ORIGINAL RESEARCH

Early Discontinuation of $P2Y_{12}$ Antagonists and Adverse Clinical Events Post–Percutaneous Coronary Intervention: A Hospital and Primary Care Linked Cohort

Daniel E. Harris, MSc; Arron Lacey, PhD; Ashley Akbari, MSc; Daniel R. Obaid, PhD; Dave A. Smith, MD; Geraint H. Jenkins, MA; James P. Barry, MA; Mike B. Gravenor, DPhil; Julian P. Halcox, MD

Background—Early discontinuation of $P2Y_{12}$ antagonists post–percutaneous coronary intervention may increase risk of stent thrombosis or nonstent recurrent myocardial infarction. Our aims were to (1) analyze the early discontinuation rate of $P2Y_{12}$ antagonists post–percutaneous coronary intervention, (2) explore factors associated with early discontinuation, and (3) analyze the risk of major adverse cardiovascular events (death, acute coronary syndrome, revascularization, or stroke) associated with discontinuation from a prespecified prescribing instruction of 1 year.

Method and Results—We studied 2090 patients (2011–2015) who were recommended for clopidogrel for 12 months (+aspirin) post–percutaneous coronary intervention within a retrospective observational population cohort. Relationships between clopidogrel discontinuation and major adverse cardiac events were evaluated over 18-month follow-up. Discontinuation of clopidogrel in the first 4 quarters was low at 1.1%, 2.6%, 3.7%, and 6.1%, respectively. Previous revascularization, previous ischemic stroke, and age >80 years were independent predictors of early discontinuation. In a time-dependent multiple regression model, clopidogrel discontinuation and bleeding (hazard ratio=1.82 [1.01–3.30] and hazard ratio=5.30 [3.14–8.94], respectively) were independent predictors of major adverse cardiac events as were age <49 and ≥70 years (versus those aged 50–59 years), hypertension, chronic kidney disease stage 4+, previous revascularization, ischemic stroke, and thromboembolism. Furthermore, in those with both bleeding and clopidogrel discontinuation, hazard ratio for major adverse cardiac events was 9.34 (3.39–25.70).

Conclusions—Discontinuation of clopidogrel is low in the first year post–percutaneous coronary intervention, where a clear discharge instruction to treat for 1 year is provided. Whereas this is reassuring from the population level, at an individual level discontinuation earlier than the intended duration is associated with an increased rate of adverse events, most notably in those with both bleeding and discontinuation. **(*J Am Heart Assoc*. 2019;8:e012812. DOI: 10.1161/JAHA.119.012812.)**

Key Words: adherence • clopidogrel • discharge therapy • discontinuation • percutaneous coronary intervention

Poor medication adherence is often associated with adverse patient events across multiple disease outcomes. This is of particular concern in the setting of modern cardiac intervention with stent implantation for acute coronary syndromes (ACS), where discontinuation of antiplatelet therapy risks both stent stenosis and non-stent-related myocardial infarction (MI). As such, the use of dual antiplatelet therapy (DAPT), aspirin plus a $P2Y_{12}$ inhibitor, in patients undergoing coronary revascularization is an established treatment strategy in the prevention of short- and long-term thrombotic complications.[1–3]

Current guidelines recommend a minimum of 12 months of DAPT for patients presenting with ACS undergoing coronary percutaneous coronary intervention (PCI) with stent implantation, reduced to at least 6 months in the presence of risk factors for bleeding.[4,5] In patients with stable coronary artery disease, a minimum of 6 months is recommended following drug eluting stents implantation and at least 1 month following a bare metal stent or in those with a high risk of bleeding. The presence of comorbidities, such as atrial fibrillation (AF), may necessitate the need for concomitant anticoagulation and therefore shorter durations of DAPT may

From the Swansea University Medical School, Swansea, United Kingdom (D.E.H., A.L., A.A., D.R.O., M.B.G., J.P.H.); Swansea Bay University Health Board, Swansea, UK (D.E.H., D.R.O., D.A.S., G.H.J., J.P.B., J.P.H.); HDR UK Wales & Northern Ireland, Swansea University, Swansea, UK (D.E.H., A.L., A.A., J.P.H.).

Accompanying Tables S1 through S7 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012812

Correspondence to: Daniel E. Harris, MSc, floor 3 Data Science Building, Singleton Campus, Swansea University, Swansea SA28PP, United Kingdom. E-mail: 885489@swansea.ac.uk

Received April 2, 2019; accepted September 11, 2019.

Clinical Perspective

What Is New?

- In this real-world study following patients discharged post–percutaneous coronary intervention where the duration of dual antiplatelet therapy was known, discontinuation of $P2Y_{12}$ antagonist therapy was low and much lower than reported in other studies.
- Despite the low discontinuation rate, it was an important predictor of major adverse outcomes in this population, especially in those with concomitant bleeding.

What Are the Clinical Implications?

- Discontinuation of $P2Y_{12}$ antagonist therapy earlier than intended is associated with an increased rate of adverse events, highlighting the importance of processes optimizing concordance with evidence-based preventative therapy post–percutaneous coronary intervention.

be warranted. Likewise, the need to undergo surgery in the future may also mandate shorter durations of DAPT.

A number of observational studies have shown that an increase in major adverse cardiac events is associated with a delay in access to prescriptions for $P2Y_{12}$ inhibitors following coronary PCI[6,7] or premature discontinuation following an MI or stent implantation.[8–13] Rates of discontinuation vary between studies, with some reporting 13% discontinuation within 30 days[10] and others up to 40% to 50% within 1 year.[8,9] However, these studies have not identified the intended duration of therapy postdischarge or taken account of comorbidities that may warrant shorter durations of DAPT. Furthermore, the study populations were predominantly medically treated ACS[8,14] or, in the case of the PARIS (Patterns of Non-Adherence to Antiplatelet Regimens in Stented Patients) registry, predominantly stable angina patients undergoing PCI.[15]

Our objectives were to (1) analyze the rate of early discontinuation of clopidogrel following discharge from hospital in a post-PCI population where the duration of DAPT was specified for 1 year, (2) explore potential factors associated with discontinuation in prescribing, and (3) analyze the risk of death and major cardiovascular events associated with discontinuation.

Methods

We undertook a retrospective observational cohort study using linked anonymized healthcare data from the SAIL (Secure Anonymised Information Linkage) Databank[16,17] for patients undergoing PCI at a tertiary cardiac center in Wales. The study population was identified from the cardiac intervention database and included patients who were discharged from the hospital (between January 2011 and November 2015) following PCI for either stable or acute coronary artery disease. Follow-up was for 18 months. Patients who underwent coronary artery bypass grafting (CABG) during the index admission or had a previous or contemporary diagnosis of AF were excluded from the study.

This study makes use of anonymized patient data; therefore, informed consent was not required. Approval for the study was granted by the SAIL IGRP (Information Governance Review Panel). All data can be made available to researchers by standard SAIL IGRP protocols.

Approval for data access and processing was granted by the SAIL independent Information Governance Review Panel (IGRP) project number: 0441. Permission was granted from the respective health board data custodians of the Cardiac intervention dataset and the hospital discharge prescribing data sets.

Data Sets and Linkage

The cardiac intervention data set contains procedural, clinical, and demographic data on patients undergoing PCI. Information on the prescribing of antithrombotic therapy was obtained from the hospital discharge summaries. These data sets were linked to the WLGP (Welsh Longitudinal General Practice) data set to record the continuity of antithrombotic therapy and presence of comorbidities, risk factors, and demographics.[18] Date of death, where relevant, was identified form the ADDE (Annual District Death Extract)[19] containing mortality records from the ONS (Office of National Statistics), and deprivation quintile was assigned using the WIMD (Welsh Index of Multiple Deprivation), an area-based deprivation measure.[20]

For each patient hospitalized in Wales, the PEDW (Patient Episode Database for Wales) records the admission and discharge dates, diagnoses, and operational procedures and demographic data. Date of death is also recorded when the patient dies within the hospital. These records are completed at finished consultant episode. Within each finished consultant episode, 1 primary and ≥1 secondary diagnosis, using the *International Classification of Disease, Tenth Revision* (*ICD-10*), are recorded. Operational and procedural codes are also applied for each finished consultant episode following the OPCS-4 (Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4). The PEDW was used to describe cardiac revascularization (either PCI or CABG) and major bleeding events preceding the index

admission (see Table S1 for *ICD-10* codes used to identify bleeding events). Major bleeding events included gastrointestinal bleeds, intracranial bleeds, urinary tract bleeds, and airway bleeds.

Both the PEDW and WLGP data sets were searched for past history or contemporary diagnosis of vascular disease (peripheral artery disease or aortic plaque), AF/flutter, MI, Ischemic stroke, thromboembolism, and heart failure.

Index Event Data

For each patient, the first entry in the cardiac intervention database occurring during the study period was identified as the index intervention. Dates of admission and discharge were identified either side of the index intervention using the PEDW data set. Prescribing data corresponding to the index intervention were extracted from the electronic discharge summaries. Where an electronic discharge summary was not available, paper copies of the discharge summary, where available, were searched and the prescribing data were recorded.

$P2Y_{12}$ Antagonist Prescribing and Discontinuation

Prescribing of $P2Y_{12}$ antagonists postdischarge was recorded within consecutive 3-month periods following the date of discharge from hospital. Discontinuation was deemed to have occurred when there was a 3-month period without a $P2Y_{12}$ antagonist prescription before the intended date of treatment cessation. The precise time to discontinuation is unknown, but was approximated as the center point within the first 3-month period where no $P2Y_{12}$ antagonist had been prescribed, that is, 46 days for the first 3-month period; 137 days for the second 3-month period; and 228, 319, 411, and 501 days for the third to sixth three-month periods, respectively.

Statistical Analyses

Baseline variables and patient characteristics, including demographics, lifestyle behaviors, and medical history, are presented as percentages and means with SDs. Differences between those prescribed $P2Y_{12}$ therapy for 1 year and all other regimes were compared using the χ^2 test for categorical variables and the 2-sample *t* test for continuous variables. A Cox proportional hazards model was used to determine the baseline characteristics associated with "time to discontinuation" from the prescribing instruction at the point of discharge from the hospital. Bleeding subsequent to PCI, occurring during the period of intended prescription duration, was included as a time-dependent covariate. Hazard ratios (HRs) and 95% CIs were calculated for the respective clinical variables. In analyzing time to discontinuation, death during the follow-up was treated as a censoring event, and hence we assumed that the time to death (or other loss to follow-up) was not related to the time-to-attrition distribution.

The primary clinical end point was a combination of death of any cause, subsequent readmission to hospital for an MI, unstable angina, acute ischemic heart disease, ischemic stroke or transient ischemic attack, or readmission after 30 days from the index discharge date for either CABG or recurrent coronary PCI (see Tables S2 and S3 for *ICD-10* and OPCS codes used to establish these end points). A Cox proportional hazards model was used to determine characteristics of the cohort associated with this adverse composite outcome; specifically the effect of discontinuation was modeled as a time-dependent covariate. In estimating the effect of discontinuation, we attempted to control for expected risk factors by including the key baseline characteristics in the Cox model. In addition, we had to control for effects of bleeding, again as a time-dependent covariate. We created a covariate with 4 levels representing the overall time-dependent classification: no discontinuation and no bleed, discontinuation occurred but no bleed, bleed occurred but no discontinuation, and, finally, both events have occurred. For those patients with an adverse outcome, only discontinuation and/or bleeding events occurring before the end point were included in the analysis. All models were run in SPSS software (version 22.0; SPSS, Inc., Chicago, IL). Variables were initially considered separately in univariable analyses; the final multivariable Cox model was selected by minimizing the Akaike information criterion (with a comparison to model selection using Bayesian information criteria).

Results

Study Population

Of the 5532 patients undergoing PCI during the study period, 3066 (55.4%) were discharged and had a complete linked healthcare data set available (Figure 1). A further 397 (7.2%) were excluded who had AF or underwent a CABG procedure during the index admission. Of the final 2770 patients meeting the inclusion criteria, 2090 (75.5%) were prescribed clopidogrel for 1 year (plus aspirin 75 mg once-daily for life). Of this cohort, mean age was 63.2 years, 73.5% were male, and 86.5% underwent PCI for an ACS (Table 1). In comparison with those prescribed any other regimen on discharges, these patients had a lower mean age; lower rate of previous diagnoses for ischemic heart disease; MI, previous coronary revascularization, heart failure, or dyslipidemia; and were less likely to have been prescribed in the year preceding the index event either aspirin, $P2Y_{12}$ inhibitors, or statins (further

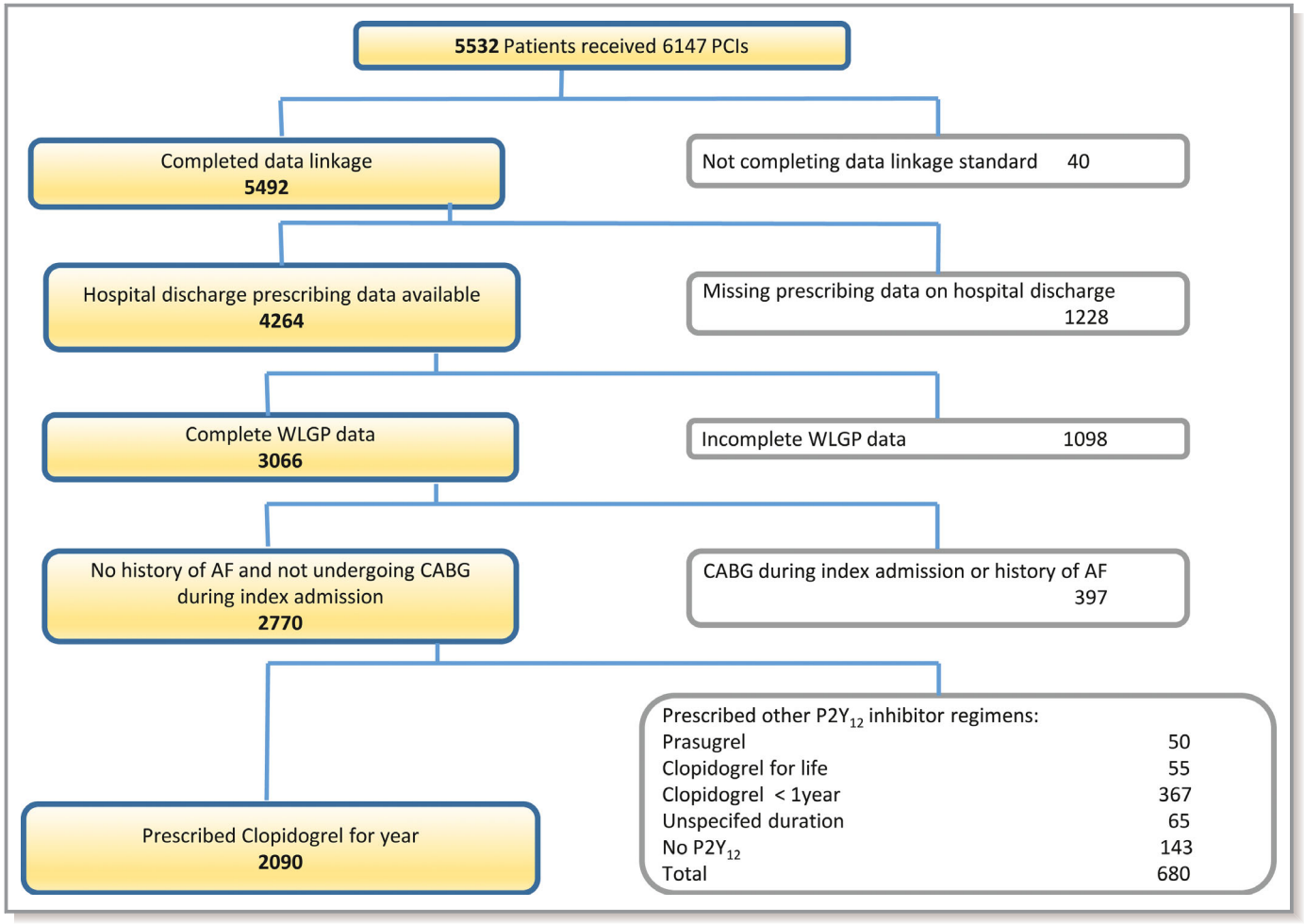

Figure 1. Study population cohort selection. AF indicates atrial fibrillation; CABG, coronary artery bypass graft; PCIs, percutaneous coronary interventions; WLGP, Welsh Longitudinal General Practice.

comparisons between those included and those excluded [with or without discharge prescribing data available] are contained in Table S4).

Clopidogrel Discontinuation

Rate of discontinuation during the periods 0 to 3, 3 to 6, 6 to 9, and 9 to 12 months postdischarge was ≈1.1%, 2.6%, 3.7%, and 6.1%, respectively (Figure 2). Between 12 and 15 months, 47% had discontinued clopidogrel and 76.2% by 15 to 18 months.

Factors associated with clopidogrel discontinuation during the first 12 months included: increasing age, hypertension, ischemic heart disease, previous MI, previous coronary revascularization, ischemic stroke, heart failure, vascular disease, previous bleeding events, and bleeding during the follow-up period (Figure 3). After adjusting for all baseline characteristics, previous revascularization, previous ischemic stroke, and age groups ≥80 years were independently associated with discontinuation (Table 2).

Death and Major Cardiovascular Events

Incidence of death or major cardiovascular events in those who had no discontinuation or bleeding events postdischarge was 9.5 per 100 person-years (95% CI, 8.39–10.74); in patients who had discontinued clopidogrel but had no bleeding events, the incidence was 15.2 (95% CI, 6.72–24.24); in patients who had a bleeding event but no discontinuation, it was 41.9 (95% CI, 21.38–60.10); and in patients who had both bleeding and discontinuation, it was 64.6 per 100 person-years (95% CI, 1.29–127.96).

Patient characteristics associated with death or major cardiovascular events included: age ≤49 or ≥60 compared with those aged 50 to 59, hypertension, previous MI, previous coronary revascularization, ischemic stroke, heart failure, vascular disease, thromboembolism, diabetes mellitus, chronic kidney disease, chronic liver disease, clopidogrel discontinuation, and bleeding during follow-up (Figure 4).

Characteristics independently associated with death or major cardiovascular events in a multivariable Cox

Table 1. Demographics and Medical History of Patients by Discharge Prescribing Intention of $P2Y_{12}$ Inhibitors (N=2770)

	Clopidogrel for 1 year	Other Regimens	
	n=2090	n=680	*P* Value
Percentage of total group	75.5%	24.5%	
Mean age, y (SD)	63.2 (11.8)	66.6 (12.3)	<0.001
Characteristic, n (%)			
Male	1537 (73.5)	450 (66.2)	0.001
Obese	511 (24.4)	181 (26.6)	0.097
Smoker	784 (37.5)	237 (34.9)	0.579
Deprivation index			0.08
1 (most deprived)	337 (16.1)	129 (18.9)	
2	411 (19.7)	129 (18.9)	
3	489 (23.4)	166 (24.4)	
4	415 (19.9)	106 (15.9)	
5 (least deprived)	398 (19.0)	138 (20.2)	
Unknown	40 (1.9)	12 (1.8)	
Past medical history, n (%)			
Hypertension	851 (40.7)	303 (44.6)	0.074
Ischemic heart disease	612 (29.3)	242 (35.6)	0.002
Myocardial infarction	351 (16.8)	144 (21.2)	0.01
Coronary revascularization	203 (9.7)	98 (14.4)	0.001
Ischemic stroke	115 (5.5)	46 (6.8)	0.22
Heart failure	259 (12.4)	67 (9.9)	<0.001
Peripheral vascular disease	81 (3.9)	46 (6.8)	0.002
Thromboembolism	14 (0.7)	9 (1.3)	0.10
Diabetes mellitus	382 (18.3)	156 (23.0)	0.007
Chronic kidney disease stage 4+	16 (0.8)	10 (1.5)	0.097
Chronic liver disease	24 (1.1)	7 (1.0)	0.80
Dyslipidemia	380 (18.2)	149 (21.9)	0.031
Dementia	9 (0.4)	4 (0.6)	0.60
Previous bleeding events	205 (9.8)	89 (13.1)	0.16
Medication prescribed within 1 y before admission, n (%)			
Aspirin	711 (34.0)	282 (41.5)	<0.001
$P2Y_{12}$ antagonist	230 (11.0)	107 (15.8)	0.001
Statins	924 (44.2)	347 (51.0)	0.002
Clinical syndrome, n (%)			0.045
Acute coronary syndrome	1808 (86.5)	563 (82.8)	
Stable coronary disease	282 (13.5)	117 (17.2)	

proportional hazards model included age <49 and ≥70 years compared with those aged 50 to 59; previous coronary revascularization; and a history of thromboembolism, chronic kidney disease stage 4 or 5, and ischemic stroke (Table 3). After adjustment for these factors, the time-dependent effects of discontinuation and bleeding were significantly associated with death or major cardiovascular events. For discontinuation alone, there was an estimated HR of 1.82 (95% CI, 1.01–3.30) compared with patients with no discontinuation and no bleeding events. Similarly, the occurrence of bleeding alone in those without discontinuation was associated with an increased risk of death or major cardiovascular events (HR=5.30; 95% CI, 3.14–8.94). Notably, the combined effect of having both discontinuation and bleeding was associated with the greatest likelihood of adverse events (HR=9.34; 95% CI, 3.39–25.70).

Model selection was also explored using Bayesian information criteria. This resulted in selection of fewer patient characteristics; however, the effects of bleeding and clopidogrel discontinuation were retained in the final model as statistically significant.

For completeness, the characteristics associated with the individual outcomes of MI, stroke, revascularization, and death are presented in Tables S5 and S6. Assessment of risk factors associated with bleeding was not a primary objective of this study, but nonetheless an important consideration. In a multivariable analysis, previous bleeding events (HR=2.82; 95% CI, 1.67–4.76), chronic kidney disease (HR=6.15; 95% CI, 2.22–17.08), and chronic liver disease (HR=3.62; 95% CI, 1.14–11.51) were independently associated with bleeding events during follow-up (Table S7). These variables were not independently associated with risk of clopidogrel discontinuation.

Discussion

This is the first real-world outcome study examining the rate of clopidogrel discontinuation following PCI where the intended prescribing duration of DAPT is known. Notably, discontinuation of $P2Y_{12}$ inhibitor therapy is low in this population, where a specified prescribing instruction to continue for 12 months is provided, in contrast to other studies where the prescribing duration was not known. Furthermore, despite the low discontinuation rate, discontinuation was still identified as an important predictor of adverse outcomes in this population, especially in those with concomitant bleeding.

The observed rate of discontinuation is in marked contrast with findings from previous studies, where it had been suggested that up to a half of patients post-MI discontinue therapy within 12 months.[8] We note that this was observed in a historical ACS patient group who were predominantly treated medically as opposed to receiving contemporary PCI therapy. Nevertheless, our observed rate of discontinuation was still lower than expected. There are a number of possible

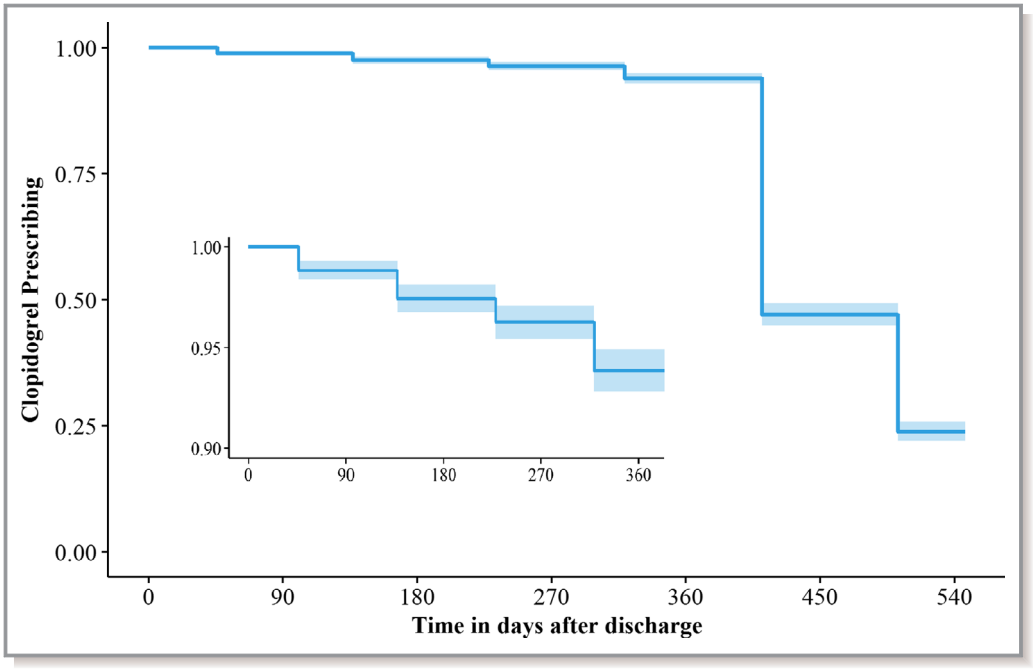

Figure 2. Discontinuation of clopidogrel post-Percutaneous Coronary Intervention.

explanations for this difference, including greater contemporary recognition of the importance of continued use of P2Y$_{12}$ inhibitors post-PCI, improved communication of the prescribing intention from secondary to primary care, and, possibly, the availability of free prescriptions to all patients in Wales. However, addressing these questions was outside the scope of this study.

Among those patients who discontinued clopidogrel earlier than the initial intended period, the hazard of death or major cardiovascular events was greater compared with those who continued therapy, as expected and in keeping with previous studies.[8,21] Other independent predictors of adverse outcomes included ischemic stroke and previous revascularization; both likely markers of diffuse or severe cardiovascular disease. However, both ischemic stroke and previous revascularization were also predictors of discontinuation. Whether these contrasting findings are a consequence of shared risk factors, such as aging, comorbidities, or the index PCI, being a consequence of poor adherence to medication is unknown.

Other independent predictors of discontinuation included advanced age, which has previously been shown to be a predictor of early discontinuation of clopidogrel post-MI. Bleeding events measured as a time-dependent variable were not an independent predictor of discontinuation, contrasting with observations from a previous study.[8] It is possible that those patients with previous bleeding events or at higher risk of bleeding may have been instructed for a shorter course of DAPT at discharge and were therefore not included in this analysis. The exclusion of patients undergoing CABG and those with AF, both groups of which are at higher risk of bleeding and subsequent discontinuation of P2Y$_{12}$ treatment, may explain this observation. We found no association between deprivation quintiles and clopidogrel discontinuation, nor deprivation quintiles and major adverse outcomes in univariable analyses. Therefore, deprivation index was not included in the final multivariable analyses.

In this study, we documented gastrointestinal bleeds, intracranial bleeds, urinary tract bleeds, and airway bleeds in order to be consistent with previous studies,[22] but bleeding events occurring in other organ systems may have had major clinical outcomes and resulted in cessation of therapy. However, the lack of an accepted standard for defining relevant bleeding events and defining their severity in real-world data sets is a recognized limitation for studies such as these.

Bleeding events were also highly predictive of adverse outcomes, as expected. Bleeding is a recognized adverse consequence of antiplatelet therapy and is associated with a greater incidence of death and ischemic events.[1,3,23,24] We found that the greatest risk of death or major cardiovascular events occurred in those with both discontinuation and bleeding events in our cohort. While it is not possible to identify the specific cause of adverse outcomes in this group, it is recognized that contributing factors to worse outcomes include the triggering of prothrombotic and -inflammatory responses following a bleed, combined with discontinuation of

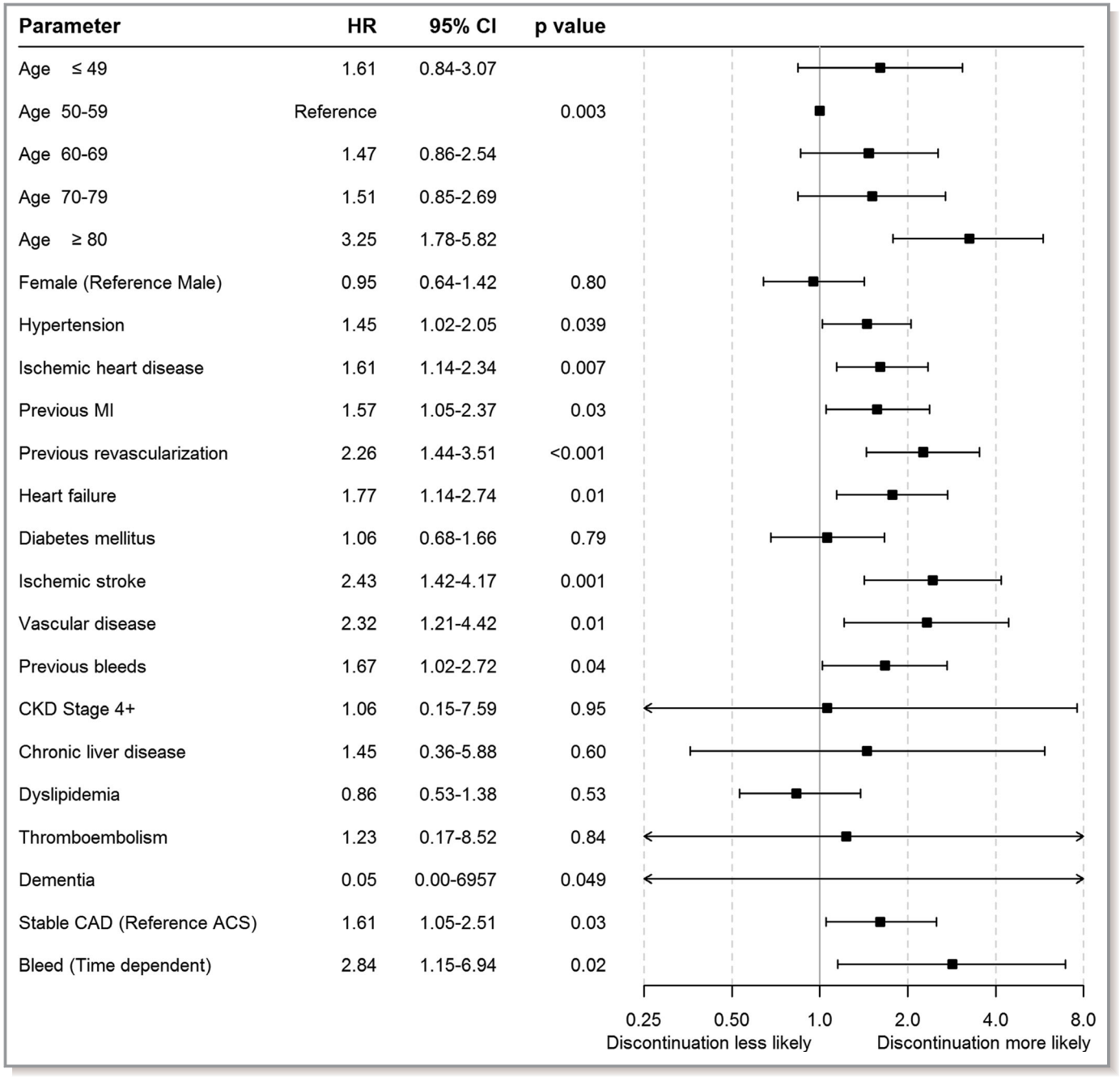

Figure 3. Characteristics associated with clopidogrel discontinuation within 1 year of discharge during follow up using univariable Cox proportional hazards model. ACS indicates acute coronary disease; CAD, coronary artery disease; CKD, chronic kidney disease; HR, hazard ratio; MI, myocardial infarction.

antiplatelet therapy leading to a rebound increased risk of ischemic events.

While discontinuation was reassuringly low in the first 12 months, it is notable that continuation of prescribing beyond 12 months was high with almost one-quarter (24% [n=427]) of patients still receiving a prescription for clopidogrel between 15 and 18 months after discharge from the index event. Possible reasons for continuation of clopidogrel include recurrent ischemic events; however, we noted that only 22.5% (n=96) within this group had a documented readmission for recurrent major cardiovascular events during follow-up. It is possible that further clinical events occurred that led to a decision to continue or change therapy, although it is unlikely that this was the case for the majority of patients. Given that prescriptions are provided free in Wales, there is no financial disincentive to stop treatment, which may explain the relatively high numbers of patients continuing treatment beyond the recommended period.

Table 2. Multivariable Cox Proportional Hazard Model of Characteristics Associated With Clopidogrel Discontinuation*

Covariate	Hazard Ratio	Lower CI	Upper CI	*P* Value
Age, y				
≤49	1.61	0.84	3.08	
50 to 59	Reference			0.005
60 to 69	1.47	0.86	2.53	
70 to 79	1.51	0.84	2.69	
≥80	3.25	1.79	5.88	
Previous revascularization	2.09	1.32	3.33	0.002
Previous ischemic stroke	1.95	1.12	3.39	0.018

*The following variables were included in the mutually adjusted model: age; sex; presenting clinical syndrome; hypertension; previous coronary revascularization; previous bleeding events; ischemic stroke; heart failure; vascular disease; thromboembolism; diabetes mellitus; chronic kidney disease stage 4+; chronic liver disease, dyslipidemia; and dementia.

Given that the data set only examined outcomes up to 18 months, there was insufficient power to explore the relationship between extended prescriptions beyond 12 months and the effect on either cardiovascular events or bleeding attributable to relatively low numbers and short exposure times.

Strengths and Limitations of this Study

We believe that this study further refines our understanding of the impact of $P2Y_{12}$ discontinuation on clinical outcomes. By identifying the discharge prescribing intention, we have avoided overestimation by excluding those with shorter durations of DAPT. Thus, although our analysis only evaluates 40% of the entire PCI population, we believe that these patients are representative of the majority of the post-PCI population who are recommended to receive 1 year of DAPT, given that our analysis has excluded patients requiring anticoagulation, those undergoing surgery, and those without a complete linked data set. There were also many clinical and demographic differences between those directed to 1 year of clopidogrel and the remaining group who had greater prevalence of risk factors for both cardiovascular and bleeding events. By keeping those higher-risk patients in the analyses, over-representation of these important risk factors would likely have led to further overestimation of the actual relationship between discontinuation and adverse cardiovascular events. Furthermore, the exclusion of those with AF and/or undergoing CABG, who are at higher risk of bleeding and subsequent discontinuation of $P2Y_{12}$ inhibitors, has likely further reduced the rate of discontinuation and the effect of bleeding events leading to discontinuation.

There are several limitations to this study. While we have identified the prescribing intention from the hospital, we were not able to identify the quantity of medication issued from either hospital or primary care; therefore, we were unable to calculate precisely when an individual's prescription would have finished if taken according to instruction. In the WLGP data set, we noted that prescriptions were usually issued every month, but occasionally repeated every 2 months. Within a 3-month period, if no prescription had been issued, it was possible to assume that either a 1- or 2-month supply made in the previous quarter had been exhausted. Discontinuation was deemed to have occurred when there was a 3-month period without a $P2Y_{12}$ antagonist prescribed. Using this method, we were able to detect periods where we had greater certainty that an individual's prescription was likely to have finished, but we lacked the precision for identification of shorter periods of discontinuation.

As with any observational studies, we cannot determine whether the association between clopidogrel discontinuation and adverse outcomes was causal or may have been confounded by the influence of unrecorded comorbidities, including unrecorded bleeding events, the underutilization of other prognostically relevant medicines, or new undocumented behaviors. The prescribing and potential discontinuation from aspirin was not accounted for in this study. In the UK, aspirin is widely available without a prescription and is inexpensive; therefore, the assessment of aspirin discontinuation from the WLGP data set may have led to classifications of periods of discontinuation when a patient may have self-medicated.

It was not possible to identify the cause of discontinuation in this study. While the recording of prescriptions issued from the WLGP data set is robust, currently it is not possible to identify the dispensing of those prescriptions. Access to prescription dispensing records in addition to the prescribing records from the WLGP data set would have improved the sensitivity of capturing periods "off treatment" and the association between nonadherence as well as discontinuation and adverse outcomes. Furthermore, it is not possible to identify whether patients took the medication as intended, as is the case in most clinical studies. Therefore, this study does not confirm whether compliance with medication and periods of discontinuation could be attributed to either intentional or unintentional patient noncompliance or intentional prescriber discontinuation. It is possible that patients recorded as having discontinued clopidogrel received prescriptions either privately or from outpatient hospital appointments, although rare in Wales, neither of which would have been captured in this study. However, this would likely further increase the true difference in the effect of discontinuation on adverse outcomes.

During the study period, international guidelines changed to preferentially recommending the use of the more-potent

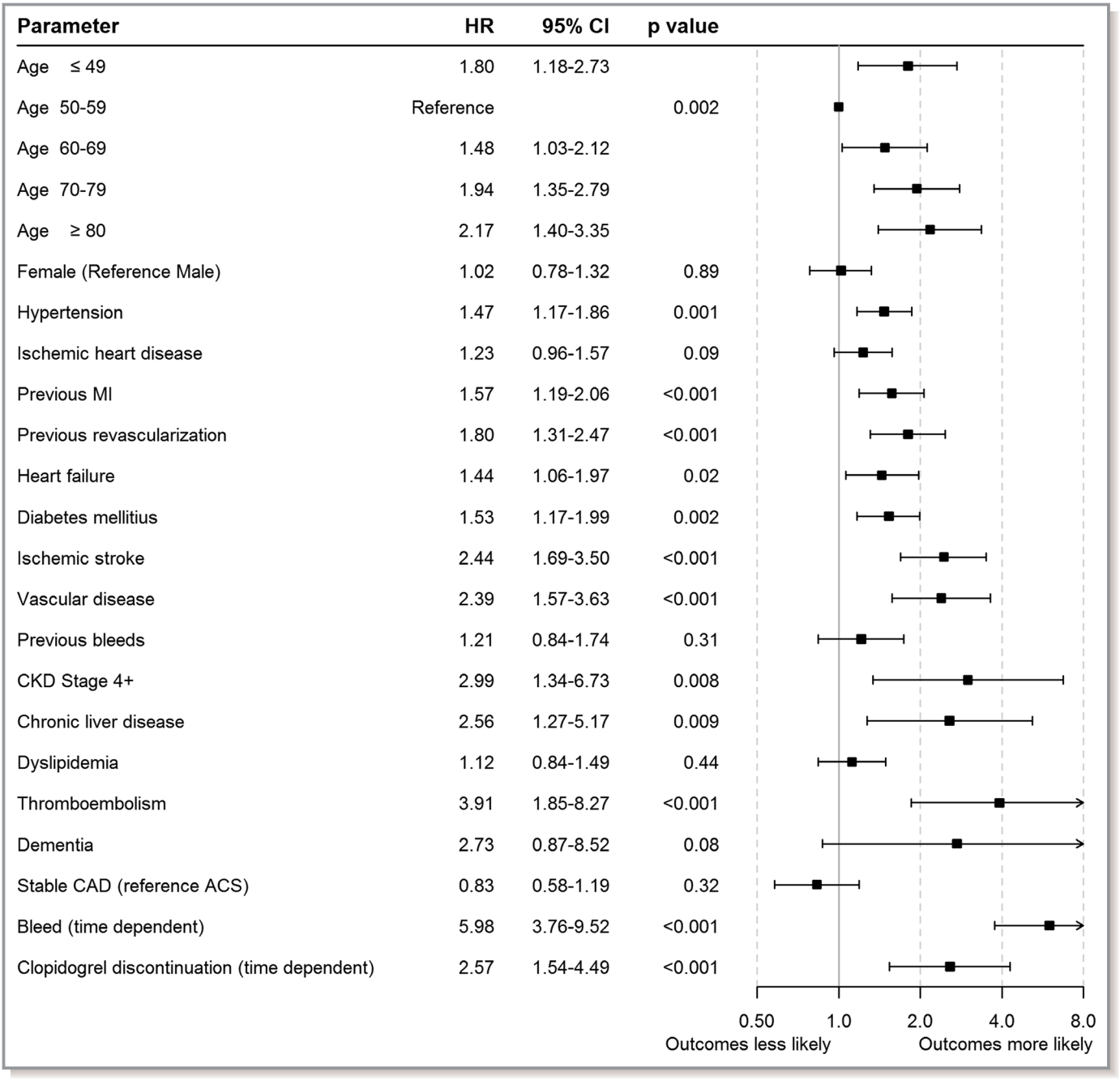

Figure 4. Characteristics associated with major adverse outcomes calculated using univariable Cox proportional hazards model. ACS indicates acute coronary disease; CAD, coronary artery disease; CKD, chronic kidney disease; HR, hazard ratio; MI, myocardial infarction.

P2Y$_{12}$ antagonists such as ticagrelor or prasugrel. However, attributable largely to financial restrictions within the Welsh health service, clopidogrel remained the mainstay of treatment for ACS during this time. Although this article addresses the use of clopidogrel post-PCI, we believe this article remains of critical value given that it illustrates the importance of knowing the schedule duration of any therapy before drawing conclusions on the impact of early discontinuation. Although not addressed in this study, one may expect the adverse impact of poor concordance with newer, more-effective therapies to be even greater.

Last, this observational study was conducted within a health service that is both accessible and free at the point of care, including the free provision of medication. This should be born in mind when comparing the results of this study with those systems where access to health care and affordability may influence therapy and outcomes at a population level.

Table 3. Multivariable Cox Proportional Hazard Model of Characteristics Associated With Adverse Clinical Outcomes*

Covariate	HR	Lower CI	Upper CI	*P* Value
Age decile, y				0.019
≤49	1.94	1.27	2.96	
50 to 59	Reference			
60 to 69	1.36	0.95	1.94	
70 to 79	1.57	1.09	2.29	
≥80	1.72	1.10	2.68	
Hypertension	1.30	1.02	1.66	0.03
Chronic kidney disease stage 4+	2.30	1.01	5.22	0.048
Previous revascularization	1.47	1.06	2.03	0.021
Previous ischemic stroke	1.96	1.34	2.86	<0.001
Previous thromboembolism	3.18	1.48	6.83	0.003
Time-dependent variable of clopidogrel discontinuation and/or bleed				<0.001
(1) Discontinuation only	1.82	1.01	3.30	
(2) Bleed only	5.30	3.14	8.94	
(3) Discontinuation and bleed	9.34	3.39	25.70	

HR indicates hazard ratio.
*The following variables were included in the mutually adjusted model: age; sex; presenting clinical syndrome; hypertension; previous coronary revascularization; previous bleeding events; ischemic stroke; heart failure; vascular disease; thromboembolism; diabetes mellitus; chronic kidney disease stage 4+; chronic liver disease, dyslipidemia; dementia; and time-dependent variables or clopidogrel discontinuation, bleeding, and both discontinuation and bleeding.

Conclusion

In conclusion, this study has demonstrated that identifying the intended duration of P2Y$_{12}$ antagonist therapy on discharge following a PCI is essential for determination of the correct rate of premature discontinuation in real-world outcome studies. The rate of discontinuation was reassuringly low in this patient group and much lower than anticipated in previous studies. While this is reassuring from the population level, at an individual level, discontinuation of P2Y$_{12}$ antagonist therapy earlier than the intended duration is associated with an increased rate of adverse events. Our data emphasize the importance of improving processes to ensure optimal concordance with evidence-based preventative therapy post-PCI.

Acknowledgments

This study makes use of anonymized data held in the Secure Anonymised Information Linkage (SAIL) Databank. We acknowledge all the data providers who make anonymized data available for research. This work uses data provided by patients and collected by the NHS as part of their care and support. This study was designed and led by Harris, Gravenor and Halcox. We thank the Consultant Cardiologist group at Morriston hospital for providing access to their cardiac intervention database; Swansea Bay University Health Board Research and Development department and Pharmacy department for supporting the first author, Mr John Fitzgerald for his IT expertise, and Mr Douglas Neil for expertise with graphics. This work was supported by Health Data Research UK, which receives its funding from Health Data Research United Kingdom Ltd (NIWA1) funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation (BHF), and the Wellcome Trust.

Sources of Funding

This study was funded by Swansea Bay University Health Board Research and Development Department.

Disclosures

None.

References

1. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, Angiolillo DJ, Hod H, Montalescot G, Miller DL, Jakubowski JA, Cairns R, Murphy SA, McCabe CH, Antman EM, Braunwald E; PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation*. 2007;116:2923–2932.
2. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.
4. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC. 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:e123–e155.
5. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, 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;39:213–260.
6. Cruden NL, Din JN, Janssen C, Smith R, Hilton JD, Klinke WP, Carere RG, Robinson SD, Siega AD. Delay in filling first clopidogrel prescription after coronary stenting is associated with an increased risk of death and myocardial

infarction. *J Am Heart Assoc*. 2014;3:e000669. DOI: 10.1161/JAHA.113.000669.

7. Ho PM, Tsai TT, Maddox TM, Powers JD, Carroll NM, Jackevicius C, Go AS, Margolis KL, DeFor TA, Rumsfeld JS, Magid DJ. Delays in filling clopidogrel prescription after hospital discharge and adverse outcomes after drug-eluting stent implantation: implications for transitions of care. *Circ Cardiovasc Qual Outcomes*. 2010;3:261–266.
8. Boggon R, van Staa TP, Timmis A, Hemingway H, Ray KK, Begg A, Emmas C, Fox KA. Clopidogrel discontinuation after acute coronary syndromes: frequency, predictors and associations with death and myocardial infarction—a hospital registry-primary care linked cohort (MINAP-GPRD). *Eur Heart J*. 2011;32:2376–2386.
9. Thim T, Johansen MB, Chisholm GE, Schmidt M, Kaltoft A, Sørensen HT, Thuesen L, Kristensen SD, Bøtker HE, Krusell LR, Lassen JF, Thayssen P, Jensen LO, Tilsted HH, Maeng M. Clopidogrel discontinuation within the first year after coronary drug-eluting stent implantation: an observational study. *BMC Cardiovasc Disord*. 2014;14:100.
10. Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, Krumholz HM, Cohen DJ. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113:2803–2809.
11. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126–2130.
12. Jeremias A, Sylvia B, Bridges J, Kirtane AJ, Bigelow B, Pinto DS, Ho KK, Cohen DJ, Garcia LA, Cutlip DE, Carrozza JP. Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation*. 2004;109:1930–1932.
13. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007;297:159–168.
14. Mazlan-Kepli W, Dawson J, Berry C, Walters M. Cessation of dual antiplatelet therapy and cardiovascular events following acute coronary syndrome. *Heart*. 2019;105:67–74.
15. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet*. 2013;382:1714–1722.
16. Lyons RA, Jones KH, John G, Brooks CJ, Verplancke JP, Ford DV, Brown G, Leake K. The SAIL Databank: linking multiple health and social care datasets. *BMC Med Inform Decis Mak*. 2009;9:3.
17. Ford DV, Jones KH, Verplancke JP, Lyons RA, John G, Brown G, Brooks CJ, Thompson S, Bodger O, Couch T, Leake K. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res*. 2009;9:157.
18. SAIL Databank. Primary care GP dataset. Available at: https://saildatabank.com/saildata/sail-datasets/primary-care-gp-dataset/. Accessed October 11, 2018.
19. Welsh Demographic Services. Available at: http://www.wales.nhs.uk/nwis/page/52552. Accessed October 11, 2018.
20. Stats Wales. Available at: https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation/Archive/WIMD-2011. Accessed October 11, 2018.
21. Wiederkehr D, Ogbonnaya A, Casciano R, Makenbaeva D, Mozaffari E, Corbelli J. Clinical impact of early clopidogrel discontinuation following acute myocardial infarction hospitalization or stent implantation: analysis in a nationally representative managed-care population. *Curr Med Res Opin*. 2009;25:2327–2334.
22. Hansen ML. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogre in patients with atrial fibrillation. *Arch Intern Med*. 2010;170:1433–1441.
23. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, French J, Held C, Horrow J, Husted S, Lopez-Sendon J, Lassila R, Mahaffey KW, Storey RF, Harrington RA, Wallentin L. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J*. 2011;32:2933–2944.
24. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, Mahaffey KW, Califf RM, Harrington RA. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol*. 2005;96:1200–1206.

SUPPLEMENTAL MATERIAL

Table S1. *ICD-10* Codes for major bleeding events.

MAJOR BLEEDING EVENTS

Major bleeding events were classified as gastrointestinal bleeds, intracranial bleeds, urinary tract bleeds and airway bleeds resulting in admission to hospital.

Bleeding event	**Code**	**Description**
Intracranial hemorrhage	I608	Other subarachnoid hemorrhage
Intracranial hemorrhage	I602	Subarachnoid hemorrhage from anterior communicating artery
Intracranial hemorrhage	I604	Subarachnoid hemorrhage from basilar artery
Intracranial hemorrhage	I600	Subarachnoid hemorrhage from carotid siphon and bifurcation
Intracranial hemorrhage	I607	Subarachnoid hemorrhage from intracranial artery unspecified
Intracranial hemorrhage	I601	Subarachnoid hemorrhage from middle cerebral artery
Intracranial hemorrhage	I606	Subarachnoid hemorrhage from other intracranial arteries
Intracranial hemorrhage	I603	Subarachnoid hemorrhage from posterior communicating artery
Intracranial hemorrhage	I605	Subarachnoid hemorrhage from vertebral artery
Intracranial hemorrhage	I609	Subarachnoid hemorrhage unspecified
Intracranial hemorrhage	I629	Intracranial hemorrhage (non-traumatic) unspecified
Intracranial hemorrhage	I613	Intracerebral hemorrhage in brain stem
Intracranial hemorrhage	I614	Intracerebral hemorrhage in cerebellum
Intracranial hemorrhage	I611	Intracerebral hemorrhage in hemisphere cortical
Intracranial hemorrhage	I610	Intracerebral hemorrhage in hemisphere subcortical
Intracranial hemorrhage	I612	Intracerebral hemorrhage in hemisphere unspecified
Intracranial hemorrhage	I615	Intracerebral hemorrhage intraventricular
Intracranial hemorrhage	I616	Intracerebral hemorrhage multiple localized
Intracranial hemorrhage	I619	Intracerebral hemorrhage unspecified

Intracranial hemorrhage	I618	Other intracerebral hemorrhage
Intracranial hemorrhage	I691	Sequelae of intracerebral hemorrhage
Intracranial hemorrhage	I692	Sequelae of other non-traumatic intracranial hemorrhage
Intracranial hemorrhage	S064	Epidural hemorrhage
Intracranial hemorrhage	S065	Traumatic subdural hemorrhage
Intracranial hemorrhage	S066	Traumatic subarachnoid hemorrhage
Gastrointestinal hemorrhage	K250	Gastric ulcer acute with hemorrhage
Gastrointestinal hemorrhage	K254	Gastric ulcer chronic or unspecified with hemorrhage
Gastrointestinal hemorrhage	K260	Duodenal ulcer acute with hemorrhage
Gastrointestinal hemorrhage	K264	Duodenal ulcer chronic or unspecified with hemorrhage
Gastrointestinal hemorrhage	K270	Peptic ulcer acute with hemorrhage
Gastrointestinal hemorrhage	K280	Gastrojejunal ulcer acute with hemorrhage
Gastrointestinal hemorrhage	K920	Hematemesis
Gastrointestinal hemorrhage	K921	Melaena
Gastrointestinal hemorrhage	K922	Gastrointestinal hemorrhage unspecified
Airway hemorrhage	J942	Hemothorax
Airway hemorrhage	R042	Hemoptysis
Airway hemorrhage	R048	Hemorrhage from other sites in respiratory passages
Urinary tract hemorrhage	R31X	Unspecified hematuria

Urinary tract hemorrhage	N028	Recurrent and persistent hematuria
Urinary tract hemorrhage	N029	Recurrent and persistent hematuria unspecified

Table S2. *ICD10* codes for major adverse outcomes.

PRIMARY END POINT CODES

The primary end point was death of any cause, subsequent readmission to hospital for an MI, unstable angina, acute ischemic heart disease, ischemic stroke or transient ischemic attack (TIA) or readmission after 30 days from the index discharge date for either CABG, or recurrent coronary PCI.

Diagnosis	**Code**	**Description of code**
MI	I219	Acute myocardial infarction unspecified
MI	I214	Acute subendocardial myocardial infarction
MI	I210	Acute transmural myocardial infarction of anterior wall
MI	I211	Acute transmural myocardial infarction of inferior wall
MI	I212	Acute transmural myocardial infarction of other sites
MI	I213	Acute transmural myocardial infarction of unspecified site
MI	I220	Subsequent myocardial infarction of anterior wall
MI	I221	Subsequent myocardial infarction of inferior wall
MI	I228	Subsequent myocardial infarction of other sites
Acute ischemic heart disease	I249	Acute ischemic heart disease
Unstable angina	I200	Unstable angina
Ischemic Stroke / TIA	I661	Occlusion and stenosis of anterior cerebral artery
Ischemic Stroke / TIA	I663	Occlusion and stenosis of cerebellar arteries
Ischemic Stroke / TIA	I660	Occlusion and stenosis of middle cerebral artery

Ischemic Stroke / TIA	I664	Occlusion and stenosis of multiple and bilateral cerebral arteries
Ischemic Stroke / TIA	I668	Occlusion and stenosis of other cerebral artery
Ischemic Stroke / TIA	I662	Occlusion and stenosis of posterior cerebral artery
Ischemic Stroke / TIA	I669	Occlusion and stenosis of unspecified cerebral artery
Ischemic Stroke / TIA	I64X	Stroke not specified as hemorrhage or infarction
Ischemic Stroke / TIA	I651	Occlusion and stenosis of basilar artery
Ischemic Stroke / TIA	I652	Occlusion and stenosis of carotid artery
Ischemic Stroke / TIA	I653	Occlusion and stenosis of multiple and bilateral pre cerebral arts
Ischemic Stroke / TIA	I658	Occlusion and stenosis of other precerebral artery
Ischemic Stroke / TIA	I659	Occlusion and stenosis of unspecified precerebral artery
Ischemic Stroke / TIA	I650	Occlusion and stenosis of vertebral artery
Ischemic Stroke / TIA	G458	Other transient cerebral ischemic attacks and related syndrome
Ischemic Stroke / TIA	G459	Transient cerebral ischemic attack unspecified
Ischemic Stroke / TIA	I636	Cerebral infarct due cerebral venous thrombosis nonpyogenic
Ischemic Stroke / TIA	I632	Cerebral infarct due unspecifed occlusion or stenos precerebral arteries
Ischemic Stroke / TIA	I630	Cerebral infarct due to thrombosis of precerebral arteries

Ischemic Stroke / TIA	I634	Cerebral infarction due to embolism of cerebral arteries
Ischemic Stroke / TIA	I631	Cerebral infarction due to embolism of precerebral arteries
Ischemic Stroke / TIA	I633	Cerebral infarction due to thrombosis of cerebral arteries
Ischemic Stroke / TIA	I639	Cerebral infarction unspecified
Ischemic Stroke / TIA	I635	Cerebral infarct due unspecified occlusion or stenos cerebral arts
Ischemic Stroke / TIA	I638	Other cerebral infarction
Ischemic Stroke / TIA	I693	Sequelae of cerebral infarction
Ischemic Stroke / TIA	I694	Sequelae of stroke not specified as hemorrhage or infarction

Table S3. OPCS codes (versions 4.5 to 4.8) for major adverse outcomes.

Procedure	Code	Description
CABG	K401	Saphenous vein graft replacement of one coronary artery
CABG	K402	Saphenous vein graft replacement of two coronary arteries
CABG	K403	Saphenous vein graft replacement of three coronary arteries
CABG	K404	Saphenous vein graft replacement of four or more coronary arteries
CABG	K408	Other specified saphenous vein graft replacement of coronary artery
CABG	K409	Unspecified saphenous vein graft replacement of coronary artery
CABG	K411	Autograft replacement of one coronary artery
CABG	K412	Autograft replacement of two coronary arteries
CABG	K413	Autograft replacement of three coronary arteries
CABG	K414	Autograft replacement of four or more coronary arteries
CABG	K418	Other specified other autograft replacement of coronary artery
CABG	K419	Unspecified other autograft replacement of coronary artery
CABG	K421	Allograft replacement of one coronary artery
CABG	K422	Allograft replacement of two coronary arteries
CABG	K423	Allograft replacement of three coronary arteries
CABG	K424	Allograft replacement of four coronary arteries
CABG	K428	Other specified allograft replacement of coronary artery
CABG	K431	Prosthetic replacement of one coronary artery
CABG	K442	Revision of replacement of coronary artery
CABG	K451	Double anastomosis of mammary arteries to coronary arteries
CABG	K453	Anastomosis of mammary artery to left anterior descending coronary artery

CABG	K454	Anastomosis of mammary artery to coronary artery NEC
CABG	K471	Endarterectomy of coronary artery
Coronary PCI	K49	Transluminal balloon angioplasty of coronary artery
Coronary PCI	K491	Percutaneous transluminal balloon angioplasty of one coronary artery
Coronary PCI	K492	Percutaneous transluminal balloon angioplasty of multiple coronary arteries
Coronary PCI	K493	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery
Coronary PCI	K494	Percutaneous transluminal cutting balloon angioplasty of coronary artery
Coronary PCI	K498	Other specified transluminal balloon angioplasty of coronary artery
Coronary PCI	K499	Unspecified transluminal balloon angioplasty of coronary artery
Coronary PCI	K503	Percutaneous transluminal injection of therapeutic substance into coronary artery
Coronary PCI	K504	Percutaneous transluminal atherectomy of coronary artery
Coronary PCI	K75	Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
Coronary PCI	K751	Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery
Coronary PCI	K752	Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery
Coronary PCI	K753	Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery
Coronary PCI	K754	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC
Coronary PCI	K758	Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
Coronary PCI	K759	Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery

Coronary PCI	Y141	Insertion of expanding covered metal stent into organ NOC
Coronary PCI	Y142	Insertion of expanding metal stent into organ NOC
Coronary PCI	Y143	Insertion of metal stent into organ NOC

Table S4. Demographics and medical history of patients included and excluded in the analysis*

N=3,459

	Included	Excluded	P
	n=2,090	N = 1,369	
Percentage of overall	60.4	39.6	
Mean age, (SD)	63.2 (11.8)	65.9 (12.2)	<0.001
Characteristic, *n* (%)			
Male	1537 (73.5)	942 (68.8)	0.003
Obese	511 (24.4)	345 (25.2)	0.62
Smoker	784 (37.5)	496 (36.2)	0.45
Deprivation index			0.12
1	337 (16.4)	250 (18.2)	
2	411 (20.0)	260 (18.9)	
3	489 (23.9)	337 (24.6)	
4	415 (20.2)	229 (16.7)	
5	398 (19.4)	264 (19.3)	
Unknown	40 (1.9)	29 (2.1)	
Prior medical history, *n*(%)			
Hypertension	851 (40.7)	608 (44.4)	0.03
Ischemic Heart Disease	612 (29.3)	525 (38.3)	<0.001
Myocardial Infarction	351 (16.8)	280 (20.5)	0.006
Coronary revascularization	203 (9.7)	209 (15.3)	<0.001
Ischemic Stroke	115 (5.5)	97 (7.1)	0.06

Heart Failure	259 (12.4)	237 (17.3)	<0.001
Vascular Disease	81 (3.9)	81 (5.9)	<0.001
Thromboembolism	14(0.7)	17 (0.7)	0.36
Diabetes	382 (18.3)	297 (21.7)	0.01
CKD Stage 4+	16 (0.8)	16 (1.2)	0.22
Chronic liver Disease	24 (1.1)	13 (0.9)	0.58
Dyslipidemia	380 (18.2)	288 (21.0)	0.04
Dementia	9 (0.4)	9 (0.7)	0.36
Prior bleeding events	205 (9.8)	164 (12.0)	0.04
Aspirin	711 (34.0)	610 (44.6)	<0.001
$P2Y_{12}$ antagonist	230 (11.0)	265 (19.6)	<0.001
Statins	924 (44.2)	733 (53.5)	<0.001
Clinical syndrome, *n* (%)			<0.001
ACS	1808 (86.5)	1030 (75.2)	
Stable	282 (13.5)	339 (24.8)	

*Comparisons made here are between those meeting the inclusion criteria and prescribed clopidogrel for one year (n=2090) and those not meeting the inclusion criteria but had linked data available before the index admission, survived at least one day after discharge but did not have AF or received CABG during the index admission. Comparisons are made using the χ^2 test for categorical variables and the independent T test for continuous variables

Table S5. Multivariable Cox proportional hazard model of characteristics associated with the independent adverse outcomes of MI, ischemic stroke, coronary revascularization or death.

INDIVIDUAL OUTCOMES OF MI, ISCHEMIC STROKE, CORONARY REVASCULARIZATION AND DEATH

The primary outcome measure (the composite of MI, ischemic stroke, coronary revascularization 30 days' post discharge and death) occurred in 286 (13.7%) of the cohort. The number of patients having an MI during follow up was 167 (8.0%), ischemic stroke 31 (1.5%), coronary revascularization 100 (4.8%) and death 46 (2.2%). For completeness we modelled baseline characteristics and the time dependent effects of discontinuation and /or bleeding against these individual outcome measures in a multivariable Cox-proportional hazard model (table S5). In these models we found no significant association between discontinuation and/or bleeding on coronary revascularization. We also calculated the event rate per 100 patient years (table S6). In the case of MI, revascularization and stroke there were no patients who had both clopidogrel discontinuation and bleeding events prior to the adverse outcome.

	Adverse outcome			
	MI	**Ischemic Stroke**	**Revascularization**	**Death**
	HR (95% CI), p value	HR (95% CI), p value	HR (95% CI), p value	HR (95% CI), p value
Covariate		-	-	-
Age decile		-	-	-
≤49	2.44 (1.42-4.2),	-	-	-
50- 59	Reference, p=0.21	-	-	-
60-69	1.71 (1.05-2.78)	-	-	-
70-79	1.96 (1.19-3.22)	-	-	-
≥80	1.99 (1.08-3.67)	-	-	-
Hypertension	-	2.29 (1.06-4.97), p=0.035	-	-
Liver disease	2.74 (1.21-6.22), p=0.016	-	-	-
CKD stage 4+	-	-	6.43 (2.35-17.45), <0.001	-

Previous revascularization	2.42 (1.64-3.59), p<0.001	-	1.83 (1.09-3.07), p=0.02	-
Previous ischemic stroke	-	5.71 (2.58-12.66), P<0.001	2.21 (1.19-4.09), p=0.01	-
Previous thromboembolism	-	-	3.33 (1.03-10.73), p=0.04	-
Heart failure	-	4.03 (1.95-8.30), P<0.001	-	-
Clinical Syndrome		-	-	-
Stable CAD	Reference			
ACS	2.09 (1.20-3.66), p=0.009			
Previous Thromboembolism	4.68 (2.15-10.19), P<0.001	-	-	-
Time dependent variable of discontinuation and/or bleed				
No discontinuation and no bleed	Reference, p<0.001	Reference, p<0.001	-	Reference, p<0.001
(1) Discontinuation only	1.76 (0.76-4.05)	-	-	6.00 (2.44-14.76)
(2) Bleed only	5.78 (2.88-11.60)	9.78 (3.30-28.95)	-	5.94 (1.79-19.72)
(3) Discontinuation and bleed	-	-	-	61.47 (21.18-178.39)

*The following variables were included in the model: age; gender; presenting clinical syndrome; hypertension; prior coronary revascularization; prior bleeding events; ischemic stroke; heart failure; vascular disease; thromboembolism; diabetes; CKD stage 4+; chronic liver disease, dyslipidemia; dementia and time dependent variables or clopidogrel discontinuation, bleeding and both discontinuation and bleeding. Only variables associated with one or more outcomes are presented. The final variables were selected in a multivariable co model by minimizing the Akaike information criterion.

Table S6. Individual event rate* for Stroke, MI, coronary revascularization and death according to presence of clopidogrel discontinuation and/or bleed.

	MI	Ischemic stroke	Coronary revascularization	Death
No discontinuation and no bleed	5.34	0.08	3.02	1.22
Discontinuation only	17.43	0.07	12.43	6.06
Bleed only	18.75	10.5	8.38	6.06
Discontinuation and bleed	-	-	-	64.6

*Event rate calculated in events per 100 patient years.

Table S7. Multivariable Cox proportional hazard model of characteristics associated with bleeding events during follow up.

Covariate	HR	CI lower	CI upper	p
Prior bleeding	2.82	1.67	4.76	<0.001
CKD stage 4+	6.15	2.22	17.08	<0.001
Chronic liver disease	3.62	1.14	11.51	<0.001

*The following variables were included in the model: age; gender; presenting clinical syndrome; hypertension; prior coronary revascularization; prior bleeding events; ischemic stroke; heart failure; vascular disease; thromboembolism; diabetes; CKD stage 4+; chronic liver disease and dyslipidemia.