10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

The following baseline data will be collected and reported:

From visit 1

- Demographic data (age, sex, ethnicity)
- Vital signs: pulse, blood pressure and temperature
- Weight and BMI
- Full blood count, urea & electrolytes, liver function tests

At visit 2

- TNF-α, IL-6, serum TXB2, urine PGI-M, platelet aggregation responses to arachidonic acid, ADP and collagen
- Bleeding time

Categorical data will be reported as proportions and percentages. Differences between the groups will be assessed using Fisher's exact contingency test. Continuous data will be reported as mean and standard deviation if normally distributed otherwise median and interquartile range. Differences between the parallel groups will be assessed with ANOVA, with Bonferroni pairwise comparisons made if any ANOVA reaches $p<0.05$.

A CONSORT flow diagram will be prepared for inclusion in the report of study findings.

10.3.2 Primary outcome analysis

The primary endpoint will be plasma TNF-α at 2 hours following endotoxin administration assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by one-way ANOVA with treatment as a factor.

10.3.3 Secondary outcome analysis

Secondary analyses will be as follows:

Between aspirin dose regimens

1. Plasma TNF-α over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

2. Plasma IL-6 at 2 hours following endotoxin administration assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by one-way ANOVA with treatment as a factor.

3. Plasma IL-6 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

4. Change in serum CRP over time following endotoxin administration (measured at 0 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by one-way ANOVA.

5. Serum TXB2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

6. Urinary PGI-M (measured at 0, 2, 4 and 6 hours, each adjusted for [divided by] urinary creatinine) over time following endotoxin administration assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

7. Serum PGE2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

8. Circulating leukocyte count over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

9. AUC of the graph of bleeding time following endotoxin administration (measured at 0 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by one-way ANOVA.

10. AUC of the graphs of platelet aggregation to arachidonic acid (0.3 and 1 mmol/L), collagen (4 and 16 µg/ml) and ADP (20 µmol/L) over time following endotoxin administration (measured at 0 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) by one-way ANOVA.

Between DAPT regimens:

11. Plasma TNF-α at 2 hours following endotoxin administration assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by one-way ANOVA with treatment as a factor.

12. Plasma TNF-α over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

13. Plasma IL-6 at 2 hours following endotoxin administration assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by one-way ANOVA with treatment as a factor.

14. Plasma IL-6 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

15. Change in serum CRP over time following endotoxin administration (measured at 0 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by one-way ANOVA.

16. Serum TXB2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

17. Urinary PGI-M (measured at 0, 2, 4 and 6 hours, each adjusted for [divided by] urinary creatinine) over time following endotoxin administration assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

18. Serum PGE2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

19. Circulating leukocyte count over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs.75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by two-way mixed ANOVA with treatment as a between-subjects factor and timepoint as a within-subjects factor.

20. AUC of the graph of bleeding time following endotoxin administration (measured at 0 and 3 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by one-way mixed ANOVA.

21. AUC of the graphs of platelet aggregation to arachidonic acid (0.3 and 1 mmol/L), collagen (4 and 16 µg/ml) and ADP (20 µmol/L) over time following endotoxin administration (measured at 0 and 3 hours post-endotoxin) assessed between aspirin groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, given in combination with ticagrelor) by one-way ANOVA.

To compare aspirin monotherapy with aspirin and ticagrelor in combination:

1. Plasma TNF-α at 2 hours following endotoxin administration) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

2. AUC of the graph of plasma TNF-α over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

3. Plasma IL-6 at 2 hours following endotoxin administration, compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

4. AUC of the graph of plasma IL-6 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

5. Change in serum CRP over time following endotoxin administration (measured at 0 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

6. AUC of the graph of serum TXB2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

7. AUC of the graph of urinary PGI-M (measured at 0, 2, 4 and 6 hours, each adjusted for [divided by] urinary creatinine) over time following endotoxin administration compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

8. AUC of the graph of serum PGE2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

9. AUC of the graph of circulating leukocyte count over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

10. AUC of the graph of bleeding time following endotoxin administration (measured at 0 and 3 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

11. AUC of the graphs of platelet aggregation to arachidonic acid (0.3 and 1 mmol/L), collagen (4 and 16 µg/ml) and ADP (20 µmol/L) over time following endotoxin administration (measured at 0 and 3 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) by paired t-tests.

And to model the effects of all variables (considering parallel groups):

12. Plasma TNF-α over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD)) with a mixed three-way ANOVA

with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

13. Plasma IL-6 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) with a mixed three-way ANOVA with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

14. Change in serum CRP over time following endotoxin administration (measured at 0 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) with a mixed three-way ANOVA with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

15. Serum TXB2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD)) with a mixed three-way ANOVA with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

16. Urinary PGI-M (measured at 0, 2, 4 and 6 hours, each adjusted for [divided by] urinary creatinine) over time following endotoxin administration compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) with a mixed three-way ANOVA with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

17. Serum PGE2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) with a mixed three-way ANOVA with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

18. Circulating leukocyte count over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD)) with a mixed three-way ANOVA with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

19. Bleeding time following endotoxin administration (measured at 0 and 3 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) with a mixed three-way ANOVA with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

20. Platelet aggregation to arachidonic acid (0.3 and 1 mmol/L), collagen (4 and 16 µg/ml) and ADP (20 µmol/L) over time following endotoxin administration (measured at 0 and 3 hours post-endotoxin) compared between each aspirin regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each without ticagrelor) and each corresponding DAPT regimen (control, 20 mg BD, 75 mg OD, 300 mg OD, each with ticagrelor 90 mg BD) with a mixed three-way ANOVA with aspirin-dose and presence or absence of ticagrelor as between-subjects factors and timepoint as a within-subject factor.

For all endpoints (primary and secondary) tested with ANOVA, pairwise comparisons with Bonferroni correction will be used to explore relationships further where the prespecified test suggests significant differences between the groups ($p<0.05$).

10.4 Subgroup analyses

No pre-specified subgroup analyses are planned.

10.5 Adjusted analysis

If variables are found to be of skewed distribution, logarithmic transformation will be performed.

10.6 Interim analysis and criteria for the premature termination of the trial

After discussion between the investigators and the Sponsor, face-to-face participant study visits were halted on 17th March 2020 due to the unprecedented circumstances arising during the coronavirus disease 2019 (Covid-19) pandemic. It was considered by the investigators that the results of the study may have important implications for the management of cardiovascular disease patients who contracted Covid-19 in terms of optimal antiplatelet medication, in view of the morbidity and mortality in Covid-19 associated with dysregulated inflammatory response. It was noted that the recruitment and study activities to date had reached the level that had originally been planned for the study, as per the application funded by the British Heart Foundation. Given the uncertainty regarding restarting the trial, the need to preserve healthcare resources and to limit face-to-face encounters, the investigators and Sponsor decided that an interim analysis should be performed.

Sample size for interim analysis

Data from all participants who have completed visit 3 (first endotoxin day) will be included in the interim analysis. This is expected to include 46 participants who have completed visit 3, 37 of whom have completed the whole study giving a total of 83 endotoxin day visits, anticipated to be split into approximately equal numbers receiving each of the eight study treatment regimens.

Statistical procedure for interim analysis

The primary endpoint of the interim analysis will be plasma TNF-α measured at 2 hours after endotoxin administration assessed between aspirin treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, without ticagrelor) using one-way ANOVA.

Should this demonstrate a significant difference between the groups ($p<0.05$), the following pre-specified pairwise comparisons will be performed, in hierarchical fashion:

300 mg OD vs. no aspirin

then, if significant ($p<0.05$)

75 mg OD vs. no aspirin

then, if significant ($p<0.05$)

300 mg OD vs 20 mg BD

then, if significant ($p<0.05$)

75 mg OD vs 20 mg BD

then, if significant ($p<0.05$)

20 mg BD vs no aspirin

Other analyses will be exploratory.

Criteria for premature termination

The trial shall be prematurely terminated if the primary interim analysis demonstrates a statistically significant ($p<0.05$) effect of aspirin dosing on plasma TNF-α two hours after endotoxin injection.

Additionally, continuing the study will be considered futile, and therefore discontinued, if the lower limit of the 95 % confidence interval of the mean change in TNF-α at 2 hours after endotoxin from the 300 mg aspirin OD group to no aspirin group is less than (more negative than) -2000 pg/mL.

Should neither of these criteria be met, the investigators will meet to review the results of the interim analysis and, in discussion with the Sponsor, decide on whether to continue the study, taking into account feasibility, including consideration of local and national restrictions.

Secondary analyses to be carried out in the event of premature termination

If the trial is prematurely terminated, data concerning other endpoints will then be analysed as follows, using methods taking best into account the cases of participant data missing from one period:

1. Plasma TNF-α over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose, presence or absence of ticagrelor treatment and treatment period (first or second) as fixed effects, and baseline value as covariate.

2. Plasma IL-6 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose, presence or absence of ticagrelor treatment and treatment period (first or second) as fixed effects, and baseline value as covariate.

3. Change in serum CRP over time following endotoxin administration (measured at 0 and 6 hours post-endotoxin) assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose, presence or absence of ticagrelor treatment and treatment period (first or second) as fixed effects, and baseline value as covariate.

4. Serum TXB2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose, presence or absence of ticagrelor treatment and treatment period (first or second) as fixed effects, and baseline value as covariate.

5. Urinary PGI-M (measured at 0, 2, 4 and 6 hours, each adjusted for [divided by] urinary creatinine) over time following endotoxin administration, assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose, presence or absence of ticagrelor treatment and treatment period (first or second) as fixed effects, and baseline value as covariate.

6. Serum PGE2 over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose, presence or absence of ticagrelor treatment and treatment period (first or second) as fixed effects, and baseline value as covariate.

7. Circulating leukocyte count over time following endotoxin administration (measured at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours post-endotoxin) assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose, presence or absence of ticagrelor treatment and treatment period (first or second) as fixed effects, and baseline values as covariate.

8. Bleeding time following endotoxin administration (measured at 0 and 3 hours post-endotoxin) assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose, presence or absence of ticagrelor treatment and treatment period (first or second) as fixed effects, and baseline values as covariate.

9. Platelet aggregation to arachidonic acid (0.3 and 1 mmol/L), collagen (4 and 16 µg/ml) and ADP (20 µmol/L) over time following endotoxin administration (measured at 0 and 6 hours post-endotoxin) assessed between treatment groups (control vs. 20 mg BD vs. 75 mg OD vs. 300 mg OD, with or without ticagrelor) using a mixed effect linear model with patient as a random effect, aspirin dose and presence or absence of ticagrelor treatment and treatment period as fixed effects, and baseline values as covariate.

10.7 Participant population

- The pharmacodynamic analysis set will include all participants who achieve at least 80% compliance with study medication during each of the two periods and who complete both endotoxin injection days.
- The safety analysis set (for the purposes of adverse event reporting etc.) will include any participant randomised into the trial that received at least one dose of trial drug or one dose of intravenous endotoxin.

10.8 Procedure(s) to account for missing or spurious data

- Missing data will be recorded by notating ‘NR’ (not recorded) in the relevant section of the CRF

- Where analysis is performed using ANOVA, missing data will be estimated by multiple imputation using the IBM SPSS software package. Sensitivity analyses will be carried out to report the robustness of this approach.

10.9 Other statistical considerations.

Not applicable to this study

10.10 Economic evaluation

Not applicable to this study.