# Bleeding risk in patients prescribed dual antiplatelet therapy and triple therapy after coronary interventions: the ADAPTT retrospective population-based cohort studies

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# Scientific summary

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# Scientific summary

## Background

Dual antiplatelet therapy (DAPT), a combination of aspirin and clopidogrel, prasugrel or ticagrelor, is recommended for up to 12 months for secondary prevention of ischaemic events (heart attack and stroke) among people undergoing coronary interventions [coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI)] and people with acute coronary syndrome (ACS) who are medically managed. Randomised controlled trials (RCTs) in these populations suggest that DAPT increases the risk of bleeding compared with aspirin monotherapy, and that more potent DAPT (with prasugrel and ticagrelor) increases the risk of bleeding compared with less potent DAPT (with clopidogrel). Adding an anticoagulant to DAPT (e.g. for the management of atrial fibrillation), known as triple therapy (TT), increases risk further. 'Real-world' bleeding among populations exposed to different DAPT and TT regimens has not been previously quantified. The economic impact of bleeding events is poorly characterised, in particular for minor bleeding, as is their impact on health-related quality of life (HRQoL).

## Objectives

1. Estimate rates of major and minor bleeding events with different DAPT (and TT) exposures among CABG, PCI and conservatively treated ACS patients.
2. Estimate hazard ratios (HRs) for bleeding for different antiplatelet regimens: for the PCI cohort, we compared aspirin and clopidogrel (AC) with aspirin and prasugrel (AP) or aspirin and ticagrelor (AT); for the CABG and ACS no-procedure cohorts, we compared aspirin with AC.
3. Review the literature to estimate the deterioration in utility (quality-adjusted life-years) of patients who have minor or major bleeding events.
4. Revise/extend existing economic models of the cost-effectiveness of different DAPT regimens to include estimates of the incidence of minor and major bleeding events and associated impacts on utility in the general population.
5. Estimate the resources required and associated costs incurred of treating major and minor events of the alternative DAPT (TT) exposures in the three specified patient populations.
6. Understand patients' perspectives of DAPT, and the factors that influence responses to nuisance bleeding focusing on adherence and information-seeking (this objective was identified through the patient and public involvement work after the start of the ADAPTT study).

## Methods

### *Objectives 1 and 2*

We conducted a study to identify confounders systematically by performing a systematic review of RCTs and cohort studies; conducting semistructured interviews with six cardiac surgeons, six cardiologists and five general practitioners (GPs); and conducting a survey of 79 cardiologists and 31 cardiac surgeons. We used linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) data to assemble populations (CABG, PCI and conservatively managed ACS patients) eligible for three 'target trials'. Inclusion criteria for the target trial were as follows: ≥ 18 years of age, ≥ 1 year of data in CPRD before the index event, no prescription for DAPT or anticoagulants in the preceding 3 months and a prescription for aspirin or DAPT within 2 months of discharge after the index event. The primary outcome was any bleeding event (CPRD or HES data) up to 12 months after the index event. We described rates of bleeding among patients prescribed different DAPT regimens and TT. We estimated adjusted HRs for time to first bleed comparing DAPT with AC (reference) versus aspirin monotherapy for

CABG and conservatively managed ACS patient, and, in the emergency PCI population, DAPT with prasugrel versus DAPT with clopidogrel for ST-elevation myocardial infarction (STEMI) patients only and DAPT with ticagrelor versus DAPT with clopidogrel for all the emergency PCI population.We prespecified five sensitivity analyses and conducted three: sensitivity analysis 1 – multiple imputation for eligible patients for whom we had no data to assign an intervention; sensitivity analysis 3 – restricted to patients at low risk of bleeding; and sensitivity analysis 4 – repeating primary outcome analysis without censoring of any CPRD or HES bleed events at transfer-out or last collection date. The transfer-out or last collection date reflect the date that a patient leaves the general practice or the date that the last capture from CPRD was made.

### *Objective 3*

A systematic review was conducted of primary research and decision-analytic modelling studies reporting utility decrements for bleeds related to DAPT through a search of MEDLINE, PubMed and references of included studies. A health elicitation study was undertaken, comprising 21 participants (PCI, CABG and conservatively managed ACS) who completed an elicitation exercise involving vignettes describing minor and major bleeds and the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L). Utility decrements were derived using linear regression, and were compared with existing estimates.

### *Objective 4*

No formal cost-effectiveness evaluation was undertaken.

### *Objective 5*

Data on health-care use were derived from the linked CPRD–HES data set. The total health-care costs associated with the different antiplatelet regimens in the three target trials were measured at 1, 2 and 3 years after the start of follow-up.We used inverse probability of treatment weighting to adjust for the same confounders identified for the main ADAPTT analysis. The total health-care costs at 1, 2 and 3 years of follow-up were estimated by fitting weighted generalised linear models with gamma distribution and log-link.

### *Objective 6*

Two focus groups were conducted with patients at the early stages of treatment (0–3 months, nine participants), and two with patients coming to the end of treatment (9–12 months, 12 participants), to explore their experiences with DAPT. Recordings were transcribed verbatim, anonymised and analysed using framework analysis.

## Research findings

### *Objectives 1 and 2*

#### Confounders study

A total of 70 potential confounders were identified by systematic review, clinician interviews and surveys; of these, 34 (49%) were classified as true confounders (factors that influence both the assigned intervention and the outcome), of which 31 (91%) were identified by systematic review and three (9%) by clinician interview, and 31 (91%) were confirmed by the survey. The clinician interviews identified hard-to-measure factors not identified in the review (drug potency, resistance to antiplatelet medication and clinician concerns about adherence). Data that would enable the characterisation of risk, including presentation risk and procedural risk factors, were unavailable for 17 of the 34 confounders (50%).

### The ADAPTT study

A proportion of eligible participants were excluded from each target trial because they could not be assigned an intervention at baseline (17%, 40% and 9% of the CABG, conservatively managed ACS and emergency PCI patients, respectively). The incidence of any bleeding was 5%, 10% and 9% in CABG patients, conservatively managed ACS patients and emergency PCI patients, respectively; the corresponding rates of minor bleeding were 4%, 7% and 7%, respectively. Compared with aspirin monotherapy, DAPT was associated with an increase in the hazards of any bleeding and of major adverse cardiovascular events (MACEs) among CABG [HR 1.72, 95% confidence interval (CI) 1.15 to 2.57, and HR 2.06, 95% CI 1.23 to 3.46, respectively] and conservatively managed ACS patients (HR 1.43, 95% CI 1.21 to 1.69, and HR 1.57, 95% CI 1.38 to 1.78, respectively). Among emergency PCI patients, compared with less potent DAPT (with clopidogrel), more potent DAPT with ticagrelor (ACS and STEMI patients only) or prasugrel (STEMI patients only) increased the hazard of bleeding (HR 1.47, 95% CI 1.19 to 1.82; HR 1.47, 95% CI 1.08 to 2.00; and HR 1.77, 95% CI 1.21 to 2.58, respectively), but there was no association with MACEs (HR 1.06, 95% CI 0.89 to 1.27; HR 1.21, 95% CI 0.94 to 1.56; and HR 1.10, 95% CI 0.80 to 1.51, respectively). Sensitivity analyses using multiple imputation to impute for the intervention assigned at baseline did not materially change these results. Non-adherence to the treatment assigned at baseline was generally higher in the CABG and conservatively-managed ACS target trials (affecting up to 46% and 44% of patients, respectively) than in the in emergency PCI (affecting up to 33% of patients).

### Triple therapy

The median duration of TT was 3.5 months. The incidence of any bleeding among patients prescribed TT was 18%. There was no difference in the incidence of any bleeding, or of major bleeding or minor bleeding, between patients on TT with warfarin and patients on TT with a non-vitamin K oral anticoagulant (NOAC). However, mortality from bleeding was higher among patients on TT with a NOAC than among patients on TT with warfarin (2% vs. 0%), as was the incidence of stroke (4% vs. 0%).

## *Objective 3*

Twelve eligible studies were included for review. Reported utility decrements ranged from −0.002 to −0.03 for minor bleeds and −0.007 to −0.05 for major bleeds. Data sources used to estimate the decrements lacked relevance to our population group, and few studies adequately reported details of their measurement and valuation approaches. Our patient health elicitation study elicited utility decrements that overlapped existing estimates, ranging from −0.000848 to −0.00828 for minor bleeds and from −0.0187 to −0.0621 for major bleeds. However, the magnitude of difference depended on the instrument (EQ-5D-5L or EQ-5D-3L), estimation method and valuation approach applied.

## *Objective 5*

The mean total health-care cost in the year prior to the index event was much higher for CABG patients (£13,601) than for conservatively managed ACS (£3528) or emergency PCI patients (£3625). For CABG patients, mean costs were similar between different antiplatelet regimens (£13,623 for aspirin monotherapy and £13,537 for DAPT with clopidogrel). For conservatively managed ACS, patients on DAPT with clopidogrel had a lower mean total health-care cost in the year prior to the index date than patients on aspirin monotherapy (£3317 vs. £3857, respectively). Among emergency PCI patients, those initiated on DAPT with clopidogrel had a higher mean total health-care cost in the year prior to the index event (£4492) than those initiated on DAPT with prasugrel (STEMI patients only) (£1660) or ticagrelor (£2829). Among the CABG population, there was no difference in mean cumulative health-care costs between initiation of DAPT with clopidogrel and initiation of aspirin monotherapy; the mean difference at 1, 2 and 3 years was £94 (95% CI −£555 to £763), £236 (95% CI −£831 to £1223) and £113 (95% CI −£1318 to £1102), respectively. Among the conservatively managed ACS population, the mean cumulative health-care costs were estimated to be slightly higher if all patients were treated with DAPT with clopidogrel than if all were treated with aspirin monotherapy; the mean difference at 1, 2 and 3 years was £610 (95% CI −£626 to £1516), £1118 (95% CI −£226 to £2206) and £1225 (95% CI −£426

to £2423), respectively, although there was considerable overlap between CIs. For emergency PCI patients, the estimated cumulative health-care costs were comparable under the different antiplatelet regimens among patients not receiving concurrent proton pump inhibitor (PPI) prescriptions, but were higher for patients receiving DAPT with ticagrelor than for patients receiving DAPT with clopidogrel. At 1 year, for example, the predicted mean difference in health-care costs if all patients received DAPT with ticagrelor rather than DAPT with clopidogrel was £72 (95% CI −£532 to £762) among those not receiving concurrent PPI therapy and £1145 (95% CI £269 to £2195) among those receiving concurrent PPI therapy. Among STEMI patients receiving concurrent PPI therapy, DAPT with prasugrel was associated with higher costs than DAPT with clopidogrel or DAPT with ticagrelor.

### *Objective 6*

Participants would adhere to DAPT when they believed that DAPT was important to ACS outcomes. Those who had experienced nuisance bleeding reported symptoms to be mild and manageable and did not report the bleed to their GP. Adherence was influenced by participants' and their families' understanding of the risks and benefits of DAPT, and their ability to manage symptoms. Factors influencing knowledge about DAPT included access to medication counselling; processing of and engaging with information communicated during medication counselling; and access to timely, relevant and expert information and advice after discharge from hospital.

## Conclusions

There is underascertainment of minor/nuisance bleeding in the CPRD, probably as a result of under-reporting of nuisance bleeding by patients to their GPs. In three retrospective population-based cohort studies emulating target trials, there was an increased risk of bleeding among patients receiving DAPT compared with those receiving aspirin monotherapy (CABG and conservatively managed ACS patients) and among patients receiving more potent DAPT than among those receiving less potent DAPT (emergency PCI patients), but not the expected decrease in MACEs. We identified several potential biases that may have influenced the results of the ADAPTT study as a result of imperfect emulation of the defined target trials: (1) selection bias – we excluded a subgroup of the eligible population because they could not be assigned an intervention; (2) confounding – we had no data for half of the confounders identified, including procedure-related characteristics and disease complexity, and evidence from clinician interviews and surveys that clinicians balance bleeding and ischaemic risk when prescribing DAPT to their patients; and (3) non-adherence to DAPT, which was substantial, and generally higher in the stronger antiplatelet treatment groups. Medication knowledge and understanding, and confidence in dealing with symptoms facilitate positive attitudes towards adherence to DAPT, but may be hindered by opportunities to access relevant, timely and appropriate medication counselling. Although we derived relevant utility decrements for the included population using a patient elicitation exercise, based on standardised definitions of minor and major bleeding events, using a validated HRQoL instrument and valued using general population tariffs, we could not conduct a formal cost-effectiveness analysis given the uncertainty around the estimates for bleeding. Nevertheless, the results using routinely collected data need to be carefully considered by clinicians and decision-makers, given that the increased risk of bleeding we observed with more potent DAPT was not offset by a reduced risk of cardiovascular events and that several recent large meta-analyses of RCTs have also failed to show a conclusive benefit of more potent antiplatelet therapy on cardiovascular events.

## Future work

Future research should explore the feasibility of using other UK data sets of routinely collected data, less susceptible to bias, to estimate the benefit and harm of antiplatelet interventions. Research is needed to develop guidance for identifying confounders and how confounders should be organised into confounding domains to facilitate consistent implementation of the Risk Of Bias In Non-randomized

Studies – of Interventions (ROBINS-I) tool. The principle of designing an observational study to emulate a RCT by first defining a target trial appears to be a robust approach, highlighting where the emulation succeeds or fails. Nevertheless, further research is required to validate instances in which an emulation is considered to have been successful, ideally prospectively (i.e. using observational data to emulate ongoing RCTs before their data are analysed and the results are known).We recommend that our utility decrements are used in future cost-effectiveness analyses of DAPT in a UK setting, particularly for minor bleeding events for which existing evidence is limited. In addition, we recommend that future research focuses on quantifying the value of information from reducing the uncertainty of our estimated utility decrements. This research would demonstrate whether or not conducting a larger, more robust study to collect additional information on the HRQoL impact of minor and major bleeds for patients taking DAPT would be an efficient use of resources. The qualitative study with patients highlighted that medication knowledge and understanding, and confidence in dealing with symptoms, facilitate positive attitudes towards adherence to DAPT, but that, currently, there are limited opportunities for patients to access relevant, timely and appropriate DAPT medication counselling. Future qualitative research should focus on developing an intervention to support service users taking DAPT.

## Trial registration

This trial is registered as ISRCTN76607611.

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