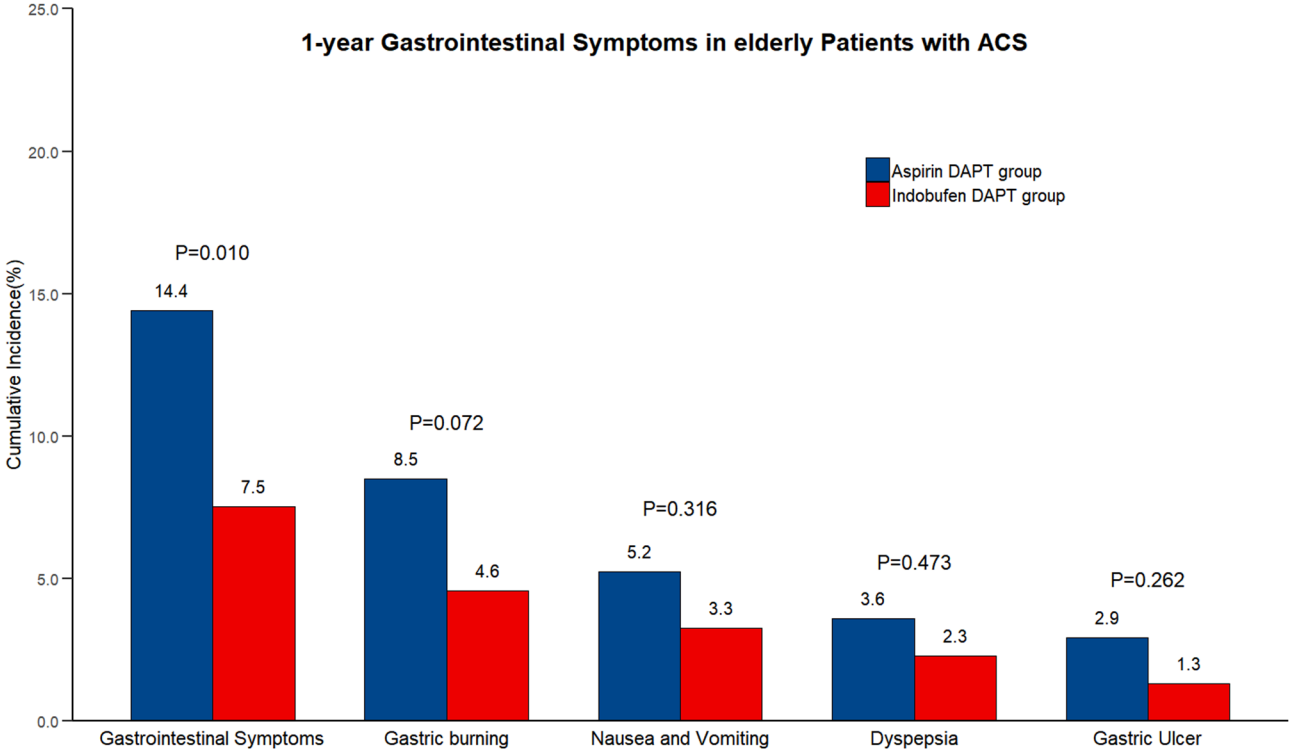

Fig. 3 1-year Gastrointestinal Symptoms in elderly Patients with ACS

Elderly ACS patients face heightened thrombotic and bleeding risks due to age-related physiological changes, including endothelial dysfunction, altered platelet reactivity, and vascular fragility[10, 16, 17]. In this context of elderly patients undergoing PCI, determining the optimal antiplatelet strategy remains a complex challenge. However, current evidence predominantly focuses on optimizing P2Y12 inhibitors[13, 18], leaving aspirin alternatives like indobufen understudied in this population.

Indobufen is a selective inhibitor of cyclooxygenase-1 (COX-1), offering effective and reversible antiplatelet activity. It has been shown that platelet function is largely restored within 24 h after discontinuation of indubufen[19]. The drug achieves a significant platelet inhibition rate of 98% within just 2 h of administration, maintains a high efficacy of 89% after 12 h, and still exhibits a moderated effect at 47% by the 24-hour mark[20]. The onset of platelet inhibition by indobufen is comparable to that of aspirin, with the added advantage of its inhibitory effects being both reversible and dose-dependent [21].

The efficacy of indobufen as an alternative to aspirin has been supported by findings from the OPTION study, which demonstrated that indobufen reduce bleeding events (2.97% vs. 4.71%) without an increase in ischemic events (1.51% vs. 1.40%) in Chinese patients with negative cardiac troponin undergoing drug-eluting stents (DES) implantation[8]. Additionally, a real-world study found that indobufen-based DAPT had a similar risk of major adverse cardiovascular and cerebrovascular events (MACCE) compared to aspirin-based DAPT (6.5% vs. 6.5%), while significantly reducing the risk of bleeding (3.0% vs. 11.9%)[9]. Despite these promising findings, the definitive efficacy and safety of indobufen in the elderly population with ACS remain to be firmly established. Notably, the subgroup analysis of ASPIRATION registry revealed that indobufen use tended to increase MACCE risk in ACS patients, which is different from our study. The efficacy discrepancies between our study and the ASPIRATION registry likely stem from key methodological and population differences. Our study focused on elderly ACS patients (≥65 years, mean age 76) on indobufen with clopidogrel, while ASPIRATION included a wider age range and varied P2Y12 inhibitor use. These differences in cohort selection, confounder adjustment, and treatment regimens highlight the need for further study to confirm the role of indobufen in ACS management.

Our study reinforces the applicability of indobufen as a viable alternative to aspirin in the elderly population with ACS. The findings demonstrating that indobufen's efficacy and safety are comparable to those of aspirin. Additionally, given its potential to reduce gastrointestinal symptoms, indobufen presents a valuable option for elderly individuals who are intolerant to aspirin.

Recent advances in interventional techniques, stent modifications, and pharmacological strategies have reduced ischemic events, making bleeding and GI adverse reactions key concerns[22]. For patients at high bleeding risk (HBR), current guidelines suggest that the duration of DAPT can be shortened to just 1 month after PCI, followed by monotherapy with either aspirin or clopidogrel[13]. However, the guidelines mainly derive from chronic coronary syndrome (CCS) studies[23, 24], nearly 40% stable angina, whereas our study specifically targets elderly ACS patients. Our study revealed comparable efficacy and safety profiles between indobufen DAPT and aspirin DAPT in elderly ACS patients undergoing PCI. This finding offers another management strategy for HBR patients post - PCI. Moreover, nearly 20% of patients taking aspirin reported GI reactions, leading to low adherence[25, 26, 27]. Notably, our findings revealed a significant decrease in the incidence of GI reactions in the indobufen DAPT group, likely due to indobufen's reversible inhibition of platelet COX-1, with little effect on prostacyclin (PGI2) production[28]. This has been supported by endoscopic studies[29].

This study has limitations inherent to its retrospective, single-center design. Despite using multiple imputation and propensity matching, residual bias from unmeasured variables (e.g., BMI, stent types) remains. GI symptom data were categorically documented without details (frequency/duration/severity) and lacked standardized patient-reported tools, risking underreporting of mild events; however, this aligns with prior evidence supporting the favorable GI tolerability of indobufen[19, 29]. Additionally, due to follow-up protocol constraints, bleeding events and GI reactions were not systematically recorded for patients with incomplete follow-up (< 1 year). However, analyses of available ischemic events in this subgroup aligned with the findings of primary cohort (Supplementary Table S3), reinforcing result consistency. Mechanical circulatory support and cardiogenic shock data were unavailable, limiting high-risk subgroup assessments. While internal validation supports robustness, generalizability is constrained by the homogeneous elderly ACS cohort and sample size. Larger multicenter trials with structured symptom monitoring are needed for confirmation.

In conclusion, Indobufen, as an alternative to aspirin, demonstrates comparable efficacy and safety in elderly patients with ACS after PCI and may reduce the risk of gastrointestinal symptoms. These findings support the use of Indobufen as a viable option for elderly ACS patients who are intolerant to aspirin.

Abbreviations

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
ARC-2	Academic research consortium-2
BARC	Bleeding academic research consortium
CCS	Chronic coronary syndrome
COX-1	Cyclooxygenase-1
CKD	Chronic kidney disease
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
ECG	Electrocardiogram
ESC	European society of cardiology
GI	Gastrointestinal
GERD	Gastroesophageal reflux disease
HBR	High bleeding risk
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiovascular and cerebrovascular events
MI	Myocardial infarction
NACE	Net adverse clinical events
PCI	Percutaneous coronary intervention
POCE	Patient-oriented composite endpoint
PSM	Propensity score matching
PPI	Proton pump inhibitor
STEMI	ST segment elevation myocardial infarction
UA	Unstable angina
PGI2	Prostacyclin

Supplementary Information

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Supplementary Material 1

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Author contributions

Y.J.W., T.L., J.M.Z., S.W.R., and K.Y.C. conceived and designed the study; W.B.D., G.M., J.R., S.H., and R.X.G. analyzed and interpreted the data; W.B.D., T.S.G., X.W., and J.K.Z. drafted or revised the manuscript; J.K.Z., J.J.C., and X.H.M. provided final approval of the submitted manuscript. All authors reviewed and approved the final version.

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Data availability

The datasets generated during and/or analysed during the current study are not publicly available as the data also forms part of another ongoing study but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki. The protocol was approved by the Clinical Research Ethics Committee of the Second Hospital of Tianjin Medical University (approved number: KY2023K078). Informed consent was waived by the Clinical Research Ethics Committee of the Second Hospital of Tianjin Medical University due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Evidence Review Committee Members, Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of dual antiplatelet therapy: A systematic review for the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American college of cardiology/american heart association task force on clinical practice guidelines. Circulation. 2016;134(10):e156–178. https://doi.org/10.1161/CIR.0000000000000405.
2. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European society of cardiology (ESC) and of the European association for Cardio-Thoracic surgery (EACTS). Eur Heart J. 2018;39(3):213–60. https://doi.org/10.1093/eurheartj/ehx419.
3. Tournoij E, Peters RJG, Langenberg M, Kanhai KJK, Moll FL. The prevalence of intolerance for Low-Dose acetylsalicylacid in the secondary prevention of atherothrombosis. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2009;37(5):597–603. https://doi.org/10.1016/j.ejvs.2009.01.009.
4. Dai C, Chen Z, Fu J, Qian J, Ge J. Cilostazol for Chinese patients with aspirin intolerance after coronary Drug-Eluting stent implantation. Thromb Haemost. 2020;120(5):857–65. https://doi.org/10.1055/s-0040-1709520.
5. Liu J, Xu D, Xia N, Hou K, Chen S, Wang Y, Li Y. Anticoagulant activities of Indobufen, an antiplatelet drug. Mol Basel Switz. 2018;23(6):1452. https://doi.org/10.3390/molecules23061452.
6. Barillà F, Pulcinelli FM, Mangieri E, Torromeo C, Tanzilli G, Dominici T, Pellicano M, Paravati V, Acconcia MC, Gaudio C. Clopidogrel plus Indobufen in acute coronary syndrome patients with hypersensitivity to aspirin undergoing percutaneous coronary intervention. Platelets. 2013;24(3):183–8. https://doi.org/10.3109/09537104.2012.686072.
7. Yang M, Ye Z, Mei L, Ullah I, Tan C, Wang G, Gu Q, Lu Y, Abdus S, Shi L, Gong X, Bai J, Eikelboom JW, Li C. Pharmacodynamic effects of Indobufen compared with aspirin in patients with coronary atherosclerosis. Eur J Clin Pharmacol. 2021;77(12):1815–23. https://doi.org/10.1007/s00228-021-03177-y.
8. Wu H, Xu L, Zhao X, Zhang H, Cheng K, Wang X, Chen M, Li G, Huang J, Lan J, Wei G, Zhang C, Wang Y, Qian J, Ge J. OPTION investigators. Indobufen or aspirin on top of clopidogrel after coronary Drug-Eluting stent implantation (OPTION): A randomized, Open-Label, end Point-Blinded, noninferiority trial. Circulation. 2023;147(3):212–22. https://doi.org/10.1161/CIRCULATIONAHA.122.062762.
9. Dai C, Liu M, Yang Z, Li Y, Zhou Y, Lu D, Xia Y, Chen A, Li C, Lu H, Dai Y, Ma J, Chen Z, Qian J, Ge J. Real-World performance of Indobufen versus aspirin after percutaneous coronary intervention: insights from the ASPIRATION registry. BMC Med. 2024;22(1):148. https://doi.org/10.1186/s12916-024-03374-3.
10. Capranzano P, Angiolillo DJ. Antithrombotic management of elderly patients with coronary artery disease. JACC Cardiovasc Interv. 2021;14(7):723–38. https://doi.org/10.1016/j.jcin.2021.01.040.
11. Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, Heestermans T, Tjon Joe Gin M, Waalewijn R, Hofma S, den Hartog F, Jukema W, von Birgelen C, Voskuil M, Kelder J, Deneer V, Ten Berg J. Clopidogrel versus Ticagrelor or Prasugrel in patients aged 70 years or older with Non-ST-Elevation acute coronary syndrome (POPular AGE): the randomised, Open-Label, Non-Inferiority trial. Lancet Lond Engl. 2020;395(10233):1374–81. https://doi.org/10.1016/S0140-6736(20)30325-1.
12. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G, Diaz Fernandez JF, Brugaletta S, Pinar-Bermudez E, Mauri Ferre J, Commeau P, Teiger E, Bogaerts K, Sabate M, Morice M-C, Sinnaeve PR. SENIOR investigators. Drug-Eluting stents in elderly patients with coronary artery disease (SENIOR): A randomised Single-Blind trial. Lancet Lond Engl. 2018;391(10115):41–50. https://doi.org/10.1016/S0140-6736(17)32713-7.
13. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan G-A, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B, ESC Scientific Document Group. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J. 2023;44(38):3720–826. https://doi.org/10.1093/eurheartj/ehad191.
14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018, *138* (20), e618–e651. https://doi.org/10.1161/CIR.0000000000000617
15. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel M-A, van Es G-A, Zuckerman B, Fearon WF, Taggart D, Kappetein A-P, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW. Academic research consortium. Standardized end point definitions for coronary intervention trials: the academic research consortium.2 consensus document. Eur Heart J. 2018;39(23):2192–207. https://doi.org/10.1093/eurheartj/ehy223.
16. Capodanno D, Angiolillo DJ. Antithrombotic therapy in the elderly. J Am Coll Cardiol. 2010;56(21):1683–92. https://doi.org/10.1016/j.jacc.2010.04.063.
17. Andreotti F, Rocca B, Husted S, Ajjan RA, ten Berg J, Cattaneo M, Collet J-P, De Caterina R, Fox KAA, Halvorsen S, Huber K, Hylek EM, Lip GYH, Montalescot G, Morais J, Patrono C, Verheugt FWA, Wallentin L, Weiss TW, Storey RF. The ESC thrombosis working group. Antithrombotic therapy in the elderly: expert position paper of the European society of cardiology working group.on thrombosis. Eur Heart J. 2015;36(46):3238–49. https://doi.org/10.1093/eurheartj/ehv304.
18. Szummer K, Montez-Rath ME, Alfredsson J, Erlinge D, Lindahl B, Hofmann R, Ravn-Fischer A, Svensson P, Jernberg T. Comparison between Ticagrelor and clopidogrel in elderly patients with an acute coronary syndrome: insights from the SWEDEHEART registry. Circulation. 2020;142(18):1700–8. https://doi.org/10.1161/CIRCULATIONAHA.120.050645.
19. Liu J, Sun P, Qi X. Reversible and Non-Competitive Inhibition of cyclooxygenase by Indobufen for efficient antiplatelet action and relief of Gastrointestinal irritation. Pharmaceutics. 2023;15(8):2135. https://doi.org/10.3390/pharmaceutics15082135.
20. Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet, drugs: American college of chest physicians Evidence-Based clinical practice guidelines (8th Edition). Chest. 2008;133(6, Supplement):S199–233. https://doi.org/10.1378/chest.08-0672.
21. Lee J-Y, Sung K-C, Choi H-I. Comparison of aspirin and Indobufen in healthy volunteers. Platelets. 2016;27(2):105–9. https://doi.org/10.3109/09537104.2015.1042853.
22. Hoole SP, Bambrough P. Recent advances in percutaneous coronary intervention. Heart Br Card Soc. 2020;106(18):1380–6. https://doi.org/10.1136/heartjnl-2019-315707.
23. Valgimigli M, Frigoli E, Heg D, Tijssen J, Jüni P, Vranckx P, Ozaki Y, Morice M-C, Chevalier B, Onuma Y, Windecker S, Tonino PAL, Roffi M, Lesiak M, Mahfoud F, Bartunek J, Hildick-Smith D, Colombo A, Stanković G, Iñiguez A, Schultz C, Kornowski R, Ong PJL, Alasnag M, Rodriguez AE, Moschovitis A, Laanmets P, Donahue M, Leonardi S, Smits PC. MASTER DAPT investigators. Dual

antiplatelet therapy after PCI in patients at high bleeding risk. N Engl J Med. 2021;385(18):1643–55. https://doi.org/10.1056/NEJMoa2108749.
24. Smits PC, Frigoli E, Tijssen J, Jüni P, Vranckx P, Ozaki Y, Morice M-C, Chevalier B, Onuma Y, Windecker S, Tonino PAL, Roffi M, Lesiak M, Mahfoud F, Bartunek J, Hildick-Smith D, Colombo A, Stankovic G, Iñiguez A, Schultz C, Kornowski R, Ong PJL, Alasnag M, Rodriguez AE, Moschovitis A, Laanmets P, Heg D, Valgimigli M. MASTER DAPT investigators. Abbreviated antiplatelet therapy in patients at high bleeding risk with or without oral anticoagulant therapy after coronary stenting: an Open-Label, randomized, controlled trial. Circulation. 2021;144(15):1196–211. https://doi.org/10.1161/CIRCULATIONAHA.121.056680.
25. Michos ED, Ardehali R, Blumenthal RS, Lange RA, Ardehali H. Aspirin and Clopidogrel Resistance. *Mayo Clin. Proc.* 2006, *81* (4), 518–526. https://doi.org/10.4065/81.4.518
26. Levy M. Aspirin use in patients with major upper Gastrointestinal bleeding and Peptic-Ulcer disease. A report from the Boston collaborative drug surveillance program, Boston university medical center. N Engl J Med. 1974;290(21):1158–62. https://doi.org/10.1056/NEJM197405232902102.
27. Graham MM, Sessler DI, Parlow JL, Biccard BM, Guyatt G, Leslie K, Chan MTV, Meyhoff CS, Xavier D, Sigamani A, Kumar PA, Mrkobrada M, Cook DJ, Tandon V, Alvarez-Garcia J, Villar JC, Painter TW, Landoni G, Fleischmann E, Lamy A, Whitlock R, Le Manach Y, Aphang-Lam M, Cata JP, Gao P, Terblanche NCS, Ramana PV, Jamieson KA, Bessissow A, Mendoza GR, Ramirez S, Diemunsch PA, Yusuf S, Devereaux PJ. Aspirin in patients with previous percutaneous coronary intervention undergoing noncardiac surgery. Ann Intern Med. 2018;168(4):237–44. https://doi.org/10.7326/M17-2341.
28. Wiseman LR, Fitton A, Buckley MM, Indobufen. A review of its pharmacodynamic and Pharmacokinetic properties, and therapeutic efficacy in cerebral, peripheral and coronary vascular disease. Drugs. 1992;44(3):445–64. https://doi.org/10.2165/00003495-199244030-00009.
29. Marzo A, Crestani S, Fumagalli I, Giusti A, Lowenthal DT. Endoscopic evaluation of the effects of Indobufen and aspirin in healthy volunteers. Am J Ther. 2004;11(2):98–102. https://doi.org/10.1097/00045391-200403000-00004.

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