ASPIRIN TO TARGET ARTERIAL EVENTS IN CHRONIC KIDNEY DISEASE (ATTACK)

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SYNOPSIS

Title	Aspirin To Target Arterial events in Chronic Kidney Disease
Acronym	ATTACK
Chief Investigators	Professor Hugh Gallagher Professor Paul Roderick
Objectives	To test the hypothesis that the addition of 75mg aspirin once daily to usual care reduces the risk of major vascular events in patients with chronic kidney disease (CKD) who do not have pre-existing cardiovascular disease (CVD)
Trial Configuration	Open label, multi-centre study
Setting	Primary care
Sample size estimate	25,210 patients (12,605 per arm). A total of 1,827 major vascular events overall are required.
Number of participants	We expect to invite approximately 198,000 patients in order to recruit the 25,210 required. Of these 12,605 will be randomised to aspirin 75 mg once daily and 12,605 to no additional treatment (with avoidance of aspirin).
Eligibility criteria	Inclusion Criteria 1. Males and females aged 18 years and over at the date of screening 2. Subjects with diagnosed CKD: • decreased estimated glomerular filtration rate [eGFR] for at least 90 days (defined as eGFR <60mL/min/1.73m^2), and/or • albuminuria or proteinuria for at least 90 days (defined as urine albumin:creatinine ratio [ACR] ≥3mg/mmol, and/or urine protein:creatinine ratio [PCR] ≥15mg/mmol , and/or +protein or greater on reagent strip [and in all cases where the most recent qualifying result is ACR ≥3mg/mmol])

	3. Subjects who are willing to give permission for their paper and electronic medical records to be accessed by trial investigators 4. Subjects who are willing to be contacted and interviewed by trial investigators 5. Subjects who can communicate well with the investigator or designee, understand the requirements of the study and understand and sign the written informed consent <u>Exclusion Criteria</u> 1. Subjects with CKD GFR category 5 2. Subjects with pre-existing cardiovascular disease (angina, myocardial infarction, stroke, transient ischaemic attack (TIA), significant peripheral vascular disease, coronary or peripheral revascularisation for atherosclerotic disease) 3. Subjects with a current pre-existing condition associated with increased risk of bleeding other than CKD 4. Subjects currently prescribed anticoagulants or antiplatelet agent, or taking over the counter (OTC) aspirin continuously 5. Subjects who are currently and regularly taking other drugs with a potentially serious interaction with aspirin 6. Subjects with a known allergy to aspirin or definite previous clinically important adverse reaction 7. Subjects with poorly controlled hypertension (systolic blood pressure [BP] ≥180 mmHg and/or diastolic BP ≥105 mmHg) 8. Subjects with anaemia: haemoglobin (Hb) <90g/L; or Hb <100g/L with mean cell volume (MCV) ≤75 fL 9. Subjects who are pregnant or likely to become pregnant during the study period 10. Subjects with malignancy that is life-threatening or likely to limit prognosis, other life-threatening co-morbidity, or terminal illness 11. Subjects whose behaviour or lifestyle would render them less likely to comply with study medication 12. Subjects in prison 13. Subjects currently participating in another interventional clinical trial or who have taken part in a trial in the last 3 months
Description of interventions	Suitable participants will be randomised to receive: 75mg non-enteric coated aspirin once daily in addition to their usual medication; or no additional treatment and avoidance of aspirin.
Duration of study	The trial will continue until 1,827 major vascular events have occurred: this is anticipated 6 years after the recruitment start date, or 2.5 years following the recruitment end date.

Randomisation and blinding	Eligible participants, based on results of blood and urine tests taken at screening, will be randomised (open label randomisation) 1:1 to general practitioner (GP) prescription of aspirin vs. no prescription, stratified by age, diabetes and CKD severity.
Outcome measures	<u>Primary outcome measure</u> Time to first major vascular event from the date of randomisation. A major vascular event is defined as a primary composite outcome of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death (excluding confirmed intracranial haemorrhage). <u>Secondary outcome measures (all time to event except quality of life)</u> <u>Efficacy</u> 1. Death from any cause 2. Composite outcome of major vascular event or revascularisation (coronary and non-coronary) 3. Individual components of the primary composite endpoint 4. Health-related quality of life <u>Safety</u> 1. Composite outcome of intracranial haemorrhage (fatal and non-fatal), fatal extracranial haemorrhage and non-fatal major extracranial haemorrhage (adjudicated) 2. Fatal and non-fatal (reported individually and as a composite) intracranial haemorrhage comprising: i) primary haemorrhagic stroke (to distinguish from haemorrhagic transformation of ischaemic stroke); ii) other intracranial haemorrhage (adjudicated) 3. Fatal and non-fatal (reported individually and as a composite) major extracranial haemorrhage: i) vascular-procedural; ii) vascular-non-procedural; iii) gastrointestinal; iv) genitourinary; v) respiratory; vi) pericardial; vii) ocular; viii) other; ix) undetermined (adjudicated) 4. Clinically relevant non-major bleeding <u>Tertiary (exploratory) outcome measures (all time to event except hospitalisation)</u> 1. Transient ischaemic attack 2. Unplanned hospitalisation 3. New diagnosis of cancer (colorectal/other) 4. CKD progression 5. New diagnosis of dementia

Statistical methods	The primary outcome measure of time to first major vascular event will be analysed for the intention-to-treat (ITT) population. Deaths from other causes (including fatal bleeding) will be treated as competing events. Patients who do not experience a major vascular event will be censored at the date of last follow-up. All primary, secondary and tertiary time to event outcomes will be described using Kaplan-Meier curves or Cumulative Hazard plots for time to event outcomes involving competing risks for the ITT population. Analyses of time to event outcomes will be performed using Cox proportional hazards models or Competing Risk regression models, both unadjusted and adjusted for stratification factors: age, diabetes and CKD severity. The adjusted Competing Risk regression model for time to first major vascular event, with deaths from other causes (including fatal bleeding) treated as competing events, and patients who do not experience a major vascular event censored, will form the primary endpoint analysis model. Other secondary and tertiary endpoints will be assessed by arm using summary statistics (e.g. Pearson's χ^2 tests) in the ITT population. The amount of missing data and reasons for the incompleteness will be explored and presented overall i.e. not by group. If the amount of missing data is deemed too high and if appropriate (i.e. assuming the missing data is either missing at random [MAR] or missing completely at random [MCAR] and censoring assumed to be non-informative), multiple imputation will be performed accordingly, for which all covariates included in the multivariable model, together with the censoring/event indicator and the cumulative baseline hazard will be included in the multiple imputation model.

ABBREVIATIONS

ACR	Albumin:creatinine ratio
ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
ASCEND	A Study of Cardiovascular Events in Diabetes
ASPREE	Aspirin in Reducing Events in the Elderly
ATC	Antithrombotic Trialists' Collaboration
ATTACK	Aspirin To Target Arterial Events In Chronic Kidney Disease
BNF	British National Formulary
BP	Blood pressure
cTn	Cardiac troponin
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case Report Form
CRN	Clinical Research Networks
CVD	Cardiovascular disease
DMEC	Data Monitoring and Ethics Committee
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQol five dimensions (EQ-5D) 5 level
EPR	Electronic Patient Record
GCP	Good Clinical Practice
GI	Gastrointestinal
GP	General practitioner
Hb	Haemoglobin
HEAT	*Helicobacter* Eradication Aspirin Trial
HES	Hospital Episode Statistics
HOT	Hypertension Optimal Treatment
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HRA	Health Research Authority
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMD	Index of Multiple Deprivation
IMP	Investigational Medicinal Product
IT	Information technology
ITT	Intention-to-treat
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	Left bundle branch block
MAR	Missing At Random
MCAR	Missing Completely At Random

MCV	Mean cell volume
MDRD	Modification of Diet in Renal Disease
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NWIS	NHS Wales Informatics Services
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys
OR	Odds ratio
OTC	Over the counter
OXVASC	Oxford Vascular Study
PCI	Percutaneous coronary intervention
PCR	Protein:creatinine ratio
PPI	Proton pump inhibitor
PI	Principal Investigator
PIS	Participant Information Sheet
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
PEDW	Patient Episode Database for Wales
R&D	Research and Development
REC	Research Ethics Committee
RR	Relative risk
RRID	Renal Risk in Derby
SHARP	Study of Heart and Renal Protection
SAE	Serious adverse event
SCTU	Southampton Clinical Trials Unit
SOP	Standard Operating Procedures
SSC	Study Site Coordinator
SHEP	Systolic Hypertension in the Elderly Program
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCR	The Computer Room
TIA	Transient ischaemic attack
TMG	Trial Management Group
TSC	Trial Steering Committee
UK-HARP-1	First United Kingdom Heart and Renal Protection Study
URL	Upper reference limit
USM	Urgent safety measure
USPSTF	US Preventative Services Task Force
WHO	World Health Organisation

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1. BACKGROUND INFORMATION AND RATIONALE

1.1 CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as any abnormality of kidney function or structure with implications for health that is present for more than three months. It is classified according to the estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (ACR). The presence of an eGFR <60mL/min/1.73m^2 or an ACR ≥3mg/mmol* for more than 90 days is diagnostic of CKD.

CKD is common, particularly in older people. The prevalence of CKD is estimated at 12-13% of adults from population data in England (1) and the USA (2). An important minority of people with CKD will develop end-stage renal disease, but the greatest significance of CKD is as a powerful and potentially modifiable risk factor for cardiovascular disease (CVD). People with CKD are categorised according to Kidney Disease Improving Global Outcomes (KDIGO) classification as being at moderate risk, high risk, or very high risk of CVD according to the level of both eGFR and ACR (3). In the USA 9.2%, 2% and 0.8% of adults are in the moderate risk, high risk and very high risk categories (4); these proportions were similar in the Health Survey of England (5).

1.2 RELATIONSHIP BETWEEN CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASE

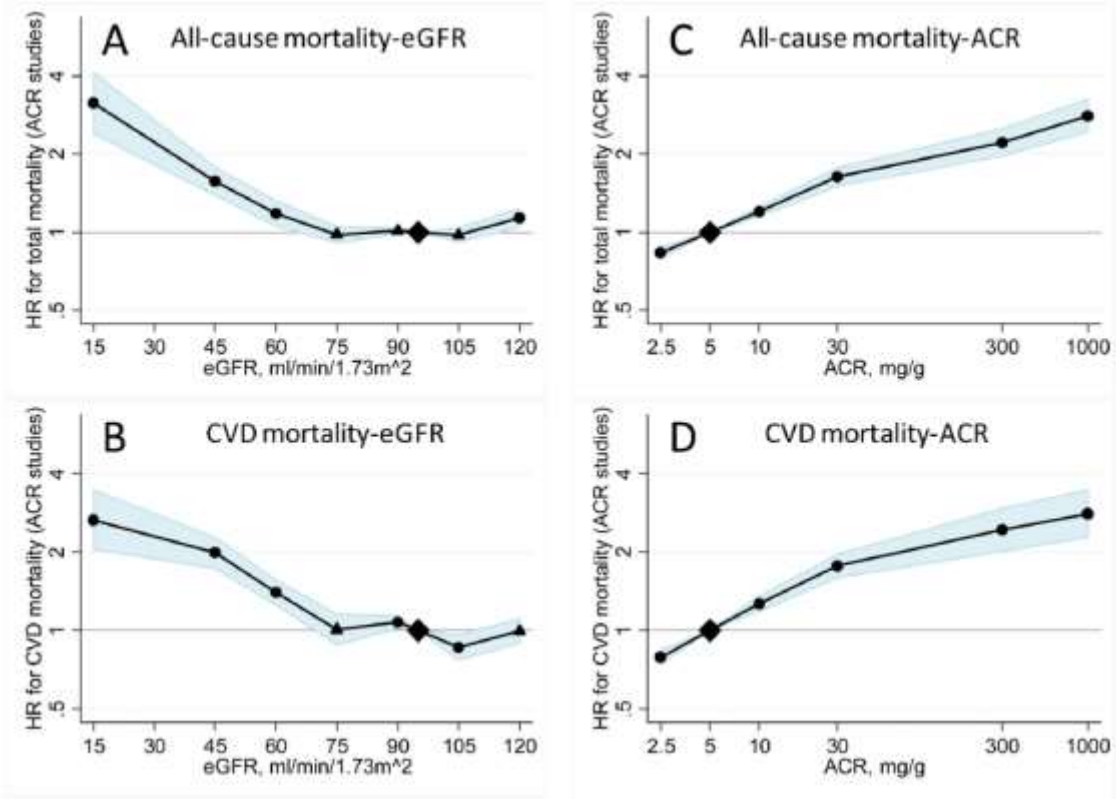
Large-scale robust epidemiological data indicate that the risks of both all-cause and cardiovascular mortality in the general population increase where the eGFR is less than 60mL/min/1.73m^2, and/or where the ACR is greater than 1mg/mmol. The risks are graded: compared with eGFR 95 mL/min/1.73 m^2, adjusted hazard ratios (HR) for all-cause mortality were 1.18 (95% CI = 1.05-1.32) for eGFR 60mL/min/1.73m^2, 1.57 (1.39-1.78) for 45mL/min/1.73m^2, and 3.14 (2.39-4.13) for 15mL/min/1.73m^2. ACR was associated with risk of mortality linearly on the log-log scale without threshold effects. Compared with ACR 0.6mg/mmol, adjusted HR for all-cause mortality were 1.20 (1.15-1.26) for ACR 1.1mg/mmol, 1.63 (1.50-1.77) for 3.4mg/mmol, and 2.22 (1.97-2.51) for 33.9mg/mmol. eGFR and ACR were multiplicatively associated with risk of mortality without evidence of interaction. Similar findings were recorded for cardiovascular mortality (6).

Albuminuria and eGFR are similarly predictive of mortality in high-risk population cohorts (7) and kidney disease cohorts (8), and in people with and without diabetes (9) and hypertension (10). These findings hold true in older people (11), both sexes (12) and across ethnic groups (13).

The pattern of vascular events in people with CKD varies according to disease severity. For those with the most severe impairment in GFR, and in particular those receiving renal replacement therapy, atherosclerotic events are less prevalent and arrhythmia and heart failure more important (14). However, in those where the GFR is less severely impaired, and where albuminuria indicates the presence of vascular damage and endothelial dysfunction (15), atherosclerotic events dominate.

* where albuminuria measurements are not available measurements of urine protein:creatinine ratio or urine reagent strips can be substituted (3)

Figure 1. Cardiovascular mortality according to eGFR and ACR in combined general population and high risk cohorts (6)



Reproduced from CKD Prognosis Consortium, Matsushita K et al. Lancet 2010;375(9731):2073–81.

1.3 ASPIRIN AND THE PREVENTION OF CARDIOVASCULAR DISEASE IN THE GENERAL POPULATION

In patients with cardiovascular disease, there is good evidence that antiplatelet therapy reduces the risk of subsequent vascular events (secondary prevention), and that overall these benefits outweigh the risks of major bleeding, which is the principal complication of therapy. A meta-analysis conducted by the Antithrombotic Trialists' Collaboration (ATC) showed that antiplatelet agents (primarily aspirin) reduced serious vascular events by 22% across five major high risk categories of patients (previous myocardial infarction (MI), acute MI, previous stroke or TIA, acute stroke and other high risk) in 195 trials: there were 7,705/71,912 (10.7%) serious vascular events in the antiplatelet treated group against 9,502/72,139 (13.2%) in adjusted controls. There was an expected increased risk of major bleeding: 95/47,158 fatal and 440/47,158 non-fatal major extracranial bleeds (1.1%) were seen in the antiplatelet group against (71+262)/47,168 (0.7%) in the controls (16). Antiplatelet therapy is recommended internationally for the secondary prevention of cardiovascular events in people with established cardiovascular disease.

In low-risk populations without pre-existing CVD the benefits of aspirin for the primary prevention of CVD are smaller and offset by an increased risk of bleeding. An ATC meta-analysis of six primary prevention studies reported a 12% proportional reduction in serious vascular events in a lower risk population (0.51% vs. 0.57% per annum) with aspirin (17). A meta-analysis in 2012 of nine randomised placebo-controlled trials indicated a clinically meaningful reduction in first myocardial

infarction but not in cardiovascular death with the use of aspirin in people without established cardiovascular disease: there were 2,107/52,145 (4.0%) events in the aspirin-treated group against 2,171/50,476 (4.3%) in the placebo group over a mean follow-up of six years. Aspirin reduced total cardiovascular events by 10% (odds ratio [OR] 0.9, 95% CI 0.85-0.96, number needed to treat 120). There was a 20% reduction in non-fatal myocardial infarction, but there was no significant reduction in cardiovascular death (0.99 [0.85-1.15]) and a significant increase in non-trivial bleeding events (1.31 [1.14-1.40]), number needed to harm 73) (18).

A 2013 HTA systematic review and overview of reviews also reported small absolute benefits and harms with the use of aspirin in primary prevention. In this analysis a risk reduction of approximately 10% for a composite outcome of cardiovascular death, non-fatal stroke and MI was observed, with an increase in the relative risks (RR) of bleeding: 37% for gastrointestinal (GI) bleeding (RR 1.37, 95% CI 1.15-1.62); between 54% (1.54 [1.30-1.82]) and 62% (1.62 [1.31-2.00]) for major bleeds; and between 32% (1.32 [1.00-1.74]) and 38% (1.38 [1.01-1.82]) for haemorrhagic stroke. Between 60 and 84 major vascular events were prevented per 100,000 patient-years of follow-up, with estimates of absolute rates of harm from aspirin use per 100,000 patient-years of follow-up of 99-178 for non-trivial bleeds, 46-49 for major bleeds, 68-117 for GI bleeds, and 8-10 for haemorrhagic stroke. Assuming equivalence of impact between cardiovascular events and bleeding episodes there was no net benefit in a low risk primary prevention population. The review emphasised a need for “further investigation in specific subgroups stratified according to reliable risk assessment tools” (19).

The difficulty of weighing the risks and benefits of aspirin for primary prevention is compounded by evidence that aspirin can reduce the risk of certain cancers. Among the 88,084 women and 47,881 men from the Nurses’ Health Study (1980-2010) and Health Professionals Follow-up Study (1986-2012) who underwent follow-up for as long as 32 years, 20,414 cancers among women and 7,571 cancers among men were documented. Compared with non-regular use, regular aspirin use was associated with a lower risk for overall cancer (RR 0.97, 95% CI 0.94-0.99), which was primarily owing to a lower incidence of GI tract cancers (0.85 [0.80-0.91]), especially colorectal cancers (0.81 [0.75-0.88]) (20). In another individual patient data meta-analysis, aspirin was associated with a reduction in cancer mortality (RR 0.66; 95% CI, 0.50-0.87), which translated to approximately 200 fewer cancer deaths (300 fewer to 80 fewer) per 100,000 patient-years (21). The effect of the use of aspirin for primary prevention on all-cause mortality has also been evaluated, with a relatively consistent probable 6-8% reduction over 10 years reported (19,22,23).

Despite the existence of a substantial body of evidence it therefore remains uncertain whether and under what circumstances aspirin should be used for primary prevention. In 2016 the US Preventative Services Task Force (USPSTF) published recommendations on aspirin use for the primary prevention of CVD (and colorectal cancer). The recommendations were based upon three commissioned systematic reviews and a microsimulation model to systematically estimate the balance of risk and harms. The USPSTF concluded that aspirin should be initiated for the primary prevention of CVD and colorectal cancer in people aged 50-59 with a 10-year CVD risk of at least 10%, no increased risk of bleeding, and a life expectancy of 10 years or more; the review recommended that the decision for people aged 60-69 should be individualised, and that there was insufficient evidence to guide a recommendation in people aged 70 and above (24). An evidence-based clinical decision support tool has recently been developed to support implementation; the algorithm takes advantage of age- and sex-specific results from randomised trials to determine the

net benefit of aspirin but does not makes reference to kidney disease (25). The European Society of Cardiology currently recommend that “aspirin be considered in the primary prevention of cardiovascular disease in both sexes at a level of risk of major cardiovascular events (death, MI, and stroke) of >2 per 100 subject-years, provided they have no clear evidence of increased risk of bleeding (GI bleeding or peptic ulcer disease and no concurrent use of other medications that increase bleeding risk)” (26).

1.4 ASPIRIN AND THE RISKS OF BLEEDING

An increased bleeding tendency is the most important complication of aspirin therapy. Bleeding most often occurs in the GI tract, where it is infrequently fatal but may be disabling particularly in older people (27). Intracranial bleeding is much rarer but more frequently fatal and/or disabling.

The results of an individual participant data meta-analysis including 95,000 individuals from six large primary prevention trials (British Doctor Study, US Physicians’ Health Study, Thrombosis Prevention Trial, Hypertension Optimal Treatment Trial, Primary Prevention Project, and Women’s Health Study) have been used to derive and compare absolute risk estimates of cardiovascular disease and bleeding for people at low, moderate and high cardiovascular risk according to the Framingham risk score (28). To derive baseline control group risk estimates it was assumed that patients at low, moderate and high risk of cardiovascular disease had a 5%, 15%, and 25% 10-year risk respectively of an MI (combined fatal and non-fatal). It was assumed that people at low, moderate and high cardiovascular risk would be in the same risk categories for bleeding. The control group risk estimates were adjusted to assume a 20% overestimation of coronary heart disease risk (and bleeding risk) by the Framingham score. To estimate the probability of each outcome, the authors used the observed ratio of non-fatal MI to fatal MI to nonfatal stroke to major extracranial bleeding events in an individual participant data meta-analysis assessing benefits and harms of aspirin in primary prevention of cardiovascular disease (17). Data were reported as absolute effects over 10 years per 1,000 patients. The Framingham risk score does not separate non-fatal and fatal MI, and these were estimated using the ratio of non-fatal: fatal MI from the individual participant data meta-analysis of approximately 2:1. Overall aspirin increased the risk of major bleeding by 54%. The data on major extracranial bleeding and non-fatal MI are summarised in Table 1 as absolute effects per 100,000 patient-years:

Table 1. Absolute risk differences of major bleeding and non-fatal MI with aspirin used for the primary prevention of CVD (28)

Outcome	**Population**	**Anticipated absolute risk without aspirin per 100,000 patient-years**	**Anticipated absolute risk difference with aspirin per 100,000 patient-years (95% CI)**
Non-fatal MI	Low CV risk	270	60 fewer (from 80 fewer to 40 fewer)
	Moderate CV risk	830	190 fewer (from 260 fewer to 120 fewer)
	High CV risk	1,360	310 fewer (from 420 fewer to 190 fewer)
Major extracranial bleed	Low CV risk	80	40 more (from 20 more to 70 more)
	Moderate CV risk	240	160 more (from 70 more to 200 more)
	High CV risk	400	220 more (from 120 more to 330 more)

In comparison, the use of aspirin in people with established coronary artery disease prevents 740 (460-940) non-fatal MI per 100,000 patient-years at a cost of 500 (80-1420) major bleeds (28).

Critical in all these analyses is the estimation of the baseline risk of bleeding. As a part of the evidence supporting their 2016 recommendations on aspirin for primary prevention (24) the USPSTF conducted a systematic review of aspirin-associated major GI bleeding; this included cases leading to death, those requiring hospitalisation or transfusion, or those described by the trial investigator as serious (29). Their data were derived from eight primary prevention studies, with simulations illustrating a range of projected excess bleeding cases with low-dose aspirin use. Because of the limitations of study reporting, lower GI bleeds were not adequately represented. The risk groups were defined as low (minimum), median, high and highest (maximum) for each outcome based upon the control group rate excluding zeros and outliers from the primary prevention studies. The absolute effects are summarised in Table 2.

Table 2. Estimated excess rates of GI bleeding events with aspirin used (for <10 years) according to CVD risk group for the primary prevention of CVD (29)

Outcome	**Population**	**Baseline risk without aspirin per 100,000 patient-years**	**Anticipated additional risk with low-dose aspirin per 100,000 patient-years (95% CI)**
Major GI bleed	Low risk	23	13 more (from 7 more to 22 more)
	Median risk	49	28 more (from 14 more to 40 more)
	High risk	58	34 more (from 17 more to 55 more)
	Highest risk	104	60 more (from 30 more to 99 more)

For haemorrhagic stroke the USPSTF reported that low-dose (<100mg) aspirin was associated with a possible but non-significant increase in haemorrhagic stroke of 27% (OR 1.27, 95% CI 0.96-1.68). The absolute effects were 0, 11 more (from 2 fewer to 29 more) and 34 more (from 5 fewer to 86 more) per 100,000 patient-years in low, high and highest risks group respectively (29).

Although assumptions around baseline bleeding rate are clearly important when applying these trial-based averages based on selected groups to the unselected general population, these data suggest an overall benefit of aspirin in higher CV risk populations. As the absolute risk of CVD rises both the benefits and bleeding complications of aspirin increase, with the benefits often exceeding the risks in people with an estimated risk of CVD above 1% per year (25). However, determination of the net clinical benefit of aspirin is more complex than a simple numerical comparison between these variables, and it is possible that a binary approach may underestimate the true benefits. In particular weighing the importance of ischaemic and bleeding events is not straightforward. Most models attribute equal weight in terms of patient preferences to a non-fatal cardiovascular event and to major bleeding. However it has been argued that with the exception of haemorrhagic stroke this is hard to concede (26). Furthermore, although clearly important in terms of consequences for deaths and disabilities, haemorrhagic stroke is much less common that major GI bleeding, and its fatal consequences are already included within estimates of total deaths associated with aspirin, which point toward a net benefit (19,22,23,26).

Survivors of an acute MI have a 30-day mortality of around 5% (30). The one-year mortality in patients enrolled in the GUSTO-IIb trial was in the order of 10% (31). UK national data (Office for National Statistics (ONS) and Hospital Episode Statistics (HES)) for 2010 reveal a 30-day case

fatality rate for MI of around 31% overall and 12% in those admitted to hospital (32). Against this, a recent systematic review and meta-analysis of 11 randomised controlled trials of aspirin which reported fatal and non-fatal GI bleeding found that although aspirin increased the risk of bleeding by 60%, a similar effect to that reported elsewhere, the risk of fatal bleeding was not significantly elevated, and the fatality rate in the event of GI bleeding was significantly reduced in people taking aspirin, perhaps because of unmasking of GI pathology by aspirin early in the natural history (33). The incidence of GI bleeding attributable to aspirin may also decrease over time. Within the first month of aspirin taking the risk is increased more than four-fold (34,35) but it then reduces rapidly, and after three to five years of use there does not appear to be a significant excess of GI bleeds (36).

The risk-benefit equation derived from historical primary prevention studies will also be modified by the use of concomitant medications in modern clinical practice. Both proton pump inhibitors and H2 receptor antagonists reduce aspirin-induced GI bleeding (see below). Rates of bleeding on aspirin are also significantly lower in patients taking statins, with an incidence rate ratio for hospitalisation for major bleeding of 0.67 (0.62-0.71) from trials and cohort studies (29), although to what extent this benefit may be offset by a reduction in absolute benefits remains unclear.

Data from cohort studies have not unexpectedly revealed higher bleeding rates than those from randomised trials due to the inclusion of less selected populations. A large-scale general population cohort reported 198 extra (558 overall) major GI and intracranial bleeds per 100,000 patient-years with aspirin use (for any indication); the risks rose sharply with age, with 108, 136, 226 and 367 additional bleeds per 100,000 patient years at age 50-59, 60-69, 70-79 and ≥80 respectively (37). The Oxford Vascular Study (OXVASC) also reported high rates of major bleeding, 187 major bleeds in 13,509 patient-years, in a cohort of patients taking long-term aspirin for secondary prevention of CVD followed for up to 10 years. The bleeding rates in the OXVASC participants, 50% of whom were aged 75 and over, are higher than those reported in randomised trials of aspirin in secondary prevention conducted in younger patients, which in turn are greater than those observed in primary prevention trials. The risk of non-major bleeding was unrelated to age, but major bleeding increased steeply with age (≥75 years HR 3.10 95% CI 2.20-4.24), particularly for fatal bleeds (5.53 [2.65-11.54]). In patients younger than 75 years, the ratio of major bleeds to ischaemic events was similar to the ratios in previous aspirin secondary prevention trials (pooled ratio 0.19 [0.17-0.21]). However, the ratio in OXVASC increased with age (75-84 years 0.32 [0.23-0.43]; ≥85 years 0.46 [0.32-0.67]), and the risk of major bleeds estimated to be attributable to antiplatelet treatment approached the risk of ischaemic events estimated to have been prevented (27).

It should be emphasised that the OXVASC cohort are very different to the population anticipated in ATTACK, in that OXVASC follows an unselected high risk secondary prevention group that also included people taking dual antiplatelet agents. In patients with TIA and ischaemic stroke, long-term recommended antiplatelet treatment was aspirin 75mg daily plus dipyridamole 200mg twice daily and in those with myocardial infarction standard initial treatment was with aspirin plus clopidogrel for 6–12 months (although the results were similar in analyses excluding bleeds occurring during treatment with aspirin plus clopidogrel). OXVASC also included patients switched from oral anticoagulants to antiplatelet therapy.

Furthermore, it is possible to mitigate these risks. Peptic ulcer bleeding in patients treated with low-dose aspirin is substantially reduced by the co-prescription of proton pump inhibitors (PPI) (38). A 2015 meta-analysis indicated that PPIs were superior to placebo (OR 0.26, 95% CI 0.14-0.49) and H2-antagonists (0.36 (0.15-0.87)) in the prevention of GI bleeding associated with low-dose aspirin (39). The risk reduction with PPIs is substantial in patients with risk factors for GI bleeding (40). Although overall the use of PPIs reduces upper GI bleeds by 70-90%, uptake in clinical practice is low. This is a key factor modifying the trade-off between benefit and risk from studies such as OXVASC (where only 24% were prescribed PPIs (27)).

1.5 ASPIRIN USE IN CHRONIC KIDNEY DISEASE: SPECIAL CONSIDERATIONS

1.5.1 BLEEDING RISK

In CKD one might expect substantial absolute benefits even if the relative reductions in the risks of CVD were no greater than in the general population. However it is not clear to what extent any benefits may be offset because people with CKD are also at increased risk of bleeding. Many people with CKD are elderly. There are additional specific mechanisms through which the bleeding tendency may be increased in CKD, including defective platelet adhesion to the sub-endothelium, defective platelet aggregation, and other intrinsic platelet defects (41). A Cochrane review (which included patients at all stages of CKD, including those receiving renal replacement) reported that the use of antiplatelet agents in people with CKD conferred an increased relative risk of major (27 studies, RR 1.33, 95% CI 1.10-1.65) and minor bleeding (18 studies, 1.49 (1.12-1.97)) compared with placebo/control. The definitions of bleeding employed within the included studies were variable. The relative risks of major bleeding due to aspirin appeared no higher than those in the non-CKD population, although the absolute excess risks were higher due to the higher risks in the CKD control groups (42). The safety of low-dose aspirin in CKD was also explored in the First United Kingdom Heart and Renal Protection Study (UK-HARP-1). 448 patients were randomly assigned 20mg simvastatin vs. placebo and 100mg aspirin vs. placebo in a 2x2 factorial design. Allocation to aspirin was not associated with an excess of major bleeds in one year of follow-up (though it was underpowered); there was a three-fold excess of minor bleeding episodes (43).

1.5.2 CHRONIC KIDNEY DISEASE PROGRESSION

Aspirin-induced cyclooxygenase acetylation may inhibit prostaglandin-induced renal vasodilatation and reduce renal blood flow. Most studies show no association between therapy with low-dose aspirin and renal injury. Data from large scale cohort studies in healthy people does not show a relationship between long-term aspirin use and the development of renal dysfunction (44,45). In people with CKD propensity matched analyses have suggested an association between low-dose aspirin use and CKD progression (46). However, this has not been borne out in cardiovascular trials of low-dose aspirin that included patients with CKD (47,48).

1.5.3 ASPIRIN RESISTANCE

It has been reported that high on-treated platelet activity (aspirin resistance) is more common in people with CKD than the general population (49,50), although other studies have found that this finding varies according to the technique employed to measure platelet activity (51) and that the effect may no longer be significant after adjustment for co-morbidities (52). There are some data suggesting that antiplatelet therapy with clopidogrel in people with mild or moderate CKD after percutaneous coronary intervention might not have the same beneficial effect as it does in patients

with normal renal function (53). It remains uncertain whether any reduced antiplatelet efficacy of aspirin in CKD leads to clinically important treatment failure.

1.5.4 GASTROPROTECTION IN CKD

2010 guidelines on the prevention of aspirin-induced upper GI bleeding recommend concomitant use of PPI in people with a past history of upper GI bleeding or multiple risk factors for GI bleeding (advanced age, concomitant use of warfarin, steroids, or NSAIDs, *Helicobacter pylori* infection). Kidney disease is not included as a risk stratification factor. It was added that H2-antagonists "may be a reasonable alternative in patients at lower risk for GI bleeding" (40).

Since these guidelines were produced, an increased incidence of acute interstitial nephritis in users of PPI has been reported. The absolute risks are small, with a nationwide nested case-control study revealing an incidence of 12.0 (95% CI 9.1-15.5) and 1.7 (0.9-1.9) per 100,000 patient-years in current and past users respectively. Observational data have also revealed associations between PPI and incident CKD (54) and of adverse chronic renal outcomes (decline in eGFR of more than 30% and end stage renal disease) in those without intervening acute kidney injury (55), although whether such pharmacoepidemiological data should be used to imply a causal link has been recently challenged (56).

Recent data have also provided some support for the role of H2-antagonists in gastroprotection. In a randomised controlled trial of 270 high-risk aspirin users (with a history of endoscopically confirmed ulcer bleeding), 7.9% (95% CI 4.2-14.7) of patients receiving an PPI (Rabeprazole) reached the primary endpoint of recurrent bleeding or ulceration at 12 months compared with 12.4% (7.4-20.4) receiving a H2-antagonist (Famotidine). The difference was not statistically significant. The authors concluded that the incidence of recurrent bleeding in high-risk users was comparably low with PPI and H2-antagonists, and that, although a small difference in efficacy could not be excluded, H2-antagonists could be considered as alternative gastroprotective agents in high-risk patients (57).

The risk of bleeding in people with CKD is likely to vary with both age and CKD category. Such heterogeneity is not captured by current clinical guidelines. ATTACK is a pragmatic study and a real-world approach will also be applied to this area of clinical uncertainty. The decision to introduce gastroprotection, and the choice of any gastroprotective agent, is not mandated under the Protocol, but rather will be at the discretion of the treating GP. Our GP training materials will provide the necessary information to support a process of shared decision-making, highlighting factors that are likely to increase the risks of bleeding.

1.6 EVIDENCE SUMMARY FOR ASPIRIN IN THE PRIMARY PREVENTION OF CVD IN CKD

There is currently insufficient evidence to recommend the use or avoidance of aspirin for the primary prevention of CVD in CKD as data on the use of antiplatelet agents in the specific setting of primary prevention in CKD are limited. The literature suggests that the efficacy of aspirin in CVD prevention is at least as great in people with CKD as the general population but the risks may also be greater, and so uncertainty remains about the net balance of benefit and risk.

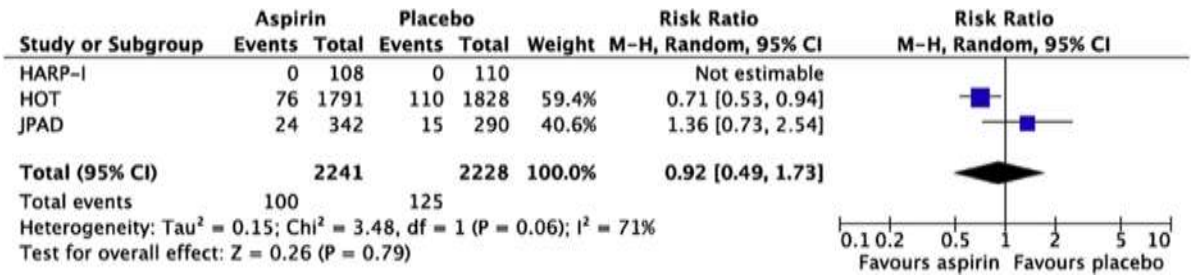
The effect of aspirin on cardiovascular outcomes in CKD was examined in a Cochrane review that examined all randomised trials of antiplatelet use in CKD, including studies on patients undergoing

coronary interventions and trials where the primary outcome measure concerned kidney disease progression and dialysis access patency. The relative risk reductions were smaller than those observed in secondary prevention in the non-CKD population: overall antiplatelet agents reduced the risk of MI (17 studies, RR 0.87, 95% CI 0.76-0.99), but not all-cause mortality (30 studies, 0.93 [0.81-1.06]), cardiovascular mortality (19 studies, 0.89 [0.70-1.12]) or stroke (11 studies, 1.00 [0.58-1.72]) (42). 21,460 patients from a total of 44 studies of antiplatelet vs. placebo were included in the review. However, and critically with respect to the hypothesis addressed by this trial, data on the effects of antiplatelet agents in primary prevention in CKD were available only from a post-hoc subgroup analysis of a single study, the Hypertension Optimal Treatment (HOT) Trial. In the overall HOT study population, aspirin reduced the risk of major cardiovascular events by 15%, but did not affect total mortality or cardiovascular mortality (58). However, there was evidence of significant heterogeneity by eGFR. Major cardiovascular events were reduced by 9% (95% CI -9% to 24%), 15% (-17% to 39%), and 66% (33% to 83%) for patients with baseline eGFR of ≥60, 45 to 59, and <45mL/min/1.73m^2 respectively (*p* for trend = 0.03). In those with an eGFR of 45-59mL/min/1.73m^2, 8 (-7 to 22) major cardiovascular events were prevented per 1,000 patients treated for 3.8 years, at a cost of 4 (-2 to 10) major bleeds; at eGFR<45mL/min/1.73m^2, 76 (31 to 121) events were prevented, at a cost of 27 (-1 to 55) bleeds. Total mortality was not affected in the CKD group as a whole but was significantly reduced in those subjects with eGFR <45mL/min/1.73m^2, although only 2.9% of the population had an eGFR <45mL/min/1.73m^2 and reporting of bleeding episodes was imprecise (47). It is also unclear how generalisable the findings are to non-hypertensive people with CKD as the criteria for entry into HOT were BP-based (58).

The primary prevention of CVD in CKD has been the subject of a recent systematic review. Three trials were identified from a total of 1,314 records screened; two of these provided previously unpublished data. 4,468 adults with pre-end stage CKD and no history of CVD were included. There were 16,740 person-years of follow-up. A random effects model was used to pool the data. The trials were assessed as showing medium to high levels of risk of bias, largely related to endpoint assessment and suboptimal identification of CKD. Only one trial, HARP (43), was CKD-specific; it did not report cardiovascular events in aspirin and placebo groups. There was no pre-specified CKD analysis in the other two studies, HOT and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (59). Neither JPAD nor HOT provided data on albuminuria, a potent amplifier of vascular risk.

Overall there was no statistically significant reduction in major cardiovascular events (RR 0.92, 95% CI 0.49-1.73, *p* = 0.79). There was a high level of heterogeneity (I^2 = 71% *p* = 0.06). In HOT there were 76/1791 cardiovascular events in the aspirin-treated group and 110/1,828 in controls, with a risk ratio of 0.71 (0.53-0.94). The numbers were smaller and the findings divergent in JPAD, with 24/342 and 15/290 events in aspirin and control groups respectively and a risk ratio of 1.36 (0.73-2.54). Overall there were 100/2,241 CVD events in aspirin-treated patients across the included studies and 125/2,228 in controls. Mortality was non-significantly reduced in the aspirin group (RR 0.74, 0.55-1.00, *p* = 0.05, I^2 0%):

Figure 2. Systematic review of aspirin for the primary prevention of CVD in CKD. Forest plot of risk ratios for CVD events using a random effects model and Mantel-Haenszel method (60)



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Aspirin increased the risk of major bleeding (34/2,241 episodes aspirin-treated patients vs. 17/2,228 in controls (RR 1.98, 1.11-3.52, p = 0.02, I^2 0%)). The authors of the systematic review concluded that the limitations of the evidence highlighted the need for definitive CKD-specific randomised controlled trials (60).

1.7 IMPORTANCE OF THE TRIAL

A number of randomised trials of aspirin in cardiovascular prevention are ongoing (61–63). These are summarised in Table 3:

Table 3. Current aspirin cardiovascular prevention trials

Trial	Study population	Design	Primary endpoint	Status
A Study of Cardiovascular Events in Diabetes (ASCEND) (61)	Individuals with diabetes (primary prevention)	Placebo-controlled randomised controlled trial n=15,480	Composite of non-fatal MI, non-fatal stroke or TIA, or vascular death, excluding confirmed cerebral haemorrhage	Follow-up completed 2017
Aspirin in Reducing Events in the Elderly (ASPREE) (62)	Healthy participants aged 65 years and above	Placebo-controlled randomised controlled trial n=19,000	Composite of death from any cause or incident, dementia or persistent physical disability	Estimated completion 2018
A Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE) (63)	People at moderate risk of CVD (primary prevention)	Placebo-controlled randomised controlled trial n=12,546	Composite of MI, stroke, CV death, unstable angina, TIA	Reported at clinicaltrials.gov 8 January 2018

In ASCEND only 12% of the enrolled subjects had an eGFR <60 mL/min/1.73m^2 and 13% an ACR ≥3 mg/mmol (64). 19% of the participants in ASPREE had an eGFR <60 mL/min/1.73m^2 (65). The presence of severe renal disease was an exclusion criterion in ARRIVE (63). These trials are therefore highly unlikely to provide definitive evidence on the role of aspirin in people with CKD, an

area of high importance given the affordability of aspirin, the wide acceptance of aspirin as potentially therapeutic by patients, and the high risk for CVD in CKD (66).

The burden of CVD in CKD is substantial. Overall CVD is responsible for about one-third of all deaths in the UK. It can have a serious impact upon quality of life and cause considerable disability. CKD is included as a vascular condition within the Department of Health's CVD Outcomes Strategy (67). The financial impact of CVD in CKD is large: assuming unit costs of £12,200 for a stroke and £7,734 for an MI and incidence of stroke and MI of 12.0 and 11.9 per 1000 patient-years respectively in people with CKD (68), the annual costs of strokes and MI in people with CKD in England is in the order of £1bn.

Our understanding of how to reduce cardiovascular risk in CKD is limited. The Study of Heart and Renal Protection (SHARP) demonstrated that primary prevention with simvastatin and ezetimibe reduced major atherosclerotic events in people with CKD. 13.4% of a control group (mean eGFR of 27mL/min/1.73m^2) experienced a major atherosclerotic event (including revascularisation) in SHARP over a median follow-up of 4.9 years (69). Even in a lower risk UK primary care cohort (mean eGFR 52mL/min/1.73m^2, 84% without albuminuria) the annual mortality from CVD in those without pre-existing CVD was as high as 0.7% (70,71)**.** Evidence on other approaches to prevent CVD in CKD is therefore urgently required. In 2014 the National Institute for Health and Care Excellence (NICE) made a research recommendation for a definitive trial of aspirin for primary prevention of CVD in people with CKD (72).

The results of this trial, whether positive or negative, will provide the evidence to improve clinical outcomes in large numbers of people. Most people with CKD who do not have CVD are not currently prescribed aspirin. In a UK primary care cohort including 31,056 individuals with an eGFR <60mL/min/1.73m^2 70% were recorded as having a history of pre-existing CVD; aspirin was prescribed to 68% of individuals with CKD and CVD and to 22% with CKD and no CVD (73). A positive result from ATTACK would imply that aspirin should be offered to more than 3 million additional people in the UK (excluding those with a contraindication or taking OTC). If use of aspirin for primary prevention of CVD in people with CKD results in a relative reduction of 12.5% in the risk of CVD, 50,000 additional major vascular events over five years may be prevented in this group. Conversely a negative trial result would provide definitive evidence to stop aspirin in one million people who are now taking it for primary prevention. If our hypothesis is correct the costs of CVD averted in people participating in the trial alone would cover approximately 50% of the research costs of the study.

1.8 SUMMARY OF RATIONALE AND SIGNIFICANCE

1. CKD is a very common long-term condition and powerful risk factor for CVD. The healthcare costs associated with CVD in CKD are substantial
2. In people with pre-existing CVD (the group at highest risk of major vascular events), aspirin is of proven benefit in the prevention of heart attack and stroke
3. In lower risk groups where the rates of heart attack and stroke are much lower, the benefits of aspirin in preventing CVD are largely balanced by an increased risk of bleeding
4. People with CKD are at greatly increased risk of CVD and so the absolute benefits of aspirin are likely to be greater than in lower risk groups even if the relative benefits are the same. Post-hoc evidence from the HOT trial also suggests the relative benefits may be greater in the CKD population. However the absolute risk of bleeding may also be higher

5. In the UK it is likely that there are more than 3 million people with CKD and no CVD who are not prescribed aspirin but around one million that are receiving aspirin in the absence of definitive evidence. The results of this trial, whether positive or negative, will therefore be directly and immediately applicable to very large numbers of patients
6. This will be the first definitive trial of aspirin as primary CVD prevention in CKD patients. As such the research will be of great interest to clinicians, guideline groups and policy-makers, in the UK and globally, particularly given the high and rising prevalence of CKD. The low cost of aspirin means that a positive result will also be of relevance to Low and Middle Income Countries and the impact not diluted in countries such as the United States by issues around income or insurance status

2. AIM AND OBJECTIVES

2.1 AIM OF THE TRIAL

The research aims to demonstrate whether the addition of low-dose (75mg non-enteric coated) aspirin to usual care reduces the risk of major vascular events (excluding confirmed intracranial haemorrhage) in people with CKD who do not have pre-existing CVD, and whether and to what extent the benefits outweigh any harms due to an increased risk of bleeding.

2.2 PRIMARY OBJECTIVE

The primary objective of the research is to test the hypothesis that low-dose (75mg non-enteric coated) aspirin reduces the risk of major vascular events (excluding confirmed intracranial haemorrhage) (primary endpoint) in people with CKD who do not have pre-existing CVD.

2.3 SECONDARY OBJECTIVES

The secondary objectives of the research are:

1. To assess the impact of the addition of low-dose aspirin to usual care in people with CKD and no CVD on the incidence of major intracranial and extracranial bleeds
2. To assess the impact of the addition of low-dose aspirin to usual care in people with CKD and no CVD on the incidence of clinically relevant non-major bleeds
3. To assess the impact of the addition of low-dose aspirin to usual care on other secondary and tertiary endpoints including: all-cause mortality; combined endpoint of major vascular events and revascularisation (coronary and non-coronary); individual components of the primary endpoint; TIA; unplanned hospitalisation; new diagnosis of cancer (colorectal/other); CKD progression; health-related quality of life (HRQoL), dementia
4. To examine a priori the effect of low-dose aspirin on primary, secondary and tertiary endpoints in various subgroups of people with CKD: high risk and very high risk CKD as defined by KDIGO (KDIGO 2012); diabetes; age ≥70; eGFR <45mL/min/1.73m^2; ACR ≥3mg/mmol; ACR >30mg/mmol
5. To assess the cost-utility of low-dose aspirin compared with usual care

3. ENDPOINTS

Follow-up for the major outcomes in ATTACK is based upon routinely collected hospital, GP and national mortality data. This will allow a full intention-to-treat (ITT) analysis on all participants who are randomised, with the exception of those who both withdraw from the study and remove their

consent for data linkage or who move abroad. Where patients move within the UK to another ATTACK practice, outcomes recorded on the primary care Electronic Patient Record (EPR) will continue to be collected as these data are linked to the NHS number. Where the patient moves to a non-ATTACK practice searches will not be possible but outcome data will continue to be collected via linked secondary care and mortality data and by patient self-reporting.

3.1 PRIMARY ENDPOINT

The primary outcome measure is the time to first major vascular event from the date of randomisation. A major vascular event is defined as a primary composite outcome of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death (excluding confirmed intracranial haemorrhage). Deaths from other causes (including fatal bleeding) will be treated as competing events. Patients who do not experience a major vascular event will be censored at the date of last follow-up.

3.2 SECONDARY ENDPOINTS

The secondary endpoints are listed below. These will be time to event except health-related quality of life (details in section 9.5.1).

<u>Efficacy</u>

1. Death from any cause
2. Composite outcome of major vascular event or revascularisation (coronary and non-coronary)
3. Individual components of the primary composite endpoint
4. Health-related quality of life

<u>Safety</u>

1. Composite outcome of intracranial haemorrhage (fatal and non-fatal), fatal extracranial haemorrhage and non-fatal major extracranial haemorrhage (adjudicated)
2. Fatal and non-fatal (reported individually and as a composite) intracranial haemorrhage comprising:
    i) primary haemorrhagic stroke (to distinguish from haemorrhagic transformation of ischaemic stroke): a) intracerebral and b) subarachnoid haemorrhage (reported individually and a composite) (adjudicated)
    ii) other intracranial haemorrhage: a) subdural and b) extradural haemorrhage (reported as a composite) (adjudicated)
3. Fatal and non-fatal (reported individually and as a composite) major extracranial haemorrhage: i) vascular-procedural; ii) vascular-non-procedural; iii) gastrointestinal; iv) genitourinary; v) respiratory; vi) pericardial; vii) ocular; viii) other; ix) undetermined (adjudicated)
4. Clinically relevant non-major bleeding (adjudicated if hospitalised)

3.2 TERTIARY ENDPOINTS

The following exploratory endpoints will also be studied. These will be time to event except hospitalisation (details in section 9.5.1).

1. Transient ischaemic attack
2. Unplanned hospitalisation
3. New diagnosis of cancer (colorectal/other)

4. CKD progression
5. New diagnosis of dementia

The definitions of clinical endpoints used in ATTACK are detailed in Appendix 1.

3.3 ASSESSMENT OF SAFETY

There are four safety endpoints within ATTACK's secondary endpoints: intracranial haemorrhage, major extracranial haemorrhage; composite of intracranial haemorrhage and major extracranial haemorrhage; and clinically relevant non-major bleeding. CKD progression is included as an exploratory endpoint.

Trial participants will be asked to contact the study team to report bleeding involving the need for hospitalisation and/or transfusion and overt bleeding requiring face-to-face healthcare professional advice. The importance of coding bleeding episodes will be highlighted in the GP training for the study. Participating GPs will be asked to log any clinically relevant bleeding episodes (and cardiovascular events) that they become aware of with their Regional Centre.

A standardised approach to the definition of our bleeding endpoints will be followed. It will be recorded whether individual events result in the discontinuation of aspirin (permanent and temporary). Any bleeding event that results in hospitalisation will be formally adjudicated. Safety data will be included in a report produced for the Data Monitoring and Ethics Committee (DMEC), annually or more frequently if requested by the DMEC.

If an eGFR has not been recorded within 15 months of the last one, we will contact the GP practice.

4. TRIAL DESIGN

ATTACK is a pragmatic multicentre open label randomised controlled trial. Recruitment is from UK primary care. Whilst there are many important strengths of a placebo-controlled approach, an open label design does offer the advantages of substantially lower trial costs. There is also the possibility of enhanced generalisability and transferability to routine medical care because the treatments more accurately reflect usual clinical practice. It is possible that the choice of an open label design increases the consent rate as potential participants may be reluctant to take placebo and wish to know their allocation (74). Patient compliance may be better in prospective randomised open label blinded endpoint trials than in placebo-controlled studies (75). Assessment of safety will be a particular issue, and it is not possible in an open trial to mitigate the risk that allocation to aspirin will increase the reporting of symptoms. However the impact of knowledge of treatment allocation on outcome measurement will be minimised with blinded independent outcome adjudication of major clinical endpoints, including all bleeding events that require hospitalisation.

A flow diagram of the trial is provided in Appendix 2.

5. TRIAL PARTICIPANTS

5.1 INCLUSION CRITERIA

1. Males and females aged 18 years and over at the date of screening
2. Subjects with diagnosed CKD, defined by:

a. estimated GFR <60mL/min/1.73m^2 using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR (at least two test results with eGFR <60mL/min/1.73m^2 at least 90 days apart with no values ≥60mL/min/1.73m^2 in the intervening period)

and/or:

b. ACR ≥3mg/mmol (at least two test results in this range at least 90 days apart with no values <3mg/mmol in the intervening period). Where no historical (within the last four years) results of ACR are available, patients with a screening ACR ≥3mg/mmol who have a PCR ≥15mg/mmol at least 90 days before with no values of PCR <15mg/mmol in the intervening period will be eligible. Where there are no historical (within the last four years) ACR or PCR results, patients with a screening ACR ≥3mg/mmol who have +protein or greater on a reagent strip at least 90 days before with no reagent strip results showing negative or trace protein in the intervening period will be eligible*

3. Subjects willing to give permission for their paper and electronic medical records to be accessed and abstracted by trial investigators for the duration of the trial
4. Subjects willing to be contacted and interviewed by trial investigators should the need arise for adverse event assessment
5. Subjects able to communicate well with the investigator or designee, to understand and comply with the requirements of the study and to understand and sign the written informed consent

5.2 EXCLUSION CRITERIA

1. Subjects with CKD GFR category 5
2. Subjects with pre-existing CVD: angina, MI, stroke (ischaemic and haemorrhagic [intracerebral/subarachnoid]), TIA, significant peripheral vascular disease, coronary or peripheral revascularisation for atherosclerotic disease; aortic aneurysm is not an exclusion criterion
3. Subjects with a pre-existing condition associated with increased risk of bleeding other than CKD: upper GI bleed or peptic ulcer in the previous five years, lower GI bleed in previous twelve months, active chronic liver disease (such as cirrhosis), bleeding diathesis (investigator opinion)
4. Subjects taking over the counter aspirin continuously
5. Subjects currently prescribed anticoagulant or antiplatelet agent, including:
   - acenocoumarol, phenindione, warfarin
   - apixaban, edoxaban, rivaroxaban
   - argatroban, bivalirudin, dabigatran
   - aspirin, cangrelor, selexipag, cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, abciximab, eptifibatide, tirofiban, epoprostenol, iloprost
   - unfractionated heparin, dalteparin, enoxaparin, tinzaparin
   - danaparoid, fondaparinux

* where albuminuria measurements are not available KDIGO state that measurements of urine protein:creatinine ratio or urine protein reagent strips can be substituted. Negative to trace on protein reagent strip is equivalent to ACR <3mg/mmol; trace to + is equivalent to ACR 3-30mg/mmol (3). The relationship between reagent strip measures and ACR depends upon urine concentration and in this context for the purposes of ATTACK we are regarding +protein or more as indicative of significant albuminuria.

6. Subjects who are currently and regularly taking other drugs with a potentially serious interaction with low-dose aspirin, including:
   - non-steroidal anti-inflammatories (except topical preparations), including: aceclofenac, acemetacin, celecoxib, dexibuprofen, dexketoprofen, diclofenac (and combination diclofenac-misoprostol preparation), etodolac, etoricoxib, felbinac, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, ketorolac trometamol, mefenamic acid, meloxicam, nabumetone, naproxen (and naproxen-esomeprazol), parecoxib, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid
   - selective serotonin re-uptake inhibitors: citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
   - serotonin and noradrenaline re-uptake inhibitors: duloxetine, venlafaxine
   - nicorandil
7. Subjects with a known allergy to aspirin or definite previous clinically important adverse reaction to aspirin
8. Subjects with poorly controlled hypertension, defined as average of three readings at screening visit of systolic BP ≥180mm Hg and/or diastolic BP ≥105mm Hg
9. Subjects with anaemia: Hb <90g/L; or Hb <100g/L with MCV ≤75 fL
10. Subjects who are pregnant or likely to become pregnant during the study period
11. Subjects with malignancy that is life-threatening or likely to limit prognosis, other life-threatening co-morbidity, or terminal illness
12. Subjects whose behaviour or lifestyle would render them less likely to comply with study medication (e.g. alcoholism, substance abuse, debilitating psychiatric conditions or inability to provide informed consent)
13. Subjects in prison
14. Subjects currently participating in another interventional clinical trial or who have taken part in a trial in the last 3 months

5.3 CONTINGENCY PLAN FOR PARTICIPANT WELL-BEING

5.3.1 BEFORE RANDOMISATION

GPs will be provided with a Study Site File outlining trial procedures and will be trained in an initiation visit. Inclusion and exclusion criteria are based on coded primary care data. Exclusions not captured with disease codes will be assessed by a GP review of the screening list and will be reconfirmed by a research nurse using a checklist of key items at the patient's screening visit. The GP will be consulted where there is remaining doubt or ambiguity, and will ultimately have the decision of who participates in the study. The training materials will make it clear that the guiding principle is that patients should be excluded where their bleeding risk is above acceptable levels such that the GP would not prescribe aspirin to the same patients outside the trial.

Previous mild dyspepsia is not an exclusion criterion for the trial. For potential participants with anaemia identified at screening the GP will be asked to follow their usual practice for investigation and management. All patients with Hb <90 g/L will be excluded. Patients with Hb 90-99 g/L will be excluded where the mean cell volume is less than 75 fL (suggestive of iron deficiency).

5.3.2 AFTER RANDOMISATION

Patient characteristics associated with a higher risk of bleeding are detailed in Sections 1.5.4 and 7.2. All decisions around gastroprotection will be at the discretion of the treating physician.

Trial participants will be advised to seek advice from their usual treating physician for any condition arising during the course of the study. Treating physicians will be asked to follow their usual practice for the management of dyspeptic symptoms or anaemia. Participants who have their study medication stopped by their GP due to side effects of the treatment (e.g. major bleeding) will continue in the trial and be observed for the development of endpoint events.

Treating physicians will be advised to commence participants in the usual care arm on aspirin where an indication arises. The patient's usual physician will be asked to discontinue aspirin therapy when participants in the aspirin arm are commenced on anticoagulation or another antiplatelet agent (except where this clinically indicated owing to a qualifying event), or where there is a clinically important reason for a patient to be commenced on any drug with a strong interaction with aspirin. These patients will also continue in the study and be observed for the development of endpoints.

Randomised patients who commence renal replacement therapy will not be withdrawn from trial treatment unless another indication for this arises.

5.4 WITHDRAWAL OF PARTICIPANTS FROM THE TRIAL

Patients may discontinue study treatment as a result of a clinical decision, due to non-compliance with the Protocol, or drug toxicity, but will still be followed up and included in the intention-to-treat analysis. Subjects will be free to withdraw (defined as the withdrawal of consent for record linkage and the collection of follow-up data) from the trial at any time. The participants will be made aware that this will not affect their future care. Participants will be informed (via the information sheet and consent form) that should they withdraw from the trial, their data collected prior to withdrawal may be used in the final analysis.

6. TRIAL PROCEDURES

6.1 INFORMATION TECHNOLOGY

The information technology (IT) infrastructure to support the trial will be provided by The Computer Room TCR (Nottingham) Ltd. A bespoke ATTACK software tool (ATTACK toolkit) and management system (ATTACK database) will underpin the trial, and allow a complete set of data collection, administration, reporting and development tools for both the research team and participating practices.

Clinical outcomes will be classified according to standard frameworks (International Classification of Disease [ICD]-10 disease codes and Office of Population Censuses and Surveys [OPCS]-4 procedure codes) linked to structured clinical vocabularies/dictionaries of clinical terms (SNOMED CT, Read version 2 and Read version 3 (CTV3)).

The practice-based ATTACK toolkit in each participating GP practice will enable identical potential patient searches to be performed at every site, and allow for electronic medical record follow-up of patients via Read and SNOMED codes. Adaptations to the trial IT architecture in response to

changes in the NHS operating environment (for example any transition from Read codes to SNOMED CT in the primary care electronic record) will be performed according to need.

Computer-held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server within the N3 NHS Private Data Network, to which only authorised study personnel will have access. This is compatible with, and has the relevant security policies in place, to obtain patient-matched hospital admission data and ONS data for consented patients from NHS Digital. Access will be restricted by user identifiers and passwords (encrypted using AES-25S encryption). Information about the trial in the participant's medical records/hospital notes will be treated confidentially in the same way as all other confidential medical information. The storage of this data will comply with all relevant information governance guidelines.

6.2 RECRUITMENT

All trial recruitment will be from UK Primary Care. There will be three geographical recruitment hubs based at Regional Centres in Southampton (South), Nottingham/Warwick (Midlands) and Newcastle-upon-Tyne (North). Each hub will be supported by a dedicated Trial Coordinator and Principal Investigator (PI). The activities of the hubs will be coordinated and monitored by the Trial Manager based at the University of Nottingham.

GPs will identify potentially eligible patients at their practice using an automated search. The practice will be able to download the ATTACK toolkit required to perform the search from the web. The toolkit will contain query files to perform searches on the GP practice clinical system based on the inclusion and exclusion criteria.

These automated searches use a combination of biochemical test results and coded clinical terms. The Read coded prevalence of CKD GFR categories 3 to 5 in England is 4.1% of people aged 18 years and over (76). This is substantially lower than the estimated actual prevalence of 6.1% of people aged 16 and over (77)**.** Unlike CKD G3-5 the coding of CKD GFR categories 1-2 has never been incentivised under the Quality and Outcomes Framework (QOF) and is therefore likely to be far less complete than that for CKD G3-5. Miscoding of CKD is also common: 11% of people with a CKD 3-5 Read code in the National CKD Audit did not have current biochemical evidence of CKD (78). For these reasons numerical values for eGFR and albuminuria/proteinuria rather than clinical terms will be used to identify potential participants.

The search will return a list of potential patients (as a .csv file), which will be held within the practice. The GPs will check the list of patients to confirm potential eligibility and are required to provide confirmation that they are happy for the patients to be contacted and screened by signing the search list and documenting any exclusions.

An electronic screening log will be generated based on the final list, and will be updated with any exclusions during the consent process. The following information will be stored in the trial database: screening number, patient initials, year of birth, and encrypted NHS number. The patient's NHS number is required to be able to uniquely identify each patient, should the practice lose their data and require a back-up. It will be encrypted as follows: at the practice, the patient's NHS number will be encrypted automatically by the toolkit prior to being uploaded to the trial database; the unique encryption key, to allow decryption of the NHS number, is the NHS number itself. There is therefore

no way that this information can be decrypted outside of the practice. In this instance, the encrypted NHS number is not a strong identifier for the patient.

An automated invitation pack will be sent to the eligible patients via Docmail, a highly secure online mail management system. The pack will include a participant invitation letter, a copy of the Research Ethics Committee (REC)-approved Participant Information Sheet (PIS) and Informed Consent Form (ICF), a reply slip and pre-paid return envelope (addressed to the Regional Centre). As people often move in and out of CKD-defining GFR categories over time and because awareness of a CKD diagnosis is lower than that of other chronic medical conditions (79), the PIS will make it clear that people have been invited because existing test results indicate they may have CKD and that confirmatory tests will be performed at screening.

People who respond to express an interest will be contacted, primarily by telephone, to give them further information and allow them to ask questions. Suitable patients will be invited to attend a screening visit at their GP practice. They will be sent a letter/email to confirm their appointment time. Their appointment confirmation letter will state that they will be expected to provide a blood and urine sample. Patients who do not respond to the initial invitation may be sent a reminder from their GP practice via letter/email/text message.

6.3 INFORMED CONSENT

All participants will provide written informed consent. The process for obtaining participant informed consent will be in accordance with REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the informed consent form (ICF) before the participant can enter the trial or undergo any interventions.

The consent will include permission for:

- electronic record linkage via NHS Digital to the ONS for mortality and cancer registration and HES, and
- access by the research team to hospital records where necessary for the purposes of endpoint adjudication
- access to their GP records

For this trial, research nurses (or a registered medical professional with suitable study training) will be obtaining informed consent, as delegated by the PI at each Regional Centre. The research nurses will receive considerable training on informed consent, the trial, and the treatment in question, prior to the trial start.

Participants will have received a PIS in advance of their consent visit (at least 24 hours), allowing them ample time to consider their participation. The research nurse will explain the details of the trial, and will answer any questions that the participant has concerning study participation.

One copy of the ICF will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the site file at the GP practice; practice staff will be asked to scan this into the patients' electronic GP record.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms. If the ICF is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended ICF by the REC and use of the amended form (including for ongoing participants). Should there be any subsequent amendment to the final Protocol which might affect participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasise that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled.

6.4 SCREENING VISIT

At the screening visit, inclusion/exclusion criteria will be checked using a checklist and the patient consented by an appropriately trained research nurse. Blood pressure (average of three readings), height and weight will be recorded. Basic demographic and clinical details will be recorded, including self-defined ethnicity, smoking history, and alcohol consumption. All participants will also complete an EQ-5D-5L questionnaire. If the research nurse has any concerns over the eligibility of a patient, they will discuss it with the GP at the practice, who will ultimately decide if the patient is suitable.

Additional information, including postcode (used to generate Index of Multiple Deprivation (IMD)), summary diagnoses, cardiovascular risk factors (for example diabetes [type and duration], hypertension and lipid profile) and concomitant medications will be automatically extracted from the EPR as required.

Patients will be asked to specify their preferred method of communication with the research team (electronic/phone/paper).

Blood samples for Hb and serum creatinine and a urine sample for ACR will be collected and analysed locally. These will be used to define the patients' current CKD stage. Patients will be advised not to eat meat for 12 hours before the blood test (72). The GFR category at entry will be determined according to the CKD-EPI eGFR, corrected for ethnicity. For sites where the Modification of Diet in Renal Disease (MDRD) eGFR is reported, CKD-EPI eGFR will be calculated from the standardised serum creatinine.

6.5 PRE-RANDOMISATION RUN-IN

There will be a "cooling-off" period for potential participants following consent of approximately two to six weeks. The inclusion of this run-in phase may result in the exclusion of significant number of patients who are less likely to comply with study treatments, increasing the sensitivity of the intention-to-treat analysis.

During this period:

- the results of the screening tests (eGFR, ACR, Hb) will be processed by the research team who will follow a strict algorithm to determine eligibility

- the results of the screening test results, and a confirmation of whether the subject is eligible will be reported back to patients (and copied to their GP) by their preferred method of communication
- the patients will be contacted and asked if they remain willing to be randomised and then required to take (or avoid) aspirin for at least 3-4 years

Patients with screening tests showing any one of the following will be automatically excluded (this will be logged in the trial database):

- screening ACR <3mg/mmol (for people invited to screening on the basis of albuminuria/proteinuria only [potential CKD G1-2 cases])
- screening eGFR ≥60mL/min/1.73m^2 (for people invited to screening on the basis of eGFR only [potential CKD G3-4 cases])
- screening eGFR <15mL/min/1.73m^2 (for all people invited to screening [potential CKD G1-4 cases])
- screening Hb is <90g/L (for all people invited to screening [potential CKD G1-4 cases])
- screening Hb is <100g/L and screening MCV is <75fL (for all people invited to screening [potential CKD G1-4 cases])
- average screening BP ≥180 mmHg systolic or ≥105 mmHg diastolic (for all people invited to screening [potential CKD G1-4 cases])

Randomisation will take place only after patients have confirmed their continued willingness to proceed at the end of the run-in phase.

The exclusion of potential participants on the grounds of bleeding diathesis is on the basis of investigator opinion (see Exclusion Criteria Section 5.2). Thrombocytopenia is an important indicator of diathesis. However, the risk of bleeding at any given platelet count is likely to be related to many factors including age, blood pressure, kidney function and, in the case of gastrointestinal bleeding, the presence of *Helicobacter pylori* infection. There are no widely accepted protocols governing the use of aspirin in thrombocytopaenia) (80), and very limited evidence to guide decision-making. It has been argued that aspirin can probably be safely continued in patients post cardiac bypass surgery with platelet counts below 50, unless clinical bleeding occurs or the count falls below 20 (81); others have recommended ("in the absence of evidence") stopping antiplatelet agents in people with stable coronary artery disease and a platelet count <50 (82). We are therefore not proposing a fixed platelet count below which participants are automatically ineligible. However, any participant in whom the platelet count taken at screening is below 70 will be automatically and electronically flagged at the Regional Centre. The Regional Centre will then telephone the patient's GP/SSC to discuss whether they would be willing to prescribe aspirin on this basis, following guidance within the Protocol that "patients should be excluded where their bleeding risk is above acceptable levels such that the GP would not prescribe aspirin to the same patients outside the trial" (Section 5.3.1). We will ask the DMEC to review bleeding risk subdivided by platelet count".

6.6 RANDOMISATION

Consenting patients whose screening tests confirm the presence of CKD and who confirm their willingness to participate after the run-in will be randomised (open label randomisation) 1:1 via an independent web-based system (TENALEA) using random-block size, to GP prescription of aspirin vs no additional treatment (and avoidance of aspirin), stratified by age, diabetes and CKD severity. Patients and study staff will be aware of the randomisation decision as there is no blinding to treatment allocation.

Participants randomised to receive aspirin will be asked to take prescribed aspirin rather than purchase OTC aspirin to assist in monitoring adherence. The method of prescribing will be at the discretion of the treating physician and is not mandated by the Protocol, but practices will be encouraged to prescribe using a system of Repeat Prescribing (3-month prescriptions), where prescriptions are re-ordered (by patient or pharmacy) in preference to Repeat Dispensing, where prescriptions are issued automatically (typically on a monthly basis). This will also help with tracking adherence to prescribed treatment and may reduce prescription costs. Patients who pay for their prescriptions will be offered reimbursement.

6.7 ENDPOINT CAPTURE AND ADJUDICATION

There is no practice-based follow up. Potential outcomes will be ascertained from four data sources:

- ONS for mortality and cancer registration
- HES for hospital admissions
- General practice EPR for coded CVD episodes, bleeding episodes, coded diagnoses of dementia, recorded eGFR, and prescription of aspirin and other relevant medications
- Self-reported information (including that from an annual patient questionnaire)

Trial participants will give consent for record linkage using their NHS number at the screening visit. HES and ONS will be accessed annually via NHS Digital. If practices in Wales are required in the face of lower than expected recruitment rates, GP records will be linked to the Patient Episode Database for Wales (PEDW) from the NHS Wales Informatics Services (NWIS). Record linkage for clinical events in Scotland will be carried out for patients within the trial if needed using national record linkage systems (Information Services Division, NHS National Services Scotland) as in the ALL-HEART trial (83). GP records will be searched and updated as regularly as the extraction system will allow.

Patients will be asked to complete follow-up questionnaires annually, either on-line, or by their preferred method of contact (paper/electronic). Those who do not agree to being contacted in this way will be followed by HES, ONS and the GP EPR. If required, reminders may be sent.

The four sources of data will be cross-referenced in order to build up a potential event record. Potential CVD and major bleeding events will be formally adjudicated by an Endpoint Adjudication Committee (EAC). Notification of a potential study endpoint will trigger the collection of information for endpoint confirmation and adjudication by the EAC.

In the pilot phase of the trial (Section 6.9) the feasibility, value and costs of obtaining specific additional information from the original hospitalisation such as electrocardiogram (ECG), imaging and laboratory results to support diagnoses made from coding records and electronic discharge summaries will be explored. Where necessary, the Clinical Research Network (CRN) system will be used to liaise with research nurses in each NHS Trust to directly access hospital test results and, if required, hard copy discharge summaries. The consent process will include permission for the participants' data to be accessed in this way. If there is good agreement the data collection will be streamlined for the remainder of the trial. All emergency admissions will be captured from HES and all new diagnoses of colorectal and other cancer from ONS.

There are two adjudication committees, one for cardiovascular endpoints and one for major bleeding. The CVD EAC will be chaired by a cardiologist or stroke physician. A key aim of our cardiovascular adjudication process is to distinguish genuine atherothrombotic events from those unlikely to be modified by aspirin (e.g. an episode of atrial fibrillation accompanied by a small troponin rise). The bleeding committee will be chaired by a gastroenterologist. The EACs will meet as frequently as is required to review all potential events. Assuming a positive predictive value of 66%, around 3000 cardiovascular events will require adjudication; the number of bleeding events is likely to be substantially smaller (Table 1). A consensus adjudication model will be followed, whereby two reviewers discuss the cases and reach agreement. In the rare cases that agreement is not reached the case will be discussed with the Chair to determine the final adjudicated outcome. The adjudication process will run in parallel to systems for safety assessment.

6.8 DURATION OF THE TRIAL

The trial will continue until at least 1,827 adjudicated primary endpoint events (major vascular events) have occurred, or before if the trial is discontinued after the internal pilot (Section 6.9) or for any other reason. It is anticipated that 3.5 years of recruitment and 2.5 years of follow-up will be required to complete the trial.

6.9 STOPPING RULES AND DISCONTINUATION

6.9.1 TRIAL STOPPING RULES

The trial will begin with an internal pilot lasting for 24 months (Section 6.10). The pilot will provide key early data on recruitment and safety to inform the funders and Sponsor of the trial whether to continue, amend procedures or stop the study.

Existing trial data indicate an absolute rate of major bleeding in people with CKD taking aspirin for primary prevention of 0.4% per annum with a relative risk vs. controls of 1.98 (95% CI 1.11-3.52) (n=4,469) (60). A Cochrane review reported that the use of antiplatelet agents in people with CKD (any indication) conferred an increased relative risk of major bleeding of 1.33 (95% CI 1.10-1.65) (27 studies). The relative risks of major bleeding due to aspirin are similar to those in people without CKD, although the absolute risks are higher due to the higher baseline risks in the CKD control groups (42).

Safety will be assessed throughout the trial, both in the pilot phase and after. The DMEC will formally review safety:

- at 27 months (at the completion of the pilot phase [9 months setup, 15 months recruitment] plus 3 months for report writing) using non-adjudicated data
- at 36 months (9 months set up, 24 months recruitment, 3 months for report writing) using non-adjudicated data
- at 45 months (9 months set up, 27 months recruitment, 9 months for adjudication and report writing) using adjudicated data
- annually thereafter (or more frequently if specified by the DMEC).using adjudicated data

The absolute and relative risks of major bleeding will be examined by the DMEC and compared with those expected from the literature. All-cause mortality and the primary event rate will also be studied in order to determine net benefit, i.e. benefits minus harms.

Aspirin use requires a consideration of the balance of risk vs. benefit in all populations. The DMEC will recommend termination of the trial if, in their view:

- the randomised comparisons provided have proven beyond reasonable doubt that the level of harm is unacceptable, or
- the use of aspirin is clearly contraindicated (or clearly indicated) in terms of the net effects.

This follows the approach adopted by the ASCEND investigators (84).

Clinical judgement will be required in interpreting these analyses and reaching a recommendation. The DMEC will consider whether the evidence meets standards for treatment recommendations and practice guidelines, mindful that less evidence should be required to stop the trial for harm than benefit given the primacy of patient safety (85). The absolute number of major bleeding events during ATTACK is likely to be low (estimated n=16 in aspirin-treated and n=8 in controls during the pilot phase), and therefore that the confidence levels around any estimates of absolute and relative risk will be initially wide but narrow throughout the course of the trial. Hazard ratios may be unstable and drift over time into marginal levels of significance. Multiple "looks'' at the data may give rise to a transient ''signal'' of benefit or harm (86). Therefore criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a difference of at least three standard deviations in an interim analysis of a major endpoint would be needed to justify halting, or modifying, such a study prematurely, especially for a comparison based on relatively few events (<100) (84).

If the DMEC have concerns that fall short of "beyond reasonable doubt" on the basis of the early unadjudicated data they will also have the option to halt the trial pending a process of formal adjudication.

There are other instances where the DMEC may consider it advisable to advise termination of the study:

- flaws in design or conduct of the study come to light
- external new information on the treatment comes to light
- resources are inadequate to complete the trial

If the trial is prematurely terminated or discontinued, the Chief Investigators will immediately notify the Sponsor and Regional Centre Principal Investigators. After notification, the Principal Investigators will contact all participants within 90 days, all trial materials will be collected in the Trial Master File and all data will be completed to the greatest extent possible.

6.9.1 INDIVIDUAL PARTICIPANT STOPPING CRITERIA

The individual trial participant stopping criteria are:

- diagnosis of a non-traumatic major bleed
- commencement of treatment with warfarin, aspirin or other anti-thrombotic drug (except where this clinically indicated owing to a qualifying event)
- where there is a clinically important reason for a patient to be commenced on any drug with a strong interaction with aspirin.

6.10 PILOT PHASE

The first 24 months of the study (9 months set up followed by 15 months recruitment) will serve as a pilot. The key objective of the pilot is to assess GP and patient recruitment. Additional objectives are to:

- finalise major event assessment procedures
- monitor safety
- assess fidelity to allocated group and patient withdrawal rates

Pilot data will be analysed from the end of month 24 and reported by the end of month 27 of the study. The non-adjudicated primary event rate in the control arm after 24 months of recruitment (33 months of study) will be assessed by the DMEC only (who may in turn raise concerns to the TSC).

6.10.1 PILOT STUDY AT 24 MONTHS

Assessment of practice and patient recruitment. We will report on the number of practices overall, and by area, that: indicate willingness to take part; perform eligibility assessment; and start patient recruitment. The number (and percent per list size) of eligible patients per practice and the number and percentage of eligible patients willing to participate, entering the run-in phase and commencing the trial will be recorded. The aim over 3.5 years is to recruit 25,210 patients, with approximately 8,000 patients in the first 15 months of recruitment for the pilot phase. At the end of the pilot phase, traffic light criteria will be used establish whether: the trial should continue without modification (green); study recruitment strategy changes are required (amber); or the trial should discontinue (red). The red option is driven by a recruitment rate under 60% of target. If patient recruitment is below estimated further practices will be recruited into the trial (Table 4).

Test searches at practices participating in the *Helicobacter* Eradication Aspirin Trial (HEAT) (87), indicated an average of 370 potentially eligible patients per practice. A rate of randomisation of 15% would give 55 participants per practice. With a more pessimistic set of assumptions the trial remains feasible. The prevalence of CKD 1-5 is in the order of 12% from population data. The National Diabetes Audit highlighted that there are over 1 million people with diabetes and CKD 1-2 (88). Not all of these patients will have blood and urine tests that are diagnostic of CKD on their GP records, but if 8% of adults can be diagnosed with CKD 1-5 on the basis of test results, and of these 70% have no pre-existing CVD, and 80% of these are not taking aspirin, then a typical practice will include around 300 eligible patients. The inclusion of a run-in phase to improve treatment adherence may reduce the proportion of invited patients who are randomised. If the rate of randomisation is 8%, full recruitment will be possible from the network of 1,200 practices participating in HEAT (1,257 enrolled, 1,163 active [96% in England]) (89), with whom the ATTACK investigators have existing links through a common trial management team. If the number of eligible patients and/or the consent rate was lower still there is nonetheless the ability to recruit additional practices outside the HEAT network: overall 48% of general practices across England take part in NIHR CRN Portfolio studies (90). As in HEAT there is also scope to extend into Scotland, Wales and Northern Ireland.

Table 4. Recruitment targets during internal pilot

	Number of practices	Patients recruited per practice	Total patients recruited	Action
Green	≥160 ≥200 ≥229 ≥267 ≥320 ≥400	≥50 ≥40 ≥35 ≥30 ≥25 ≥20	≥8,000	Continue trial without modification
Amber	A combination of a sufficient number of practices and patients to recruit at least 4,800 patients but insufficient to recruit 8,000 patients		4,800-8,000	Apply recruitment strategy changes
Red	<96 <120 <137 <160 <192 <240	<50 <40 <35 <30 <25 <20	<4,800	Stop trial

Major cardiovascular event assessment. The CVD adjudication team will be recruited in the early stages of the trial and the adjudication process honed during the pilot phase. Hospital discharge summaries will serve as the primary source of potential endpoint events. These will be assessed and categorised into: i) clear major event or no event; or ii) more information required. In the latter situation the feasibility, value and costs will be explored of obtaining specific additional information from the original hospitalisation such as ECGs, CT scan results, photocopied medical notes to assess symptoms and post mortem results if in-hospital death. Events that are uncertain will be reassessed using whatever additional information can be obtained. The results will clarify the extent of data collation the Regional Centres will need to undertake post-pilot and how to best organise the adjudication teams cost effectively. Information on deaths in trial participants will be obtained from the ONS after 9 months of recruitment. For those certified as CVD in the community without hospitalisation the availability of data from GPs and post mortem will be specifically examined.

The pilot report will also report information on:

- safety from any bleeding events requiring hospitalisation in both arms using non-adjudicated coded GP data, HES data, and any other serious adverse events
- fidelity to allocated group by examining repeat prescribing data from GP systems. Where scripts are issued by Repeat Prescribing the electronic record will record whether prescriptions have been requested by the patient or pharmacy (although it will not be possible to determine whether they have been collected). We intend to explore this after six months and twelve months. If the results indicate a high proportion of aspirin-allocated subjects are not collecting aspirin prescriptions we will review the run-in process described in Section 6.5. This information on adherence will be supplemented by questions on the annual patient questionnaire related to taking medication

- whether patients on usual care had taken OTC aspirin from follow-up questionnaires in those reaching 12 months after recruitment
- withdrawal as the number (%) of patients who withdraw from the study and refuse access to linked routine data

6.10.2 ASSESSMENT OF EVENT RATE

A report to the DMEC on adjudicated major CVD events and bleeding events (by arm) will be issued 45 months into the study based on 27 months of actual recruitment (estimated 23% of primary endpoint events, 226 in the control arm).

Data on adjudicated major CVD events and bleeding events (overall, not by arm) will be reviewed by the TSC at its regular meetings. The TSC will have the option of increasing the sample size or prolonging the scheduled treatment period if the event rate is substantially lower than anticipated.

7. TRIAL TREATMENT

7.1 DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT

7.1.1 DESCRIPTION

Active treatment will be aspirin (CAS 50-78-2) 75mg non-enteric coated tablets given once daily. Control subjects will receive no additional treatment to their usual medication.

Aspirin will be prescribed using the standard NHS prescribing system which is automatically logged in the GP practice electronic system. Standard labelling and packaging will be used. There is no placebo in this study; aspirin will be compared to no additional therapy.

Aspirin exerts an antiplatelet action through the irreversible inhibition of cyclooxygenase-1. This prevents the generation of prostaglandins, including thromboxane A2, and endothelial prostacyclin. Thromboxane A2 is an inducer of platelet aggregation and prostacyclin an inhibitor of platelet aggregation. As aspirin is less effective at reducing prostacyclin production than thromboxane A2 generation, the net effect favours reduced platelet aggregation and less thrombus formation (91). 75mg is the lowest proven effective antiplatelet dose of aspirin (16). Equivalent doses of the enteric-coated aspirin are not as effective as plain aspirin (92). No clear clinical benefits in terms of reduction of GI bleeding or ulceration with enteric coating have been demonstrated (93).

7.1.2 MANUFACTURE/MARKETING AUTHORISATION

There are several different manufacturers of generic aspirin in the UK. Because the aspirin will be prescribed using the standard NHS prescribing system, any of the available preparations may be used within the study.

7.1.3 STORAGE

Standard storage conditions apply.

7.1.4 KNOWN SIDE EFFECTS

Full details of aspirin side effects, including drug interactions, are provided in the Summary of Product Characteristics.

7.1.5 MANAGEMENT OF STUDY DRUG OVERDOSE

This will be in accordance with the recommendations of the Summary of Product Characteristics.

7.2 CONCOMITANT AND RESCUE MEDICATIONS AND TREATMENTS

There is no concomitant or rescue medication mandated in the Protocol. GPs may prescribe gastroprotection in those patients randomised to aspirin who are felt to be at the greatest risk of bleeding (Sections 1.5.4 and 6.6), but these decisions will be at the discretion of the GP.

7.3 ADHERENCE TO PRESCRIBED TREATMENT

An analysis of aspirin primary prevention trials reported persistence rates (proportions still taking trial medications/not withdrawing from trial treatments) that varied between 50 and 90% over 3 to 5 years (94)**,** with an average persistence across the six studies of 73% at 4.5 years, very similar to the figure of 13,012/19,114 seen at 5 years in the Aspirin to Reduce Events in the Elderly (ASPREE) trial (95)**.**

In ASPREE 2-3% of participants came off study medications for the purpose of going on open-label aspirin (95)**.** Incomplete adherence in the aspirin arm will also dilute the treatment effect measured by ITT, reducing the relative risk towards the null. However, the estimated risk reduction in ATTACK is conservative and has been carefully considered in the light of other aspirin trials analysed using ITT. This effect has therefore already been factored into our sample size estimations. As near-complete routine outcome follow-up data will be available, the threat to internal validity as a result of different withdrawal rates between the two arms will be minimal.

Post-consent and prior to randomisation, all patients will have a run-in period to consider and confirm their participation in the study. Self-reported compliance with prescribed aspirin and OTC aspirin consumption in the usual practice arm will be assessed in the annual ATTACK questionnaire. Treatment adherence will also be assessed from routine downloads of GP prescribing data.

Where poor adherence is demonstrated the project team will intervene pro-actively to try and address the issue. The Regional Centres will play a key role in these processes. During the setup phase we will include a dedicated session on the importance of adherence in our staff training that will include discussion of strategies to re-engage patients. Where needed, research staff may attempt to contact patients directly to discuss and emphasise the importance of taking the study medication.

7.4 URGENT SAFETY MEASURES

In the event of a situation requiring an Urgent Safety Measure (USM), immediate action will be taken to manage the event and protect the participant(s). It is the responsibility of the Chief Investigators to take appropriate action to protect study participants from any immediate hazard to their health and safety, and to notify the Sponsor of any safety concerns as well as any USM implemented. The Sponsor can also implement an USM. Should the Chief Investigators not be available the responsibility to introduce and report any USM will pass to the PI at the relevant Regional Centre. The Sponsor will ensure that any necessary USM are being implemented, that the Medicines and Healthcare products Regulatory Agency (MHRA) and the Health Research Authority (HRA) REC have been notified within the specified timelines and that hosting organisations are aware of the

need to implement USM. It is the responsibility of the research team to notify the CIs/PIs immediately after they have become aware of any issues that may put health and safety of participants at risk.

Should an urgent safety issue be identified the Sponsor or Investigator will contact the MHRA within 24 hours of identifying the safety issue. The Sponsor or Investigator will also notify the HRA REC (the REC which issued the favourable ethical opinion) immediately by phone and in writing within 3 days. These communications will be followed up by a written notification from the Sponsor or Investigator within three days of the incident. The notification should be in the form of a substantial amendment and should describe the event, the measures taken and justification for the measures taken.

Examples of situations requiring urgent safety measures might include:

- an increase in the frequency of Serious Adverse Events (SAEs) which is deemed clinically important
- a new event or information relating to the Investigational Medicinal Product (IMP) that could affect patient safety. This is exceptionally unlikely in the case of aspirin which has been widely taken by patients for many decades.

7.5 TRANSPORT AND STORAGE OF SAMPLES

Blood and/or urine samples collected at screening will be labelled, transported and analysed according to local NHS procedures.

8. TRIAL MANAGEMENT

The **Sponsor** of the trial will be the University of Southampton. The trial will be managed from a central **Trial Coordinating Centre** based at the University of Nottingham, with a designated **Trial Manager**. The activities of the Trial Coordinating Centre will be agreed and documented in the Task Allocation Matrix for the trial, and will include but not be limited to: communication with the CRN, liaison with potential centres, trial set-up and permissions, recruitment, central coordination, and management and monitoring of trial documents and patient data.

A **Trial Management Group** (TMG), led by the two **Chief Investigators**, will meet regularly to discuss the design and progress of the trial. Patients will be represented on this group and advice will be sought by TMG on relevant decisions from local patient and public involvement bodies.

The Chief Investigators will have overall responsibility for the trial and shall oversee all study management. **Regional Centres** will coordinate the study sites in their area, led by a regional **Principal Investigator**. Regional centres will be responsible for recruiting and liaising with local study sites. A **Study Site** will be a participating general practice. Each practice will have at least one **Study Site Coordinator** (SSC) who will be a primary care physician. The SSC will be responsible for selecting suitable patients from the general practice population. There will be two **Endpoint Adjudication Committees** who will each independently adjudicate possible cardiovascular endpoints and bleeding events.

The Southampton **Clinical Trials Unit** (SCTU) will support all statistical processes, including ongoing central statistical monitoring and preparation of open and closed trial reports, randomisation design, set-up, and support.

A **Trial Steering Committee** (TSC) will provide overall supervision on behalf of the Sponsor and Funder and ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The TSC will:

- provide advice, through its Chair, to the Funder, Sponsor, Chief Investigators, Host Institution and Contractor on all appropriate aspects
- concentrate on progress of the trial, adherence to the Protocol, patient safety and the consideration of new information of relevance to the research question
- emphasise that the rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society
- ensure appropriate ethical and other approvals are obtained in line with the project plan
- agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- provide advice to the investigators on all aspects of the trial/project

The TSC will include an independent Chair, a statistician with clinical trials expertise, two clinicians with expertise in the clinical area, a Health Economist, the Trial Manager, the Chief Investigators (one of which will attend each meeting) and two lay members. A representative from the Sponsor will act as an observer. All TSC meetings will have a minimum of 75% majority of independent members. The minimum quoracy for a meeting to conduct business will be 67% of appointed members. TSC meetings will be held at the start of the study and then at least annually thereafter.

The meeting schedule of the TSC will be aligned with that of the **Data Monitoring and Ethics Committee (DMEC)**. The DMEC is the only body involved in the trial with access to the unblinded comparative data. Its role is to monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue, ensuring that the safety, rights and well-being of the trial participants are paramount. The DMEC may be asked by the TSC, Sponsor or Funder to consider data emerging from other related studies.

The DMEC will comprise an independent Chair, a statistician and at least one clinician with expertise in the relevant clinical area. All members will be independent. The Trial Management Team will provide a safety report to the DMEC at a frequency (at least annual) specified by the DMEC. We will obtain contemporaneous safety data from regular searches of the GP EPR for new coded bleeding (and cardiovascular) episodes and from event reporting by Study Site Coordinators to the Regional Centres, and obtain HES data on hospital admissions. The DMEC may wish to meet on a regular basis but will be required, at a minimum, to meet at the following defined time points:

- once the pilot study has been completed to review safety and assess study recruitment and feasibility criteria of the pilot phase of the trial (27 months from the start of the trial)
- 36 months from the start of the trial to assess safety, recruitment and the control event rate
- 45 months from the start of the trial to assess safety, study recruitment and the control event rate

The Trial Coordinating Centre will undertake monitoring of Regional Centres, focussing on quality assurance, data integrity, adherence to the protocol and checking training. The Sponsor will undertake proportionate monitoring of the processes of the Trial Coordinating Centre, Regional Centres and SCTU.

9. STATISTICS

9.1 SAMPLE SIZE

A total of 25,210 patients (12,605 per arm) will be required in order for the required 1,827 major vascular events to be observed.

9.1.1 INITIAL SAMPLE SIZE ESTIMATE (NOT ACCOUNTING FOR COMPETING RISKS)

An initial sample size was calculated using NQuery v4.0 assuming a 2% annual usual care event rate and powered to detect a HR of 0.868 for the risk of experiencing a major vascular event with aspirin (proportion event-free at 5-years: 90.4% (usual care) vs. 91.6% (aspirin)). With 85% power, 5% two-sided alpha, 3.5 years for recruitment, 2.5 years follow-up and 1% dropout (withdrawal of consent for follow-up), a total of 1,792 major vascular events would be required overall.

9.1.2 DEFINITIVE SAMPLE SIZE ESTIMATE (ACCOUNTING FOR COMPETING RISKS)

As the primary outcome measure involves competing risks (deaths from other causes, including deaths from fatal bleeding which are anticipated to be higher in the aspirin arm), a sample size adjustment calculated using the Cumulative Incidence approach is required as recommended by Pintilie and Tai (96,97). Methods to calculate the sample size in the presence of competing risks (96,97) were used under the following assumptions:

- proportional hazards assumption holds between the two arms
- a 2% annual major vascular event rate in the usual care arm
- an initial HR of 0.868 (equivalent to a 1.74% annual major vascular event rate in the aspirin arm)
- a 1.8% annual event rate in the usual care arm for deaths from other causes (including fatal bleeding)
- a 1.85% annual event rate in the aspirin arm for deaths from other causes (including fatal bleeding) i.e. assuming that patients in the aspirin arm will experience a 0.05% annual rate increase of fatal bleeding compared to patients in the usual care arm
- 85% power
- 5% two-sided alpha
- 1% dropout rate
- 1:1 usual care: aspirin arm allocation
- 3.5 year recruitment period
- 2.5 year follow-up period

The corresponding sample size information was calculated as follows (all values rounded to 4 decimal places):

- cumulative incidence at 5 years (in the presence of competing risks) for the usual care arm of 0.0911
- cumulative incidence at 5 years (in the presence of competing risks) for the aspirin arm of 0.0796
- subdistribution HR of 0.8692
- proportion of main event failures in the usual care arm of 0.0782
- proportion of main event failures in the aspirin arm of 0.0682
- pooled proportion of main event failures of 0.0732

- number of major vascular events required of 1,827
- number of patients required (prior to an allowance of dropout) of 24,958
- number of patients required (after an allowance of dropout) of 25,210 (12,605 per arm)

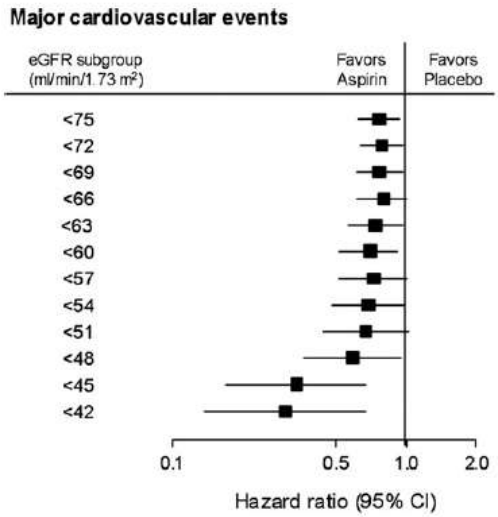
9.2 ESTIMATION OF EFFECT SIZE

An initial HR of 0.868 (12.5% RR reduction at five years) is both clinically important and appropriate for the ATTACK study population. This estimate is based upon: current knowledge on the use of aspirin for primary and secondary prevention; the risk profile of people with CKD; and the results observed in the subgroup of participants in the HOT study who had CKD.

Aspirin reduces major vascular events by more than 20% in patients with pre-existing CVD and other groups regarded to be at an annual risk of a major vascular event of more than 3% (16). By contrast in primary prevention, where the annual risk of vascular events is far lower, risk reductions of 10-12% are observed (17–19).

Cardiovascular risk is significantly increased in patients with CKD. It has been argued that CKD should be added to the list of criteria defining people at highest risk of future coronary events (98). The implication that the relative as well as the absolute benefits of aspirin in the primary prevention of major vascular events may be greater in high-risk individuals with CKD is supported by interventional data of aspirin use in this setting from the HOT study, where major cardiovascular events were reduced by 9%, 15% and 66% in those with a baseline eGFR of >60, 45-59 and <45mL/min/1.73m^2 respectively (47). The relationship between observed effect size and eGFR from this post-hoc analysis is shown in Figure 3. In this context we believe a risk reduction of 12.5% in a CKD population to be conservative.

Figure 3. The effects of aspirin on major cardiovascular events in the subgroup below each cutoff value of GFR (47)



Reproduced from Jardine MJ et al. J Am Coll Cardiol 2010;56(12):956–65.

9.3 ESTIMATION OF EVENT RATE

A summary of the findings from the trials considered when deriving an estimate of the control event rate in ATTACK, together with event rate data from additional CKD cohorts/populations and non-renal cardiovascular trials is presented in Table 5:

Table 5. Summary of annual event rates from CKD and CVD cohorts and trials from 1991-2017 ordered by year published

Trial	Year published	Age	Study population	Annual event rate
Systolic Hypertension in the Elderly Program (SHEP) (99)	1991	Mean 73	Historical trial population with hypertension 1% history of stroke 5% history of MI	2.7% non-fatal stroke/MI + CV death in controls
Systolic Hypertension in Europe (SYS-EUR) Trial (100)	1997	Mean 70	Historical trial population with hypertension 4% history of stroke 11% history of MI	3.4% fatal + non-fatal CV disease and stroke (includes heart failure) in controls 2.5% excluding heart failure
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (101)	2002	Mean 67	Historical high risk hypertensive trial population 23% with history of stroke or MI 13% with history of coronary revascularisation	1.9% non-fatal MI + fatal coronary heart disease
The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial (102)	2007	Mean 62	Contemporary trial population of higher risk type 2 diabetes 33% with pre-existing CVD Mean eGFR 92 and mean ACR 1.4	2.1% non-fatal stroke/MI + CV death
Cardiovascular Health Study (103)	2008 (but historical cohort)	65+	Cohort aged 65+ with CKD No diabetes or previous MI	1.5% CV death
Study of Heart and Renal Protection (SHARP) Trial (69)	2011	Mean 62	Contemporary high risk but relatively young CKD primary prevention trial population	1.8% non-fatal stroke/MI + CV death in controls
Alberta CKD cohort (98)	2012	Mean 72	Contemporary non-selective CKD cohort without diabetes and without previous MI 74% eGFR 44-59 80% no proteinuria	Rate of patients admitted to hospital for MI 0.7% Excludes patients at higher risk due to diabetes and CKD Excludes as outcomes any stroke and community deaths
Alberta CKD cohort population aged 50+ (104)	2014	50+	Contemporary unselected CKD cohort	1.7% coronary death or non-fatal MI Excludes stroke
Alberta CKD cohort	2014	50+	Contemporary unselected CKD cohort without	1.3% coronary death or non-fatal MI

population aged 50+ (104)			diabetes and without previous MI	Excludes stroke
Systolic Blood Pressure Intervention Trial (SPRINT) (105)	2015	Mean 68	Contemporary trial population of people at increased CV risk but without diabetes 17% with clinical CVD 28% with CKD	1.5% fatal + non-fatal MI/stroke
Renal Risk in Derby (RRID) Cohort (70,71)	2017	Mean 72	Contemporary selected primary care cohort	0.77% CV mortality in those without pre-existing CVD
National CKD Audit (106)	2017	Mean 72	Contemporary unselected primary care CKD cohort (England and Wales)	1.8% from HES data (acute MI + acute cerebral infarction + other acute CV disease + stoke non-specified) for elective and emergency admissions Excludes community deaths

It is not possible to predict the control event rate for this trial with certainty. The findings of the SHARP trial have been an important influence on the risk of vascular events anticipated in ATTACK. Based upon extrapolation from epidemiological data, the investigators in the SHARP trial estimated an annual rate of major vascular events of 3% in pre-dialysis patients attending nephrology clinics. Definite previous MI or coronary revascularisation were exclusion criteria. The final SHARP study population included 23% with diabetes and 15% with pre-existing vascular disease (angina, stroke or peripheral vascular disease). The mean age was 62 years. In those not on dialysis, the mean eGFR was 27mL/min/1.73m^2; 36% had CKD GFR category 3 and 43% category 4; the ACR was less than 3mg/mmol in 20%, 3-30mg/mmol in 38% and >30 in 42%.

Overall 13.4% of control group in SHARP experienced a major vascular event in a mean of 4.9 years follow-up. For patients with CKD GFR category 3 and 4 these figures were 10.4% and 12.7% respectively. Excluding revascularisation the control annual event rate was 1.8% overall. Major vascular events were more common where there was proteinuria: for ACR 3-30mg/mmol and >30mg/mmol they were seen in 11.9% and 13.8% respectively of controls, and 9.0% and 10.2% of the intervention subjects (69). These findings are consistent with those from HOT where hypertensive participants with eGFR 30-44mL/min/1.73m^2 experienced a five-year major cardiovascular event rate of 15.5% (47).

In extrapolating these findings to ATTACK, the following factors have been considered: i) the mean eGFR of the primary care CKD population in ATTACK will be higher than that in SHARP, with large numbers in CKD GFR category 3, lowering the anticipated event rate; ii) the primary endpoint in ATTACK excludes revascularisation which will also reduce the number of events; iii) compared with SHARP, the primary care population of ATTACK are likely to be older (for example the mean age of the CKD GFR category 3 to 5 population in the Quality Improvement in CKD Trial (n=23,311) was 75 years (107)).

Age is a strong predictor of vascular events: in the Oxford Vascular Study 75% of coronary vascular events occurred in the 14% of people age over 65 and 54% in the 6% aged over 75 (108). In the Systolic Hypertension in the Elderly Program (SHEP), the annual event rate of major vascular events

(fatal- or non-fatal stroke, non-fatal MI or CV death) was 2.7% in the control group (five-year average systolic blood pressure of 155mmHg) and 1.9% of the intervention group (five year average 143mmHg); the mean age of the study population was 73 years, with 5%, 1.5% and 10% with a pre-existing history of MI, stroke and diabetes respectively. Importantly, less than 1% had a history of "renal dysfunction" (99). In the Sys-Eur study, an annual event rate (fatal and non-fatal CVD, including heart failure) of 3.4% and 2.3% was seen in the control and intervention arms of a population of mean age 70 years where 30% had pre-existing "cardiovascular complication" (4% stroke, 11% MI) (100).

The observed rate of major vascular events in a given trial population is however likely to be lower now than it would have been 10-20 years ago. More contemporary CKD cohorts also offer important insights. The annual cardiovascular mortality in those without pre-existing CVD in the contemporary Renal Risk in Derby (RRID) primary care cohort was 0.77% (70,71) with an implied event rate of 2.3% assuming non-fatal:fatal cardiovascular events of 1.8:1 (69). The RRID participants had a mean age of 72 and a mean eGFR of 52mL/min/1.73m^2; only 16% had albuminuria. In the Alberta CKD cohort the rate of coronary death or non-fatal MI (i.e. excluding stroke) was 1.3% in an older (age ≥50 years) but lower risk CKD population without either diabetes or pre-existing coronary heart disease (104)

ATTACK is a pragmatic study and the estimated event rate of 2% assumes that the trial participants will be rather more representative of the real-world CKD population than a very highly selected group of younger and fitter patients that one might expect to see in a more demanding placebo-controlled study involving multiple visits and additional tests.

As the event rate will be highly dependent upon the age and CKD severity of patients recruited, the age distribution and CKD stage of participants will be closely monitored during the first phase of the pilot in advance of the formal estimation of the control event rate which will take place during the second phase. This will allow time to titrate the number of practices according to the recruitment rate per practice and top up our practice numbers in anticipation of a lower event rate, and to focus recruitment on more severe CKD, thereby enriching the ATTACK population with people at higher risk, should the trial population be younger than expected.

Advice will be sought from TSC should the event rate differ significantly from that anticipated. Table 6 presents alternative scenarios based upon event rates of 2%, 1.8% and 1.6%, and the effects of mitigating the effect of a lower event rate on sample size by accepting a lower power of 80%. ATTACK is powered to detect a modest risk reduction of only 12.5%. A power of 80% has been employed in, for example, the ALL-HEART study (to detect a much larger risk reduction of 20%) (83) and the major HOPE-3 trial (to detect a risk reduction of 22.5%) (109):

Table 6. Sample size and statistical power for ATTACK based upon annual event rate of 2.0%, 1.8% and 1.6%

Control event rate	Initial HR[1]	Proportion event free at 5-years [Usual Care]	Proportion event free at 5-years [Aspirin]	Alpha (2-sided)	Power	Total number of events required[1]	Number of patients required[1]
2.00%	0.868	90.4%	91.6%	5%	**85%**	1,827	**25,210**
2.00%	0.868	90.4%	91.6%	5%	**80%**	1,597	**22,036**
1.80%	0.868	91.3%	92.4%	5%	**85%**	1,823	**27,838**
1.80%	0.868	91.3%	92.4%	5%	**80%**	1,594	**24,342**
1.60%	0.868	92.3%	93.2%	5%	**85%**	1,820	**31,140**
1.60%	0.868	92.3%	93.2%	5%	**80%**	1,591	**27,222**

[1] Sample sizes calculated using an initial HR of 0.868 and accounting for deaths from other causes as competing risks, with competing risk annual event rate of 1.8% and 1.85% in the usual care and aspirin arms respectively (see Section 9.1.1 for more details).

Even with the number of eligible patients per practice lower than expected at 300 and a consent rate of approximately 7.5%, full recruitment from HEAT's existing network of 1,200 practices should be possible for:

- >85% power to detect a risk reduction of 12.5% with an annual event rate of 1.8%, or
- >80% power to detect a risk reduction of 12.5% with an annual event rate of 1.6%.

9.4 DROPOUT RATE

Follow-up for the major outcomes in ATTACK is based upon routinely collected hospital, GP and national mortality and cancer data. We will obtain baseline consent for these data to be collected. This will allow an ideal full intention-to-treat (ITT) analysis on all participants who are randomised with the exception of those who both withdraw from the study and remove their consent for data linkage, and it is for these participants that we are applying the term dropout. Patients who do not participate in annual follow-up for EQ-5D-5L and self-reported health events and health service contacts will still be followed up for major outcomes. Hence we have only factored in a small dropout rate of 1% in our sample size calculations. It is possible that the numbers stopping aspirin (especially because of side effects) and then not agreeing to follow-up may be greater than those experiencing usual care, but we believe this effect is likely to be very small and hence unlikely to be a source of significant bias, and we will monitor this.

9.5 DATA ANALYSIS

A detailed statistical analysis plan will be developed and all data and appropriate documentation will be stored according to the archiving guidelines of the Sponsor.

9.5.1 ASSESSMENT OF EFFICACY AND SAFETY

Primary outcome measure:
Time from randomisation to first major vascular event. A major vascular event is defined as a primary composite outcome of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death (excluding confirmed intracranial haemorrhage).

Secondary outcome measures:

Efficacy

1. Time from randomisation to death from any cause
2. Time from randomisation to composite outcome of major vascular event or revascularisation (coronary and non-coronary)
3. Time from randomisation to individual components of the primary composite endpoint
4. Health-related quality of life

Safety

1. Time from randomisation to composite outcome of intracranial haemorrhage (fatal and non-fatal), fatal extracranial haemorrhage and non-fatal major extracranial haemorrhage (adjudicated)
2. Time from randomisation to fatal and non-fatal (reported individually and as a composite) intracranial haemorrhage comprising: i) primary haemorrhagic stroke (to distinguish from haemorrhagic transformation of ischaemic stroke): a) intracerebral and b) subarachnoid haemorrhage (reported individually and a composite) (adjudicated); ii) other intracranial haemorrhage: a) subdural and b) extradural haemorrhage (reported as a composite) (adjudicated)
3. Time from randomisation to fatal and non-fatal (reported individually and as a composite) major extracranial haemorrhage: i) vascular-procedural; ii) vascular-non-procedural; iii) gastrointestinal; iv) genitourinary; v) respiratory; vi) pericardial; vii) ocular; viii) other; ix) undetermined) (adjudicated)
4. Time from randomisation to clinically relevant non-major bleeding

Tertiary (exploratory) outcome measures:

1. Time to TIA
2. Rate of unplanned hospitalisation
3. Time to new diagnosis of cancer (colorectal/other)
4. Time from randomisation to CKD progression (defined in Appendix 1)
5. Time to new diagnosis of dementia

The primary outcome measure will be analysed for the ITT population. Deaths from other causes (including fatal bleeding) will be treated as competing events. Patients who do not experience a major vascular event will be censored at the date of last follow-up.

As non-fatal major bleeding and anticoagulation are events which, in the intervention arm, may lead to aspirin cessation, sensitivity analyses of the primary outcome measure (for the ITT population) will also include:

- Censoring patients who experience non-fatal major bleeding (adjudicated), clinically relevant non-major bleeding, or anticoagulation at the date of the event (whichever occurs first)
- Censoring only patients who experience non-fatal major bleeding (adjudicated) at the date of the event

For the secondary outcomes of time to fatal/non-fatal major haemorrhage (both intracranial and extracranial), the following competing risk models will be used to assess impact of assumptions over competing risk and censoring:

- Deaths from other causes (excluding fatal bleeding) will be treated as competing events. Patients who experience a major vascular event will be censored at the date of the event. Patients who

do not experience either a major vascular event or fatal/non-fatal major event will be censored at the date of last follow-up

- Major vascular events and deaths from other causes (excluding fatal bleeding) will be treated as competing events. Patients who do not experience a fatal/non-fatal major event will be censored at the date of last follow-up
- Major vascular events and deaths from other causes (excluding fatal bleeding) will be treated as competing events. Patients who experience anticoagulation or clinically relevant non-major bleeding will be censored at the date of the event (whichever occurs first). Patients who do not experience either anticoagulation, clinically relevant non-major bleeding, or a fatal/non-fatal major event will be censored at the date of last follow-up
- Deaths from other causes (excluding fatal bleeding) will be treated as competing events. Patients who experience anticoagulation, clinically relevant non-major bleeding, or a major vascular event will be censored at the date of the event (whichever occurs first). Patients who do not experience either anticoagulation, clinically relevant non-major bleeding, a major vascular event or a fatal/non-fatal major event will be censored at the date of last follow-up

All primary, secondary and tertiary time to event outcomes will be described using Kaplan-Meier curves (or Cumulative Hazard plots for time to event outcomes involving competing risks) for the ITT population. Analyses of time to event outcomes will be performed using a Cox proportional hazards model (or Fine and Gray's adaptation of the Cox proportional hazards model for the subdistribution of a competing risk (110) i.e. a Competing Risk regression model for time to event outcomes involving competing risks), both unadjusted and adjusted for stratification factors: age, diabetes and CKD severity.

The adjusted competing risk regression model for time to first major vascular event, with deaths from other causes (including fatal bleeding) treated as competing events, and patients who do not experience a major vascular event censored at the date of last follow-up, will form the primary endpoint analysis model.

Other secondary and tertiary endpoints will be assessed by arm using summary statistics (e.g. Pearson's χ^2 tests) in the ITT population.

9.5.2 PROCEDURES FOR MISSING, UNUSED AND SPURIOUS DATA

The amount of missing data and reasons for the incompleteness will be explored and presented overall i.e. not by group. If the amount of missing data is deemed too high and if appropriate (i.e. assuming the missing data is either missing at random (MAR) or missing completely at random (MCAR) and censoring assumed to be non-informative), multiple imputation will be performed accordingly, for which all covariates included in the multivariable model, together with the censoring/event indicator and the cumulative baseline hazard will be included in the multiple imputation model.

9.5.3 DEFINITION OF POPULATIONS ANALYSED

All analyses will be carried out on the intention-to-treat (ITT) population. The ITT population is formed of all patients recruited and randomised to the trial.

9.5.4 ECONOMIC ANALYSIS

Economic analysis will follow the methods and 'reference case' recommended by NICE (111). Modelling will be used to estimate of the net effect of aspirin prescribing on healthcare costs and quality-adjusted survival over a lifetime horizon, using trial data to estimate effects on vascular and bleeding risks, cancer incidence, CKD progression and mortality. Trial data will also be used to estimate health-related quality of life and healthcare costs for the population and associated with adverse events.

Costs will be estimated using individual level linked HES/GP data, supplemented where necessary with information from the patient questionnaire. Costs will be estimated for services potentially affected by aspirin use, including:

- prescriptions (aspirin, gastroprotective and other related drugs)
- primary care consultations
- unplanned admissions for bleeds and vascular events, with related follow-up (e.g. revascularisations)
- renal replacement therapy following CKD progression

Unit costs for services will be obtained from standard national sources: NHS Reference Costs for admissions and other hospital services; Personal Social Services Research Unit (PSSRU) estimates for primary care and community services; and British National Formulary (BNF)/Drug Tariff for drug prices.

Quality-adjusted life years (QALYs) will be estimated using data on survival and quality of life (EQ-5D-5L) questionnaires. EQ-5D-5L data will be collected from all patients at baseline and at annual intervals. EQ-5D-5L scores ('utilities') will be calculated using a UK general population value set, as recommended by NICE at the time of analysis (112,113) Costs and QALYs will be discounted at NICE recommended rates (currently 3.5% per year for both).

The model structure, parameter sources and methods of analysis will be specified in a protocol paper, informed by a review of high quality CKD and CVD prevention models (identified from selected sources including relevant NICE technology appraisals and NIHR Journals Library publications) and agreed within the project team. We expect to use an individual-level discrete-event simulation approach to reflect the multiple, competing risks of vascular, haemorrhagic and other related events in this population over a lifetime horizon, taking advantage of the large pragmatic trial dataset (114). Distributions of baseline characteristics and risk factors will be estimated from trial data. Control arm data will be used to characterise event rates under usual care: e.g. using Cox proportional hazards predictive equations for CVD events and CKD progression; and parametric survival models (e.g. Gompertz) for all-cause survival (pre- and post- event, and by CKD stage or severity) (115). Relative treatment effects will be taken from the main trial analyses described in section 9.5.1 above (Cox proportional hazards or competing hazards regressions). The impact of events on patients' quality of life (EQ-5D-5L utility scores) and NHS costs will be estimated from trial data by an appropriate regression approach (116). If an effect on cancer incidence is found, this will be included in the economic model, although we may need to source background risk, cost and utility parameters for this outcome from the literature.

Uncertainty over model results will be explored through sensitivity analysis. Deterministic analysis will be used to investigate the sensitivity of results to input parameters and key modelling

assumptions. Probabilistic analysis will be used to assess the extent and impact of uncertainty over model inputs. Results will be stratified by pre-defined subgroups and CVD risk.

Validity of the model will be assessed by a Health Economist not involved in its development. This will include tests of internal validity: checks that input parameters match specified sources and inspection of coding (white box validation); stress testing of model behaviour (black box validation); and comparison of modelled event rates during the trial follow-up period with trial observations. External validity will be assessed by comparison of intermediate model results (event rates) with relevant estimates from the literature (identified by systematic review).

10. ADVERSE EVENTS

10.1 DEFINITIONS

Standard definitions related to adverse event reporting are summarised in Tables 7, 8 and 9.

Table 7. Defining adverse events

Adverse Event (AE)	Any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study. An AE does include a/an: 1. Exacerbation of a pre-existing illness 2. Increase in frequency or intensity of a pre-existing episodic event or condition 3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study 4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study An AE does not include a/an: 1. Medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE 2. Pre-existing disease or conditions present or detected at the start of the study that did not worsen 3. Situations where an untoward medical occurrence has not occurred (e.g. hospitalisations for cosmetic elective surgery, social and/or convenience admissions) 4. Disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition 5. Overdose of concurrent medication without any signs or symptoms
Adverse Reaction (AR)	Any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study which is related to IMP administered.
Serious Adverse Event (SAE)	Any adverse event occurring following study mandated procedures, having received the IMP, which results in any of the following outcomes: 1. Death 2. A life-threatening adverse event 3. Inpatient hospitalisation or prolongation of existing hospitalisation (excluding: hospitalisation for routine treatment or monitoring; and treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and has not worsened)

	4. A disability/incapacity 5. A congenital anomaly in the offspring of a participant Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardise the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse event that is "unexpected", meaning that its nature and severity are not consistent with the information about the medicinal product in question set out in the summary of product characteristics is classed as a SUSAR and requires expedited reporting as per clinical trials regulations.

Table 8. Defining causality

Not related or improbable	A clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.
Possible	A clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This definition will be used when drug causality is one of other possible causes for the described clinical event. It will be counted as "related" for notification purposes.
Probable	A clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.
Definite	A clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction (ADR). With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Table 9. Defining expectedness

Expected	A clinical event which is consistent with the information about the IMP listed in the Summary of Product Characteristics (SPC).
Unexpected	A clinical event which is not consistent with the information about the IMP listed in the SPC.

10.2 REPORTING OF ADVERSE EVENTS

Participating GPs/Study Site Coordinators will be asked to contact the Regional Centres and provide details of potential SAE that are not excluded in this Protocol (see below) as soon as they become aware of the event. Participants will also be asked to contact the study site in the event of any emergency hospital admission. They will carry a Trial Participant ID card which asks admitting hospitals to inform the Regional Centre of hospitalisations. Standard information will be collected and recorded on the CRF by the Regional Centre, including the nature and date of event, and reasons for attribution to study treatment. Further information will be sought as necessary.

Any participant who experiences an adverse event may be withdrawn from study treatment at the discretion of the Investigator(s), but will remain in the trial for follow-up unless they withdraw consent for this.

10.2.1 SERIOUS ADVERSE EVENTS

Aspirin was developed more than 100 years ago and has a very well-established side effect profile. There is extensive experience of the use of aspirin in people with kidney disease and it is recommended for the secondary prevention of CVD in people with CKD by NICE (72).

In this context the following events are exempted by the Protocol from expedited reporting using an SAE report form (in accordance with Section 32 Paragraph 4 of the Medicines for Human Use (Clinical Trials) Regulations 2004):

- events meeting the definition of SAE but which are listed as Undesirable Effects in the current Summary of Product Characteristics for aspirin (with the exception of hypersensitivity/allergic reactions which will subject to expedited reporting)
- anything that constitutes a trial endpoint, as this will be assessed as part of the trial
- SAE which in the opinion of the Investigator are with reasonable probability unrelated to aspirin

The Regional Centre will screen all potential SAEs (reported by Study Site Coordinators, trial subjects or admitting hospitals). Those not excluded within the Protocol will be recorded on an SAE report form. The Regional Principal Investigator (delegated responsibility from the Sponsor) will review causality, relatedness and expectedness, and forward the SAE report form to the Trial Coordinating Centre (as soon as possible and within 24 hours of becoming aware of the event) who will notify the Chief Investigator. SAEs identified in this way will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. Confirmed reports will be promptly forwarded “unblinded” to the Chair of the DMEC.

Safety information relating to adverse events not subject to expedited reporting that are captured as trial endpoints will be closely monitored by the DMEC throughout the trial. The DMEC will be provided with a report (at a frequency [at least annual] specified by the DMEC) which will include the key safety-related trial outcomes.

10.2.2 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

All serious adverse events that fall or are suspected to fall within the criteria for a SUSAR shall be treated as such until deemed otherwise. The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

1. Assess the event for seriousness, expectedness and relatedness to the study IMP
2. Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
3. If the event is deemed a SUSAR, within seven days, enter the required data on the Medicines and Healthcare products Regulatory Agency (MHRA) eSUSAR web site
4. Inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event
5. Within a further eight days send any follow-up information and reports to the MHRA and REC
6. Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

10.2.3 DEVELOPMENT SAFETY UPDATE REPORTS

The Trial Coordinating Centre will provide the Sponsor, REC and MHRA with Development Safety Update Reports. The reports will be submitted within 60 days of the anniversary date of the MHRA clinical trial authorisation (Developmental International Birth Date) of the trial each year until the trial is declared ended.

10.3 PREGNANCY

Participants will be asked to inform their Regional Centre of any pregnancies (i.e. of female participants or female partners of male participants) which occur during the trial participation period. All pregnancies will be recorded on the CRF and followed up for outcome. Where it is the partner of a trial participant, consent will be obtained for this observation from both the partner and her medical practitioner. Any outcome meeting the definition of an AE/SAE will be reported to the Trial Coordinating Centre. The responsible clinician will adjust all medication as required for the pregnancy to continue as needed.

11. ETHICAL AND REGULATORY ASPECTS

11.1 ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the Protocol, ICF and PIS have received approval/favourable opinion from the Sponsor, MHRA, REC, and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the Protocol will not be instituted until the amendment and revised ICF and PIS (if appropriate) have been reviewed and received approval/favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard

to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with: the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of GCP, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments; and the Department of Health Research Governance Framework for Health and Social care, 2005.

11.2 RECORDS

11.2.1 CASE REPORT FORMS (CRF)

Each participant will be assigned a screening number, and a trial randomisation number, allocated at randomisation, for use on trial documents and the electronic database. The documents and database will also use their initials and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. A separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log) will be held securely on the trial database, to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.' All paper forms shall be filled in using a dark pen. Errors shall be scored through and the correction inserted, initialled and dated. The Investigator shall sign a declaration attesting to the accuracy of data recorded in the CRF.

11.2.2 SOURCE DOCUMENTS

Source documents will include the patient's electronic GP record, and their hospital records. In addition to this, a source data worksheet will be completed at the patient's consent visit by the research nurse, which will record basic demographic and clinical information about the patient, along with confirmation of inclusion/exclusion criteria. This will be filed in the Trial Master File held at each of the Regional Centres, along with a copy being stored in the site file at each trial practice (which can be scanned and uploaded to the patient's electronic GP record if desired). Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

The CRF and all source documents shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

11.3 DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above).

Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method). Information about the trial in the participant's medical records/hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

12. QUALITY ASSURANCE & AUDIT

12.1 INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and staff is provided through NHS schemes (under cover of HSG [96] 48) and public liability insurance/clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm. The sponsor holds Public Liability (negligent harm) and Clinical Trials (negligent harm) insurance policies which apply to this trial. Indemnity for GP Study Site Co-ordinators is available through personal professional indemnity arrangements.

12.2 TRIAL CONDUCT

Trial conduct will be subject to systems audit where appropriate of: the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol; adverse event recording and reporting; and equipment calibration logs.

12.3 TRIAL DATA

Monitoring of trial data shall include: confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures; back-up and disaster recovery of any local databases; and validation of data manipulation. The Regional Centre team, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on the trial database will be verified by inspection against the source data (a percentage as defined in the Monitoring Plan). Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

The Sponsor will undertake proportionate annual review of the Regional Centres using a trial monitoring checklist.

12.4 RECORD RETENTION AND ARCHIVING

In compliance with the International Conference on Harmonisation (ICH) GCP guidelines, the Chief or Regional Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for up to 10 years after the date of any publication based on the research data. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Southampton. This archive shall include all trial databases and management software and associated meta-data encryption codes.

12.5 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

12.6 STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Southampton representatives, the REC, local R&D Departments and the regulatory authorities.

13. PUBLICATION AND DISSEMINATION POLICY

The study results will be presented at scientific meetings and will be the subject of peer-reviewed publications. Trial participants will not be identified in any publications. Patients will be informed of the results of the trial once they have been published.

14. USER AND PUBLIC INVOLVEMENT

There will be a lay advisor on the Trial Management Group. Their role will be to advise on strategies for recruitment and follow up of participants, comment on study documents and advise on dissemination. There will also be two independent lay advisors on the Trial Steering Committee to give strategic input from a patient perspective.

The lay member on the TMG will have influence over the design of the trial and study documents and will be consulted at all stages of the research project.

15. STUDY FINANCES

15.1 FUNDING SOURCE

This study is funded by grants from the National Institute of Health Research Health Technology Assessment programme and the British Heart Foundation.

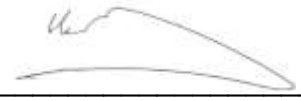
15.2 PARTICIPANT STIPENDS AND PAYMENTS

Participants will not be paid to participate in the trial. Travel expenses will be offered.

16. SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Prof Hugh Gallagher

Signature: 

Date: 16/10/18

Chief Investigator: Prof Paul Roderick

Signature: 

Date: 16/10/18

Trial Statistician: Tom Maishman

Signature: 

Date: 6-Nov-18

Sponsor: _____

Signature: _____

Date: _____

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APPENDIX 1: DEFINITION OF CLINICAL ENDPOINTS

Major vascular event	Composite outcome of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death (excluding confirmed intracranial haemorrhage)

Non-fatal myocardial infarction	Defined according to the Third Universal Definition of MI (117).
	An acute MI is defined by any one of the following criteria:
	• Detection of a rise and/or fall in cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit [URL] and with at least one of the following:
	  ○ Symptoms of ischaemia
	  ○ New or presumed new significant ST-segment/T-wave changes or new left bundle branch block (LBBB)
	  ○ Development of pathological Q waves in the ECG
	  ○ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
	  ○ Identification of an intracoronary thrombus by angiography or autopsy
	• Percutaneous coronary intervention (PCI)-related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile ULN) in patients with normal baseline values (≤99th percentile ULN) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required
	• Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial infarction and with a rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile URL
	• Coronary artery bypass grafting (CABG)-related MI is arbitrarily defined by elevated of cardiac biomarker values (>10 x 99th percentile ULN) in patients with normal baseline values (≤99th percentile ULN). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality
	
	ECG criteria consistent with myocardial ischemia include:
	• ST elevation. New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women
	• ST depression and T-wave changes. New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1
	
	In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

Non-fatal stroke	Defined in accordance with the World Health Organization (WHO) definition as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, with no apparent cause other than of vascular origin" (118). This excludes cases of primary cerebral tumour, cerebral

	metastasis, subdural haematoma, post-seizure palsy, brain trauma and TIA. Haemorrhagic stroke (fatal and non-fatal) which has been confirmed on appropriate imaging (see below) is excluded from the primary composite endpoint and included within the secondary endpoints. Haemorrhagic transformation of a primary ischaemic stroke is included within the primary endpoint. Haemorrhagic stroke includes both intracerebral and subarachnoid haemorrhage (119,120)
Cardiovascular death	Defined largely according to the work of the Standardised Data Collection for Clinical Trials Initiative (121,122), with the difference that deaths due to intracranial haemorrhage (haemorrhagic stroke, non-stroke intracranial haemorrhage) are, as safety events rather than efficacy targets, excluded from the primary composite endpoint and included within the secondary endpoints. Other elements of death due to cardiovascular haemorrhage (for example non-procedural or non-traumatic vascular rupture, or haemorrhage causing cardiac tamponade) are unlikely to be negatively influenced by aspirin and are included within the primary composite endpoint. The aim of adjudication is to capture the primary cause of death, defined as the underlying disease that initiated the chain of events resulting in death (as opposed to the mode of death which is the physiological derangement or biochemical disturbance produced by the cause of death). Non-cardiovascular causes of death may culminate in a cardiovascular mode of death (from example renal failure cause dysrhythmia) – these will not be regarded as CV deaths (122). Cardiovascular death is subdivided as follow: • Death due to acute MI, defined as one of: o Death by any cardiovascular mechanism ≤30 days after a MI (definite or suspected (123)) o Death resulting from a procedure to treat a MI or a complication resulting from MI o Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased (117) • Sudden cardiac death is a death that occurs unexpectedly, not following an acute MI, and includes the following deaths: o Death witnessed and occurring without new or worsening symptoms o Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI o Death witnessed and attributed to an identified arrhythmia (e.g. captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review) o Death after unsuccessful resuscitation from cardiac arrest (e.g. implantable cardioverter defibrillator unresponsive sudden cardiac death, pulseless electrical activity arrest) o Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac aetiology o Unwitnessed death in a subject seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death • Death due to stroke (excluding confirmed haemorrhagic stroke), where the death is either a direct consequence of the stroke or a complication of the stroke

	• Death due to heart failure, where the death is in association with clinically worsening symptoms and/or signs of heart failure regardless of HF aetiology • Death due to cardiovascular procedures, where the death is caused by the immediate complications of a cardiac procedure (excluding deaths from procedures to treat an MI) • Death due to cardiovascular haemorrhage is a cardiovascular death related to haemorrhage (excluding intracranial haemorrhage) such as non-procedural or non-traumatic vascular rupture, or haemorrhage causing cardiac tamponade • Death due to other cardiovascular causes is a cardiovascular death not included in the above categories (and not due to intracranial haemorrhage) but with a specific, known cause (e.g. pulmonary embolism or peripheral arterial disease)
Haemorrhagic stroke	Defined in accordance with the World Health Organization (WHO) definition of stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (118), and following the approach of the ASPREE investigators, where: • CT scanning demonstrates an area of hyperdensity within the brain parenchyma with or without extension into the ventricles or subarachnoid space or, for scans performed beyond 1 week, an area of attenuation with ring enhancement after injection of contrast, or • MRI scanning shows an area of hypointensity or isointensity on T1-weighted images or an area of marked hypointensity on gradient echo and T2-weighted images, or • autopsy demonstrates the origin of the hemorrhage as the cerebral parenchyma (123)
Intracranial haemorrhage	Includes intracerebral haemorrhage, subarachnoid haemorrhage, subdural haemorrhage, and epidural haemorrhage. For reporting purposes, subdural and epidural haemorrhage will be grouped and recorded as other intracranial haemorrhage
Major extracranial haemorrhage	Major extracranial bleeding is defined as: • Fatal bleeding, or • Symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, or • Bleeding that leads to the transfusion of two or more units of whole blood or red cells It will be emphasised to the EAC that major bleeds are those that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources. In particular, to be classified as major, bleeds in a critical area or organ should: • Be associated with a symptomatic clinical presentation (not following an incidental finding) • Be the cause of the symptoms The definitions follow the recommendations of the International Society for Thrombosis and Haemostasis (ISTH) (124), with the difference that "bleeding causing a fall in hemoglobin level of 20 g/L or more" is included within the ISTH definition but excluded in ATTACK. Change in Hb has been removed because

	patients with CKD may have, or develop, anaemia as a direct result of the kidney disease, and may be treated with erythropoietin which will result in fluctuations in the Hb concentration, making the relationship between bleeding and haemoglobin level less clear. This approach is in line that adopted in ASPREE and ASCEND. In ASPREE "clinically significant bleeding" is defined as bleeds at any site that require hospitalisation, prolonged hospitalisation, transfusion, surgery or are fatal (123). In the case of ASCEND "major haemorrhage" is any bleeding episode (excluding cerebral haemorrhage) that requires hospitalisation or transfusion, or is fatal or disabling (84). The source of major bleeding will be categorised as: i) vascular-procedural; ii) vascular-non-procedural; iii) gastrointestinal; iv) genitourinary; v) respiratory; vi) pericardial; vii) ocular; viii) other; ix) undetermined).
Clinically relevant non-major bleeding	Defined in accordance with the ISTH as any sign or symptom of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: • Requiring medical intervention by a healthcare professional • Leading to hospitalisation or increased level of care • Prompting a face to face (i.e. not just a telephone or electronic communication) evaluation (125) This definition includes all minor bleeding episodes that lead to medical evaluation involving direct patient contact.
Death from any cause	Will be ascertained from death certificates or post-mortem reports.
Revascularisation	Will include open and percutaneous coronary and non-coronary (including carotid, aortic and limb) procedures (as defined in OPCS-4 procedure codes) and will be ascertained from HES data.
Hospitalisation	Defined as an official admission that is for a duration greater than 24 hours or a minimum of 2 calendar days where exact time of stay is unavailable.
CKD Progression	Defined as at least one of: • >30% fall in eGFR over two years (126), or • need for renal replacement therapy or 50% decline in eGFR (127)**,** or • new eGFR<15mL/min/1.73m^2, or • 25% decline in GFR together with a drop in GFR category (3)
Health-related quality of life (HRQoL)	A combination of a person's physical, mental and social well-being, not merely the absence of disease. A 'utility' is the measure of the preference or value that an individual or society gives a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost-utility analysis is the quality-adjusted life year (QALY), which combines quality of life with length of life. One QALY is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a 0 to 1 scale). It can be measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance (128).

APPENDIX 2: TRIAL FLOW DIAGRAM