Early Discontinuation of P2Y₁₂ Antagonists and Adverse Clinical Events Post–Percutaneous Coronary Intervention: A Hospital and Primary Care Linked Cohort

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**Background**—Early discontinuation of P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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...
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 P2Y12 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 P2Y12 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.

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. Date of death, where relevant, was identified from the ADDE (Annual District Death Extract) 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.

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 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 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 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 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 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 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.

P2Y12 Antagonist Prescribing and Discontinuation

Prescribing of P2Y12 antagonists post discharge 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 P2Y12 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 P2Y12 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 P2Y12 therapy for 1 year and all other regimes were compared using the χ² 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, P2Y12 inhibitors, or statins (further
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
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Table 1. Demographics and Medical History of Patients by Discharge Prescribing Intention of P2Y₁₂ Inhibitors (N=2770)

| Characteristic, n (%) | Clopidogrel for 1 year | Other Regimens | P Value |
|-----------------------|------------------------|----------------|---------|
| Percentage of total group | 75.5% | 24.5% |         |
| Mean age, y (SD) | 63.2 (11.8) | 66.6 (12.3) | <0.001 |
| 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 |
| P2Y₁₂ antagonist | 230 (11.0) | 107 (15.8) | 0.001 |
| Statins | 924 (44.2) | 347 (51.0) | 0.002 |
| Clinical syndrome, n (%) | | | |
| 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, 1.41–11.51) 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 P2Y₁₂ 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

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explanations for this difference, including greater contempor-ary recognition of the importance of continued use of P2Y12 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 P2Y12 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 2. Discontinuation of clopidogrel post-Percutaneous Coronary Intervention.
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.

![Graph showing characteristics associated with clopidogrel discontinuation](image)

**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.
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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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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

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.
P2Y₁₂ 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.

### 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.

| Parameter                                | HR   | 95% CI     | p value |
|------------------------------------------|------|------------|---------|
| Age ≤ 49                                 | 1.80 | 1.18-2.73  |         |
| Age 50-59                                 |      | Reference  | 0.002   |
| Age 60-69                                 | 1.48 | 1.03-2.12  |         |
| Age 70-79                                 | 1.94 | 1.35-2.79  |         |
| Age ≥ 80                                  | 2.17 | 1.40-3.35  |         |
| Female (Reference Male)                   | 1.02 | 0.78-1.32  | 0.89    |
| Hypertension                             | 1.47 | 1.17-1.86  | 0.001   |
| Ischemic heart disease                    | 1.23 | 0.96-1.57  | 0.09    |
| Previous MI                              | 1.57 | 1.19-2.06  | <0.001  |
| Previous revascularization               | 1.80 | 1.31-2.47  | <0.001  |
| Heart failure                            | 1.44 | 1.06-1.97  | 0.02    |
| Diabetes mellitus                        | 1.53 | 1.17-1.99  | 0.002   |
| Ischemic stroke                          | 2.44 | 1.69-3.50  | <0.001  |
| Vascular disease                         | 2.39 | 1.57-3.63  | <0.001  |
| Previous bleeds                          | 1.21 | 0.84-1.74  | 0.31    |
| CKD Stage 4+                              | 2.99 | 1.34-6.73  | 0.008   |
| Chronic liver disease                    | 2.56 | 1.27-5.17  | 0.009   |
| Dyslipidemia                             | 1.12 | 0.84-1.49  | 0.44    |
| Thromboembolism                          | 3.91 | 1.85-8.27  | <0.001  |
| Dementia                                 | 2.73 | 0.87-8.52  | 0.08    |
| Stable CAD (reference ACS)               | 0.83 | 0.58-1.19  | 0.32    |
| Bleed (time dependent)                   | 5.98 | 3.76-9.52  | <0.001  |
| Clopidogrel discontinuation (time dependent) | 2.57 | 1.54-4.49  | <0.001  |

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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                            | 1.94 | 1.27     | 2.96     | 0.019   |
| ≤49                                      |      |          |          |         |
| 50 to 59                                  |      |          |          |         |
| 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 P2Y12 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 P2Y12 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.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL
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                                       |
| Condition                                      | Code | Description                                      |
|-----------------------------------------------|------|-------------------------------------------------|
| 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                           |
| Location                  | Code | Code Description                                      |
|---------------------------|------|-------------------------------------------------------|
| 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 |
| Condition                        | Code | Description                                           |
|---------------------------------|------|-------------------------------------------------------|
| Ischemic Stroke / TIA           | I64  | Occlusion and stenosis of multiple and bilateral cerebral arteries |
| Ischemic Stroke / TIA           | I664 | Occlusion and stenosis of other cerebral artery        |
| Ischemic Stroke / TIA           | I668 | Occlusion and stenosis of posterior cerebral artery    |
| Ischemic Stroke / TIA           | I662 | Occlusion and stenosis of unspecified 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 precerebral arteries |
| 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 unspecified 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 |
| Procedure                                              | Code  | Description                                                                 |
|--------------------------------------------------------|-------|-----------------------------------------------------------------------------|
| Anastomosis of mammary artery to coronary artery NEC   | K454  | CABG                                                                        |
| Endarterectomy of coronary artery                      | K471  | CABG                                                                        |
| Transluminal balloon angioplasty of coronary artery     | K49   | Coronary PCI                                                                |
| Percutaneous transluminal balloon angioplasty of one coronary artery | K491  | Coronary PCI                                                                |
| Percutaneous transluminal balloon angioplasty of multiple coronary arteries | K492  | Coronary PCI                                                                |
| Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery | K493  | Coronary PCI                                                                |
| Percutaneous transluminal cutting balloon angioplasty of coronary artery | K494  | Coronary PCI                                                                |
| Other specified transluminal balloon angioplasty of coronary artery | K498  | Coronary PCI                                                                |
| Unspecified transluminal balloon angioplasty of coronary artery | K499  | Coronary PCI                                                                |
| Percutaneous transluminal injection of therapeutic substance into coronary artery | K503  | Coronary PCI                                                                |
| Percutaneous transluminal atherectomy of coronary artery | K504  | Coronary PCI                                                                |
| Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery | K75   | Coronary PCI                                                                |
| Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery | K751  | Coronary PCI                                                                |
| Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery | K752  | Coronary PCI                                                                |
| Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery | K753  | Coronary PCI                                                                |
| Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC | K754  | Coronary PCI                                                                |
| Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery | K758  | Coronary PCI                                                                |
| Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery | K759  | Coronary PCI                                                                |
| Procedure                          | Code | Description                                           |
|-----------------------------------|------|-------------------------------------------------------|
| Coronary PCI Insertion            | Y141 | Insertion of expanding covered metal stent into organ NOC |
| Coronary PCI Insertion            | Y142 | Insertion of expanding metal stent into organ NOC     |
| Coronary PCI Insertion            | 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

| Characteristic | Included n=2,090 | Excluded N = 1,369 | P    |
|----------------|------------------|--------------------|------|
| Percentage of overall | 60.4 | 39.6 |       |
| Mean age, (SD) | 63.2 (11.8) | 65.9 (12.2) | <0.001 |
| 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 |
| Condition                     | Included (n, %) | Excluded (n, %) | p-value |
|------------------------------|-----------------|-----------------|---------|
| 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    |
| 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    |

| Medication                  | Included (n, %) | Excluded (n, %) | p-value |
|------------------------------|-----------------|-----------------|---------|
| Aspirin                      | 711 (34.0)      | 610 (44.6)      | <0.001  |
| P2Y12 antagonist             | 230 (11.0)      | 265 (19.6)      | <0.001  |
| Statins                      | 924 (44.2)      | 733 (53.5)      | <0.001  |

*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 $\chi^2$ 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.

| Covariate        | MI HR (95% CI), p value | Ischemic Stroke HR (95% CI), p value | Revascularization HR (95% CI), p value | Death HR (95% CI), p value |
|------------------|-------------------------|-------------------------------------|---------------------------------------|---------------------------|
| 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             | -                         |
| Clinical Syndrome                        | Reference | p<0.001 | p<0.001 | p<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

| Reference, 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 of 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.