APT-KIDNEY

ASPIRE CKD - Aspirin for cardiovascular protection in patients with advanced kidney disease

Domain-Specific Appendix

Protocol appendices version and date

Version 1.21, 23-10-2026

Applicable protocol registration numbers

Corresponding core protocol version and date: v 1.22, 21-10-2026

Core protocol registration numbers:

EU CT number: 2026-527443-17-00

WHO Universal Trial Number: U1111-1331-7534

ClinicalTrials.gov Identifier: NCT07595952

Summary of changes

This section summarizes all changes to the domain-specific appendix after initial submission for approval.

Protocol version	Date	Major changes

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1 Protocol Summary

1.1 Synopsis

Protocol title: Aspirin for cardiovascular protection in patients with advanced kidney disease: an APT-KIDNEY platform trial domain investigating benefit of low-dose aspirin as primary prophylaxis on cardiovascular outcomes in patients with eGFR < 30ml/min/1.73m2 including end-stage kidney disease

Acronym: ASPIRE CKD

Rationale: Advanced chronic kidney disease (CKD) confers substantial cardiovascular risk. Primary prevention with low-dose acetylsalicylic acid (aspirin) has been associated with a 10-20% benefit on risk of cardiovascular events offset by increased risk of bleeding. Primary prevention with low-dose aspirin in advanced CKD may confer benefit on cardiovascular risk, albeit net benefit may be attenuated by increased risk of bleeding.

Design: Investigator-initiated, open-label, pragmatic, parallel-group platform domain.

Inclusion and exclusion criteria: Adults with eGFR < 30 ml/min/1.73 m^2 ≥3 months or end-stage kidney disease (ESKD) on maintenance hemo- or peritoneal dialysis, and either patient age ≥50 years, or any adult ≥18 with diabetes. Exclusions include preceding antiplatelet or anticoagulation treatment, prior bleeding < 3 months, thrombocytopenia, severe liver disease, prior intolerance to aspirin.

Number of participants: Event-driven, target E=631 primary events; planning assumptions imply ~949 participants per arm (1:1 randomization).

Interventions and comparisons: Follow-up from randomization to study end (event-driven data cut) or death, with a minimum follow-up of 24 months and an administrative cap of 60 months after randomization.

Intervention: Aspirin 75 mg QD

Control: No treatment

Outcomes:
Primary (superiority): Major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction and/or non-fatal ischemic stroke (time-to-first event).

Secondary (superiority): Major bleeding (time-to-first event), defined as Bleeding Academic Research Consortium (BARC) type 3-5.[1]

Tertiary (exploratory): All-cause mortality, individual components of 3-point MACE, hemorrhagic stroke, intracranial hemorrhage, major gastrointestinal bleeding (BARC type 3–5), health-related quality of life (HRQOL) (EQ-5D-5L index values), and net clinical benefit.

Abbreviated statistics: Analyses follow intention-to-treat. Primary endpoint will test superiority of low-dose aspirin (75mg) as primary prophylaxis on MACE outcomes based on a Cox proportional hazards model. Major bleeding (BARC 3–5) will be assessed at prespecified intervals and reported regardless; treatment effect will be estimated as a hazard ratio with 95% confidence interval. Tertiary endpoints will be analyzed using standard survival models for time-to-event outcomes and count-rate models for recurrent events. HRQOL (EQ-5D-5L index; national value sets; deaths weighted as dead) will be compared between groups at prespecified timepoints using linear models adjusted for baseline EQ-5D-5L and site, and supportive longitudinal analyses using a repeated-measures model. No planned efficacy interim analyses: risk-proportionate safety monitoring with IDSMC safety reviews broadly aligned with event accumulation and ad hoc as needed.

Funding: Applications pending to Sundhedsdonationer.

1.2 Administrative information

1.2.1 Protocol and domain-specific appendix structure

This document is a domain-specific appendix (DSA) to the APT-KIDNEY core and forms part of the clinical trial documentation for this investigational medicinal product (IMP) study. Procedures and provisions described in the core protocol apply to this domain unless explicitly stated otherwise in this DSA.

In accordance with the APT-KIDNEY core protocol, the platform sponsor holds overall responsibility for IMP accountability, with operational implementation delegated to the domain lead. ASPIRE CKD is a prescription-based IMP domain: aspirin is provided through standard clinical prescribing and commercial pharmacy dispensing, so IMP-specific manufacturing, importation, labeling, and packaging obligations do not apply, and the domain lead's delegated responsibility is limited to ensuring that the prescription strategy is implemented as specified in this DSA.

This DSA provides domain-specific details including eligibility refinements, intervention procedures, endpoints, and statistical considerations that are not fully specified in the core protocol and should be read in conjunction with the core protocol and other applicable appendices. The domain-specific statistical analysis content is provided in the Statistical Considerations section and will be finalized in a domain statistical analysis plan (SAP) prior to database lock and analysis in accordance with the core protocol.

1.2.2 Modifications of the domain-specific appendix

Changes to this DSA will be managed in accordance with the APT-KIDNEY core protocol and applicable regulatory requirements for IMP trials.

- **Substantial amendments** (i.e., changes likely to have a substantial impact on participant safety or rights, or on the reliability/robustness of trial data) will be submitted via the Clinical Trials Information System (CTIS) for authorization as substantial modifications of the APT-KIDNEY platform trial (core protocol Section 7.2) prior to implementation, except where urgent safety measures are required.
- **Non-substantial changes** (e.g., minor administrative edits or clarifications without impact on safety, rights, or data integrity) will be version-controlled and filed in the Trial Master File (TMF) and Investigator Site File (ISF) and implemented in accordance with sponsor procedures.

Where amendments necessitate changes to participant-facing materials i.e. Participant Information Sheet and/or Consent Form, revised documents will be submitted for approval and implemented only after approval, unless urgent safety measures apply. Following approval and/or authorization, relevant updates will be communicated to investigators and study staff, and the current approved version will be filed and distributed under document control. Version history and prior approved versions will be retained in the TMF / ISF.

1.2.3 Domain lead, domain steering committee, and contributors

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Key persons at the domain coordinating center are listed on the APT-KIDNEY website.

Domain-specific appendix contributors:

The ASPIRE CKD domain-specific appendix was developed by the domain lead and members of the domain steering committee. Individual contributors and their roles are recorded in the trial master file.

1.2.4 Domain independent data and safety monitoring committee (IDSMC)

The ASPIRE CKD IDSMC will comprise a clinical trialist (chair), a clinician with expertise in cardiovascular prevention and antithrombotic therapy, and a biostatistician, all independent of the sponsor and trial operations. Members will be appointed before the first inclusion and listed in the IDSMC charter.

2 Abbreviations and definitions

ACC/AHA	American College of Cardiology / American Heart Association
APT-KIDNEY	Adaptive Platform Trial for Kidney Disease
ASPIRE CKD	Aspirin for cardiovascular protection in advanced kidney disease
BARC	Bleeding Academic Research Consortium
CTIS	Clinical Trials Information System
CKD	Chronic kidney disease
CVD	Cardiovascular disease
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQol 5-Dimension, 5-Level questionnaire
EQ-VAS	EuroQol Visual Analogue Scale
ESC	European Society of Cardiology
ESKD	End-stage kidney disease
EPR	Electronic patient record
HR	Hazard ratio
HRQOL	Health-related Quality of life
IDSMC	Independent data and safety monitoring committee
IMP	Investigational medicinal product
INR	International normalized ratio
ISF	Investigator Site File
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MMRM	Mixed model for repeated measures
PDC	Proportion of Days Covered
PI	Principal Investigator
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SmPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischemic attack
TMF	Trial master file

3 Introduction

3.1 Background

Chronic kidney disease (CKD) represents a major global health burden, with an estimated prevalence of 10-15%[2,3] and projections indicating that CKD will become the fifth leading cause of death worldwide by 2040.[4] The increasing prevalence is primarily driven by aging populations and the rising incidence of hypertension and type 2 diabetes.[5] CKD is associated with considerable morbidity, impaired quality of life, and increased mortality, with prognosis worsening in parallel with declining kidney function.[6–8] As such, patients with kidney failure treated with dialysis have a markedly reduced life expectancy, up to 25 years shorter than that of the general population.[9]

3.1.1 Cardiovascular disease in chronic kidney disease

Cardiovascular disease is the leading cause of death among patients with CKD and many patients die before reaching kidney failure.[6,7] Among patients receiving dialysis, cardiovascular disease accounts for more than 50% of deaths[10], corresponding to a 10-30-fold higher cardiovascular mortality compared with the general population.[11] The excess risk is partly attributable to a higher prevalence of traditional risk factors – such as advanced age, diabetes, dyslipidemia, hypertension, and modifiable lifestyle factors – and partly to kidney disease-specific mechanisms.[6,7] In addition, platelet function is altered with defective platelet adhesion to the sub-endothelium, impaired platelet aggregation, and other intrinsic platelet defects.[12–14] Collectively, this results in an increased risk of both bleeding and thromboembolic events in patients with CKD.[15,16] Accordingly, the recently reported TRACK trial, a randomized, placebo-controlled trial of low-dose rivaroxaban in 1,458 patients with CKD stage 4–5 or dialysis-dependent kidney failure at elevated cardiovascular risk, found no reduction in major adverse cardiovascular events (HR 1.09, 95% CI 0.87–1.36) and a significant increase in major bleeding (HR 1.51, 95% CI 1.02–2.22), leading to early termination for futility and net harm. Notably, while TRACK evaluated an anticoagulant rather than an antiplatelet agent, the study results underscore the balance of a high cardiovascular event rate with substantial bleeding penalty in patients with advanced CKD, reinforcing the need for dedicated evaluation of aspirin specifically.[17]

3.1.2 Guideline-recommendations for primary and secondary prophylaxis of cardiovascular disease

Due to the systematic exclusion of patients with CKD from randomized clinical trials investigating cardiovascular diseases, the available evidence is limited, and current guidelines are largely based on *post hoc* and subgroup analyses.[18] To reduce the elevated risk of cardiovascular disease in patients with CKD, KDIGO guidelines recommend optimization of lifestyle factors, systolic blood pressure below 120 mmHg (when tolerated), and statin treatment in all patients aged ≥50 years.[19] These recommendations primarily rely on findings from the *Systolic Blood Pressure Intervention Trial* (SPRINT)[20] and *Study of Heart and Renal Protection* (SHARP).[21] In contrast, the European Society of Cardiology and the American Heart Association/American College of Cardiology advocate for a more individualized risk-stratified approach defining blood pressure and lipid targets.[22,23] With regard to aspirin therapy, the guidelines concur in recommending low-dose aspirin for secondary prophylaxis, while none support routine use for primary prevention in either patients with or without CKD (see Table below).[19,22,23]

	Primary prophylaxis	Secondary prophylaxis
KDIGO 2024[19]	"Not possible to provide definitive recommendations"	Aspirin (75-100 mg) recommended
ESC 2021[23]	CKD considered a high- or very high-risk condition. Risk assessment based on SCORE2-OP is recommended. "We cannot exclude that in some patients at high or very high CVD risk, the benefits outweigh the risks"	Aspirin (75-100 mg) recommended

ACC/AHA 2019[22]	"Low-dose aspirin might be considered among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk." "Low-dose aspirin should not be administered on a routine basis among adults >70 years of age."	Aspirin (75-100 mg) recommended

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; SCORE2-OP, Systematic Coronary Risk Estimation 2-Older Persons;
2024 Kidney Disease Improving Global Outcomes Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[19]
2021 European Society of Cardiology Guidelines on cardiovascular disease prevention in clinical practice [23]
2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease[22]

In contrast to international guidelines, some national and regional recommendations including the Danish guidelines for diabetes management endorse consideration of low-dose aspirin for primary prevention in select high-risk individuals, such as those with diabetes mellitus and additional cardiovascular risk factors.[24–26] These more permissive recommendations likely reflect a pragmatic approach that weighs the elevated cardiovascular burden in these populations against the uncertain, but potentially meaningful, benefits of antiplatelet therapy. This divergence underscores the ongoing clinical equipoise regarding aspirin use in high-risk groups, especially in advanced CKD, where both thrombotic and bleeding risks are accentuated, and robust trial data remain lacking.

3.1.3 Aspirin treatment in general populations

In the general population, the 2009 Anti-thrombotic Treatment Trialist's Collaboration meta-analysis combined data from six primary prevention trials of (~95,000 low-risk participants) and sixteen secondary prevention trials (~17,000 high-risk participants). In the primary prevention cohort, aspirin reduced the risk of serious vascular events by 12%, mainly due to a lower incidence of non-fatal myocardial infarction, but the benefit was accompanied by a 0.03% absolute increase in major bleeding risk. Among high-risk individuals in the secondary prevention trials, aspirin reduced the risk of serious vascular events by approximately 20%. Notably, the primary prevention trials in this analysis were conducted between 1978 and 1998.[27]

More recent meta-analyses incorporating data from three large 2018 trials — A Study of Cardiovascular Events in Diabetes (ASCEND)[28], Aspirin in Reducing Events in the Elderly (ASPREE)[29], and Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE)[30] — found no benefit of aspirin for the primary prevention of mortality.[31,32] However, the risk of cardiovascular events was reduced by up to one fifth, mainly, though not consistently, driven by a lower incidence of myocardial infarction.[31–35] These benefits were offset by a 30-48% increase in the major bleeding risk[31,32,35], with relative risk estimates of 28% for major bleeding, 23% for intracranial hemorrhage, and 37% for gastrointestinal bleeding,[35] corresponding to an absolute increase in risk ~0.5-1%, with evidence regarding benefit in patients with diabetes overall inconsistent.[32,33,35]

3.1.4 Aspirin treatment in patients with chronic kidney disease

Evidence from primary prevention trials comparing aspirin with placebo including CKD subgroups is limited. In a post hoc analysis of the CKD subgroup (n = 4758) from the ASPREE trial of elderly patients, aspirin conferred no survival benefit and only marginal reduction in major cardiovascular events, most apparent among individuals with a urine albumin-creatinine ratio ≥3 mg/mmol. This modest benefit was offset by an increased risk of major bleeding, and results were consistent across eGFR strata.[36]

In contrast, a subgroup analysis of approximately 1000 participants with CKD from The International Polycap Study-3 (TIPS-3) demonstrated an overall cardiovascular benefit of aspirin, with greater relative reductions in risk observed at lower eGFR levels (<70 ml/min/1.73 m^2 compared with 70-90 ml/min/1.73 m^2 and ≥90 ml/min/1.73 m^2).[37] Similarly, in the

Hypertension Optimal Treatment (HOT) study, aspirin use among ~500 patients with eGFR <45 ml/min/1.73 m^2 was associated with reductions in major cardiovascular events and total mortality, although with a non-significant increase in major bleeding.[38]

Conversely, no benefit of aspirin on atherosclerotic events was observed among 630 participants with type 2 diabetes and eGFR <60 ml/min/1.73 m^2 in the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial. In contrast, patients with higher eGFR (60-89 ml/min/1.73 m2) derived cardiovascular benefit.[39]

A prospective analysis from the Chronic Renal Insufficiency Cohort (CRIC) Study (n=3664, mean eGFR 47 ml/min/1.73 m^2) found no association between aspirin use and reductions in all-cause mortality or a composite cardiovascular outcome, regardless of presence or absence of pre-existing cardiovascular disease[40]

Trials enrolling only CKD patients are scarce. The Aspirin for Primary Prevention of Cardiovascular Disease and Renal Disease Progression in Chronic Kidney Disease Patients (AASER) trial, a small multicenter randomized study published in 2018, included 111 participants with eGFR 15-60 ml/min/1.73 m^2. Despite limited statistical power, the study suggested a potential reduction in coronary events and possible benefit in slowing kidney disease progression, without differences in the composite cardiovascular outcome or minor bleeding, and no major bleedings were reported.[41] The ongoing Aspirin to Target Arterial events in Chronic Kidney disease trial (ATTACK) aims to enroll approximately 25,000 patients with CKD stages G1-G4 from UK primary care to compare 75 mg aspirin versus no treatment for the time to first major vascular event.[42] Completion was anticipated by December 2025, results remain unpublished.[43]

Finally, two meta-analyses — one from 2012 including 31 trials (~12,000 participants)[44] and another from 2016 including 3 trials (~4500 participants)[45] reported inconsistent results. The 2012 analysis demonstrated a reduction in myocardial infarction risk but no effect on mortality, accompanied by an increased incidence of minor bleeding[44], whereas the 2016 analysis found no benefit on either cardiovascular outcomes or survival, but an elevated risk of bleeding.[45] Lastly, a 2022 Cochrane meta-analysis including CKD subgroups from aspirin vs placebo trials (n≈40,000) and trials comparing different antiplatelet agents (n≈12,000) found that antiplatelet therapy reduced the risk of myocardial infarction by 12%, had uncertain effects on stroke, and little or no effect on death, offset by an increased risk of minor and major bleeding. Of note, this analysis did not differentiate between primary and secondary prevention populations.[46]

3.1.4.1 Mitigation of gastrointestinal bleeding risk

As previously discussed, platelet function is impaired[12–14] in patients with CKD, leading to an increased bleeding tendency across all CKD stages, including among kidney transplant recipients.[46] In elderly individuals, this risk may be further amplified.[47] However, a meta-analysis reported that although aspirin therapy was associated with up to 60% increase in overall bleeding risk, there was no corresponding increase in fatal bleeding compared with no treatment.[48] As such KDIGO guidelines[19] recommend the concomitant use of proton pump inhibitors in patients receiving antiplatelet therapy, as proton pump inhibitors are considered effective, safe, and inexpensive, with only minimal risk of interstitial nephritis.[49]

3.2 Benefit-risk assessment and safety outcomes

3.2.1 Risk classification

ASPIRE CKD evaluates the benefit and safety of low-dose aspirin (75 mg OD) for primary prevention of cardiovascular outcomes in patients with advanced CKD. The safety profile of low-dose aspirin is well established from extensive authorized use, whereas its net clinical benefit for primary cardiovascular prevention in advanced CKD remains uncertain; post-hoc analyses of randomized trials suggest potential net benefit i.e. reduction of risk of cardiovascular events not offset by comparable increased risk of bleeding.[36–39,41,44,45] Patients with advanced CKD are classified as high- or very high-risk for cardiovascular events,[23] and are routinely monitored at outpatient clinics (standard care entails three (3) annual visits for patients with eGFR < 30 ml/min/1.73m^2, and more frequent monitoring of patients with ESKD).[50]

ASPIRE CKD is designed to meet the low-intervention criteria of the platform (core protocol Section 6.3). Low-dose aspirin is authorized in Denmark. Its use for primary cardiovascular prevention is not a listed indication in the Danish SmPC, which covers secondary prevention in patients with established coronary artery disease, and is therefore off-label. This use is evidence-based and supported by published scientific evidence on safety and efficacy: meta-analyses of randomized trials show reductions in major vascular events, mainly myocardial infarction, alongside increased bleeding,[27,31–35]and analyses of CKD populations report reductions in cardiovascular events of variable magnitude;[36–38,41,46] European guidance acknowledges that benefit may outweigh risk in some patients at high or very high cardiovascular risk,[23] and Danish recommendations support use in selected patients with type 2 diabetes at high cardiovascular risk.[24–26] The uncertainty addressed by this domain is the net clinical benefit in advanced CKD, not the established effects of aspirin. The domain adds no protocol-mandated diagnostic or monitoring procedures, and follow-up is aligned with routine nephrology care.

Given the established safety profile of low-dose aspirin and the minimal additional burden, ASPIRE CKD is classified as Risk level 1 for safety management (core protocol Section 10.3.2.1), including DSA-defined aspirin-related serious adverse reactions (SARs) (SmPC-based, with clinically relevant additions) and 24-hour site-to-domain lead notification of potential suspected unexpected serious adverse reactions (SUSARs).

3.2.2 Domain-specific safety outcomes

The prespecified domain-specific safety outcomes for ASPIRE CKD will be registered electronically in the eCRF with local and national adaptations as applicable.

- Major bleeding (BARC 3-5) defined as BARC type 3 denoting significant bleeding (3a: with hemoglobin drop 1.86 - <3.11 mmol/L and/or transfusion, 3b: with hemoglobin drop ≥3.11 mmol/L and/or tamponade, surgery or vasoactive therapy, and 3c: intracranial hemorrhage or intraocular bleeding with vision loss), or BARC type 4 as defined by bleeding related to coronary bypass grafting procedures, or BARC type 5 denoting fatal bleeding.[1]
- All-cause mortality i.e. death due to any cause

3.2.3 Safety assessment and reporting

Safety assessment and reporting will follow the APT-KIDNEY risk-proportionate framework for Risk level 1 domains. AEs and ARs are not recorded. The prespecified serious safety outcomes (BARC 3–5 major bleeding and all-cause mortality) and core outcomes are recorded in the eCRF as trial outcomes; other SAEs and SARs are not recorded. Investigators do not report SAEs or SARs to the sponsor unless they consider it warranted (core protocol Section 10.3.2.2; Article 41(2) of Regulation (EU) No 536/2014). Potential SUSARs are the only events that require notification.

For the purposes of safety escalation and SUSAR assessment, aspirin-related SARs (SmPC-based) will be defined as serious events consistent with the aspirin SmPC,[51] including:

(i) major bleeding (captured as BARC 3–5)
(ii) peptic ulcer complications/gastrointestinal hemorrhage requiring hospitalization or intervention
(iii) severe hypersensitivity reactions i.e. anaphylaxis, severe bronchospasm and/or angioedema requiring urgent treatment or hospitalization

Hemorrhagic stroke, also listed in the aspirin SmPC, is captured within the BARC 3c definition (intracranial hemorrhage) and is additionally recorded as a prespecified tertiary safety endpoint (Section 8.2.3).

Potential SUSARs will be notified from the site to the domain lead (or delegate) within 24 hours; the platform sponsor will report them to EudraVigilance (within 7 days for fatal or life-threatening cases and 15 days for others) and include them in the annual safety report submitted via CTIS.

3.2.3.1 Pregnancy and contraception

Although fertility in women with advanced CKD and ESKD is markedly decreased, pregnancy remains possible.[52,53] The aspirin SmPC contraindicates use in the third trimester due to risk of premature closure of the ductus arteriosus and inhibition of labor,[51] with use in the first and second trimesters based on individual benefit–risk assessment. However, low-dose aspirin (75–150 mg/d) is not classified as teratogenic and is recommended for preeclampsia prophylaxis in women with CKD and other high-risk conditions from 12 weeks' gestation,[54–56] reflecting an established safety profile in pregnancy at doses comparable to the dose used in this domain.

Given the low teratogenic risk of 75 mg aspirin, the established indication for low-dose aspirin in pregnancy for preeclampsia prophylaxis at comparable doses, and the substantially reduced fertility in the study population, mandatory contraception and routine pregnancy testing are not required in this domain. Pregnancy will be recorded in the eCRF if reported or identified during routine clinical care. In pregnant participants, continuation, modification, or discontinuation of aspirin will follow current obstetric guidelines and be at clinician discretion; the participant will remain in the domain for intention-to-treat follow-up.

3.2.4 Benefit/Risk Assessment

CKD is associated with an increased risk of both bleeding and thromboembolic events, with an inverse relationship between risk and kidney function.[15,16] Current clinical guidelines do not recommend routine use of aspirin for primary prevention in patients with CKD;[19,22,23] however, Danish national guidelines recommend aspirin treatment for patients with diabetes, who constitute approximately one third of the CKD population, and an eGFR <60 ml/min/1.73 m^2.[24] This recommendation diverges from the majority of international guidelines[19,22,23], with only the ESC guideline supporting consideration in patients with diabetes and advanced CKD.[23] Available evidence suggests aspirin may reduce cardiovascular events, particularly myocardial infarction, while benefit on overall survival remains uncertain, and net benefit possibly offset by bleeding risk. Evidence in advanced CKD remains limited despite high baseline cardiovascular risk, supporting clinical equipoise. Participants will be managed according to standard clinical practice, with protocol-defined documentation of clinically indicated initiation/discontinuation of antithrombotic therapy and safety oversight by the IDSMC. The incremental trial-related risk is expected to be low and primarily related to bleeding, while potential benefit is reduction in major cardiovascular events.

4 Domain aim and objectives

Cardiovascular disease remains a leading cause of morbidity and mortality in advanced CKD. In general populations, low-dose aspirin has been reported to be associated with an approximately 10-20% reduction in serious vascular events, offset by an increased risk of bleeding.[28–30,37,39–41] In advanced CKD, the benefit–risk balance remains uncertain due to heightened bleeding susceptibility and competing risks,[8,9,57,58] warranting a definitive randomized trial focused on hard ischemic outcomes and major bleeding. The main objective of ASPIRE CKD is to determine whether primary prevention with long-term low-dose aspirin reduces major adverse cardiovascular events compared with no treatment in adults with advanced CKD including ESKD.

ASPIRE CKD will test superiority of primary prevention using low-dose aspirin 75mg QD versus no aspirin for time to first MACE over event-driven follow-up (administrative cap 60 months), with key absolute-risk summaries at 36 months; major bleeding (BARC 3-5) will be evaluated as the key safety outcome and reported regardless, with confirmatory testing (if applicable) contingent on demonstration of MACE superiority.

5 Study design

5.1 Overall design

ASPIRE CKD is designed as an investigator-initiated, pragmatic, randomized, parallel-group, open-label domain within the APT-KIDNEY platform. The ASPIRE CKD domain compares the benefit and safety of aspirin 75 mg once daily with no aspirin in patients with eGFR < 30 ml/min/1.73 m^2 or ESKD on maintenance dialysis. The primary endpoint is time to first three-point MACE (cardiovascular death, non-fatal myocardial infarction, and/or non-fatal ischemic stroke). The ASPIRE CKD domain is event-driven, with recruitment and follow-up continuing until the prespecified number of primary events has accrued; the final sample size and enrollment duration will ultimately depend on the observed event rate. Based on planning assumptions, entailing accrual over five years, a minimum follow-up of 2 years for all participants, and an administrative follow-up cap of 60 months, enrollment (n=400/year) is expected to be complete within approximately five years. Based on 8–12 active sites recruiting from the prevalent CKD4-5d population, this corresponds to approximately 35–50 participants per site per year, which is considered feasible given routine outpatient volumes at participating nephrology departments. Recruitment will be monitored centrally and strategies including international site expansion may be considered if sustained shortfalls are observed.

This domain-specific appendix describes all required items in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 statement[59] except those covered by the core protocol where no domain-specific adaptations were made.

5.2 Study procedures overview

Participants will be identified among patients with advanced CKD (eGFR < 30 ml/min/1.73 m^2 for ≥3 months) and patients with ESKD on maintenance hemo- or peritoneal dialysis at participating sites. Following provision of oral and written study information, eligibility will be assessed using available clinical information. After informed consent, participants will be randomized 1:1 to a prescription of low-dose aspirin 75 mg QD or no treatment. The assigned strategy will be initiated as soon as feasible after randomization and continued until study end or death, with protocol-defined documentation of clinically indicated initiation/discontinuation of antithrombotic therapy and other intercurrent events.

Follow-up will be conducted through routine clinical care contacts (outpatient CKD clinics and planned dialysis-related encounters) in both randomized groups; no additional trial-mandated in-person follow-up visits are required. Outcomes will be registered by site staff from routinely collected clinical data, with registers used for verification where available. Sites record the prespecified serious safety outcomes (major bleeding [BARC 3–5] and all-cause mortality) and antithrombotic changes in the eCRF and notify potential SUSARs within 24 hours (Section 3.2.3). Participants will be invited to complete patient-reported outcome measures (including EQ-5D-5L) aligned with routine contacts and/or remotely, as specified in the assessment schedule.

Follow-up will be event-driven, with participants to be followed until death or study end with administrative cap at 60 months after randomization and censoring as defined in the DSA. A schematic overview of participant flow and the assessment schedule is provided in Domain appendices 1–2.

5.3 Justification for using an open-label design

The domain will employ an open-label, pragmatic design because aspirin is widely available as a generic medication and the intervention is implemented as a prescription strategy consistent with usual care. An open-label approach enables efficient conduct and permits monitoring and description of treatment exposure and adherence using routinely collected data i.e. prescription and dispensing records from central administrative registers, supporting feasibility and external validity.

The primary endpoint (MACE) and key safety endpoint (major bleeding [BARC 3–5]) are based on objectively verifiable clinical information from source records and routinely collected data, which reduces the risk of ascertainment and classification bias. Potential limitations of an open-label design, including differential co-interventions and treatment changes, will be addressed through prespecified guidance, documentation of relevant antithrombotic therapies and intercurrent events, and analysis according to the intention-to-treat principle with supplementary estimand / sensitivity analyses as prespecified. Endpoint events are registered from source documentation against prespecified definitions, with register data used for verification.

5.4 Data registration

Data registration at baseline and follow-up will be performed in accordance with the APT-KIDNEY core protocol baseline and outcome variable sets, and the defined domain-specific safety outcomes.

Registration during follow-up will be performed at the platform's 4-monthly timepoints (±4 weeks), counted from the participant's first platform randomization (core protocol Section 8.9.1.1). The assessment window applies to capture and verification only; event outcomes will be recorded with their actual date of occurrence from source documentation. Sites will record discontinuation of allocated aspirin, or initiation of antiplatelet or anticoagulant therapy, with date and reason.

5.5 End of Study Definition

A participant is considered to have completed ASPIRE CKD when the participant has been followed until the prespecified domain primary analysis data-cut date (event-driven) or until death, withdrawal of follow-up consent (where applicable), emigration, or administrative censoring at 60 months after randomization (whichever occurs first).

The end of ASPIRE CKD (for the primary analysis) is defined as the date of the first prespecified domain data-cut after confirmation that the prespecified primary-event target has been reached, followed by database lock and unblinding as described in the Statistical Considerations section. The domain is planned such that, at the time of the primary analysis data cut, the last randomized participant is expected to have accrued approximately 24 months of follow-up; however, achievement of the prespecified primary-event target will not be delayed solely to ensure a minimum follow-up duration for all participants. Follow-up for secondary endpoints and safety may continue until administrative censoring at 60 months after randomization, as applicable.

The end of the APT-KIDNEY platform trial is defined in the APT-KIDNEY core protocol. Handling of withdrawal from the domain and discontinuation of the assigned treatment is described in Section 7.7.

5.6 Data sharing

Data may be shared as described in the core protocol.

6 Study population

Participants eligible for ASPIRE CKD will be adults with advanced CKD defined as eGFR < 30 ml/min/1.73 m^2 ≥ 3 months or ESKD on maintenance hemo- or peritoneal dialysis. The eGFR < 30 ml/min/1.73 m^2 threshold is a domain-specific restriction per core protocol Section 8.2, reflecting concentrated equipoise and sufficient event rates for feasible powering. The prevalent population of CKD4-5d in Denmark is estimated to be approximately 18.000-25000 persons.[60,61] Participants will be recruited from participating sites within the APT-KIDNEY platform. In addition to the general APT-KIDNEY eligibility criteria, the following domain-specific criteria apply.

6.1 Inclusion Criteria

- eGFR < 30 ml/min/1.73 m^2 ≥ 3 months *or* ESKD on maintenance hemo- or peritoneal dialysis
- Patient age ≥50 years *or* any adult ≥ 18 years with diabetes

6.2 Exclusion Criteria

- Ongoing antiplatelet or anticoagulation therapy
- Intracranial hemorrhage < 6 months
- Major gastrointestinal bleed < 3 months
- Any active bleeding
- Thrombocytopenia as defined by platelet count $<100\times10^9$/L
- Anemia as defined by a hemoglobin <4.6 mmol/L
- Severe liver disease or coagulopathy (INR >1.5)
- Known intolerance or hypersensitivity to aspirin
- Planned imminent kidney transplant <3 months

Kidney transplant recipients who meet the domain inclusion criteria and do not meet any exclusion criterion (including ongoing antiplatelet or anticoagulation therapy) are eligible for enrollment.

Participants that have previously been randomized to ASPIRE CKD may not be re-randomized in the domain.

7 Study Intervention and Concomitant Therapy

7.1 Aspirin 75 mg QD (intervention)

Patients randomized to the intervention arm will receive a prescription for aspirin 75 mg once daily (QD). Decisions regarding concomitant medications will be left to the discretion of the treating physician. Treatment monitoring will follow standard local practice.

Preparation and administration

Aspirin will be prescribed by the study site and dispensed by community pharmacies through standard Danish prescription procedures. Participants will obtain aspirin under the usual Danish reimbursement scheme and may be required to pay an initial co-payment; patient out-of-pocket expenditure on prescription medicines is subject to annual reimbursement thresholds. The annual pharmacy cost of aspirin 75 mg is approximately 325 DKK (0.89 DKK/day). Given the substantial background medication use in this population, most participants are expected to exceed annual co-payment reimbursement thresholds regardless of participation in the domain, reducing the incremental out-of-pocket cost attributable to aspirin to a negligible amount. No additional study-related costs are expected.

Aspirin is provided through routine prescribing, community-pharmacy dispensing, and regional reimbursement because this is the intervention under evaluation, and exposure and adherence are measured from redeemed prescriptions; provision free of charge outside this pathway would defeat the purpose of the domain. Reimbursement of co-payments by the trial would require individual calculation of each participant's share, which varies with the regional reimbursement already applied, and would add trial-specific contacts to a domain designed without them. The sponsor therefore applies to the Danish Medicines Agency for dispensation from Article 92 of Regulation (EU) No 536/2014 under § 15, no. 1, of the Danish Act on Clinical Trials of Medicinal Products.

Dose adjustments

The aspirin dose will be fixed at 75 mg once daily, with no planned dose adjustments.

Treatment adherence

Treatment adherence will be assessed using pharmacy prescription redemptions to compute Proportion of Days Covered (PDC). Consistent with KDIGO CKD 2024 guidance,[19] clinicians may consider concomitant proton pump inhibitor therapy for participants receiving aspirin.

7.2 No aspirin (control)

Patients randomized to the control arm will receive their usual medication, but no aspirin. If aspirin or other antithrombotic therapy becomes clinically indicated after randomization, it may be initiated at the treating physician's discretion and will be documented in accordance with the protocol.

7.3 Randomization and stratification

Participants will be randomized 1:1 using a centralized web-based eCRF system with computer-generated permuted blocks of random sizes, stratified by site and diabetes, with allocation concealment maintained until assignment. Co-enrollment is permitted per the core platform protocol; compatibility rules will prevent incompatible cross-domain allocations.

7.4 Intervention period

Participants will be followed from randomization until the earliest of death, withdrawal of follow-up consent (where applicable), emigration, or administrative censoring at 60 months after randomization. The primary analysis will be based on events accrued up to the event-driven domain primary analysis data-cut date.

The primary analysis is event-driven and will use a locked database extract from the next scheduled 4-monthly platform timepoint after the prespecified primary-event target has been reached, following standard data quality checks. The domain is planned such that, at the time of the primary analysis data-cut, the last randomized participant is expected to have accrued approximately 24 months of follow-up; however, achievement of the prespecified primary-event target will not be delayed solely to ensure a minimum follow-up duration for all participants.

Follow-up will continue after the primary analysis data cut for safety surveillance and end-of-domain reporting as described in the APT-KIDNEY core protocol. Data accrued after the primary analysis data cut will not be included in the primary analysis but may be included in prespecified safety updates and long-term follow-up analyses/publications, in accordance with the protocol/SAP and applicable approvals.

7.5 Cross-over Policy and Predefined Rescue Criteria

Participants allocated to aspirin may interrupt or discontinue study treatment when clinically indicated. Decisions will follow local clinical practice and be at clinician discretion. Interruptions/discontinuations may be temporary or sustained and will be recorded with dates and clinical rationale.

Strong indications for interruption/discontinuation in the aspirin arm include:

- Major bleeding or intracranial hemorrhage
- New indication for therapeutic anticoagulation
- Clinically significant intolerance or hypersensitivity to aspirin

Strong indications for initiation in the no aspirin arm include:

- Acute ischemic indication requiring antiplatelet therapy including acute coronary syndrome / myocardial infarction, coronary revascularization, ischemic stroke, or transient ischemic attack
- Other new guideline-recommended indications for antithrombotic therapy

Temporary interruption is permitted when clinically indicated i.e. hospitalization, acute illness, periprocedural periods, or transient increased bleeding risk. Participants may resume aspirin once clinically stable and bleeding risk is acceptable, at clinician discretion.

7.6 Continued Access to Study Intervention after the End of the Study

After completion of domain follow-up, aspirin prescribed under the protocol will be discontinued unless clinically indicated. Subsequent prescribing will follow routine clinical practice at clinician discretion.

7.7 Participant Discontinuation/Withdrawal from the Study

Participants who discontinue the assigned treatment will remain in follow-up for the full planned follow-up period under the intention-to-treat principle, unless they withdraw consent for follow-up (where applicable). If a participant withdraws consent for follow-up, no further data will be collected, except as permitted under applicable law/regulatory approvals i.e. data already collected up to the date of withdrawal.

7.8 Lost to Follow-up

Follow-up data will be sought through EHR review and, where approved, linkage to administrative health care registers, with participant contact as needed. A participant will be considered lost to follow-up if no outcome data can be obtained for 90 days despite ≥3 documented attempts; transfer to a non-participating site does not constitute loss to follow-up.

7.9 Co-enrollment and collaboration

Participants enrolled in ASPIRE CKD may co-enroll in other APT-KIDNEY domains and/or other clinical studies in accordance with the guiding principles and procedures described in the APT-KIDNEY core protocol including assessment of potential conflicts with study interventions, participant safety, and data integrity.

Co-enrollment with the INITIATE domain is permitted; no biological interaction between aspirin and dialysis frequency is expected, and the interventions do not modify treatment or outcome assessment across domains.

8 Statistical Considerations

8.1 General considerations

The ASPIRE CKD domain will use intention-to-treat analyses including all randomized participants, analyzed as assigned. Supportive per-protocol analyses will exclude participants with prespecified major protocol deviations (including predefined criteria related to exposure to the allocated strategy and prohibited/mandatory concomitant antithrombotic therapy, as detailed in the SAP). Clinically indicated treatment modifications will be documented: in the aspirin arm, interruption or discontinuation of aspirin (temporary or sustained); and in the no-aspirin arm, initiation of aspirin or other antiplatelet therapy for a new clinical indication. Participants will remain in follow-up and be retained in intention-to-treat analyses.

Treatment adherence and treatment modifications (including cross-over) will be assessed using routinely collected prescription redemptions to calculate PDC, supplemented by protocol-defined documentation of antithrombotic changes. Aspirin is available over the counter in Denmark; however, any OTC use in the control arm is expected to be intermittent i.e. short-lived analgesic use, rather than sustained antiplatelet exposure, limiting its impact on the primary comparison.

Unless otherwise specified, analysis conventions and reporting will follow the framework described in the APT-KIDNEY core protocol. A definitive SAP will be finalized and approved prior to database lock and prior to any analyses using unmasked treatment allocation codes. An abbreviated study design is summarized in domain appendix 3.

8.2 Domain endpoints

8.2.1 Primary Endpoint

The primary outcome is time from randomization to first occurrence of three-point MACE (myocardial infarction, ischemic stroke, or cardiovascular death). For the primary endpoint, participants will be followed from randomization until the earliest of first MACE, withdrawal of follow-up consent (where applicable), emigration, administrative censoring at 60 months after randomization, or the event-driven domain primary analysis data-cut date (whichever occurs first). Participants who die without prior MACE and whose death is not classified as cardiovascular death will be censored at the date of death.

The primary estimand is defined in the intention-to-treat population, with participants analyzed according to randomized allocation. The primary analysis will estimate the treatment effect of low-dose aspirin 75 mg once daily versus no aspirin using a Cox proportional hazards model for time to first three-point MACE and will report hazard ratios with 95% confidence intervals. Cardiovascular death is included as a MACE event; deaths not meeting the cardiovascular death definition will be treated as censoring at the date of death. Given the high rate of non-cardiovascular mortality in this population, a competing-risk sensitivity analysis (Fine–Gray) will be reported alongside the primary cause-specific Cox model, as prespecified in Section 8.3.4.

Prespecified supportive and sensitivity analyses will include a covariate-adjusted Cox model incorporating key baseline prognostic factors (age, sex, diabetes, and dialysis status) and site/region as specified in the SAP. If proportional hazards appear materially violated based on prespecified diagnostics, restricted mean event-free survival time through 36 months (and, secondarily, through 60 months) will be reported as an additional summary. Per-protocol analyses will be presented as supportive.

8.2.1.1 3-point MACE definition

- Myocardial infarction: Myocardial infarction consistent with the 4th universal definition,[62] excluding periprocedural myocardial infarction (types 4/5) unless occurring in the setting of acute coronary syndrome.
- Ischemic stroke: Focal neurological deficit lasting ≥24 hours or imaging-confirmed infarct, excluding intracerebral, subarachnoid, and subdural hemorrhage.
- Cardiovascular death: Death due to myocardial infarction, stroke, sudden cardiac death, or heart failure.

8.2.2 Secondary Endpoints

The key safety endpoint will be time from randomization to first major bleeding (BARC 3–5). Participants will be followed for the safety endpoint until the earliest of first major bleeding, withdrawal of follow-up consent (where applicable), emigration, administrative censoring at 60 months after randomization, or the event-driven domain primary analysis data-cut date (whichever occurs first). Key absolute-risk summaries will be reported at 36 months.

The key safety estimand will be the between-group hazard ratio for major bleeding (aspirin versus no aspirin) in the intention-to-treat population, analyzed as assigned. The primary analysis will use a cause-specific Cox proportional hazards model and report hazard ratios with 95% confidence intervals; participants who die without prior major bleeding will be censored at death in the cause-specific analysis. Prespecified supportive analyses will include a covariate-adjusted Cox model incorporating key baseline prognostic factors (age, sex, diabetes, and dialysis status) and site/region as specified in the SAP. A competing-risk analysis such as Fine–Gray may be reported as a sensitivity analysis.

Safety monitoring will be conducted by the domain IDSMC in accordance with the APT-KIDNEY core protocol, including access to strictly confidential unblinded safety data and written recommendations to the domain and platform steering committees. Any statistical monitoring guidelines or decision rules used for safety surveillance will be prespecified for the domain and implemented under IDSMC oversight; IDSMC recommendations will be advisory and non-binding.

Major bleeding will be subclassified as gastrointestinal, intercranial., and other.

8.2.3 Tertiary endpoints

Tertiary endpoints will be evaluated to further characterize ischemic and bleeding outcomes and are not confirmatory. Unless otherwise stated, endpoints will be analyzed as time-to-event outcomes.

- **Neurologic outcomes**
  - Transient ischemic attack (TIA) (exploratory)
  - Hemorrhagic stroke (safety outcome)

- Composite of TIA or ischemic stroke

- **Expanded ischemic composites**
  - 3-point MACE plus urgent coronary revascularization for acute coronary syndrome
  - 3-point MACE plus heart-failure hospitalization
  - 3-point MACE plus TIA and heart-failure hospitalization

- **Individual components and additional outcomes**
  - Individual components of 3-point MACE
  - All-cause mortality
  - Intracranial hemorrhage (safety outcome)
  - Major gastrointestinal bleeding (BARC 3–5) (safety outcome)

- **Health-related quality of life**
  - EQ-5D-5L utility index (baseline and each nominal endpoint window)
  - EQ VAS and dimension-level outcomes (if analyzed)

- **Net clinical benefit composites (descriptive)**
  - 3-point MACE or major bleeding (BARC 3–5)
  - 3-point MACE or major bleeding (BARC 3–5) or all-cause mortality

Composites will be analyzed as time to first occurrence of any component. Transient ischemic attack, heart-failure hospitalization, and urgent coronary revascularization are derived from register linkage where approved and are exploratory.

EQ-5D-5L is included as a tertiary rather than secondary endpoint because the primary clinical question concerns hard ischemic and bleeding outcomes; quality-of-life effects of low-dose aspirin are expected to be modest and are not the basis for domain powering.

EQ-5D-5L index values will be derived using applicable national value sets as specified in national appendices (Denmark: Danish value set); death will be coded as zero utility (weighted as dead), consistent with the APT-KIDNEY core protocol. Between-group differences in mean utility at each nominal endpoint window (aspirin minus no aspirin) will be estimated in the intention-to-treat population using linear models adjusted for baseline EQ-5D-5L and site; supportive longitudinal analyses will use a repeated-measures model including treatment and visit effects, as specified in the SAP. EQ VAS and dimension-level outcomes, if analyzed, will be assessed while alive with death treated as a distinct terminal event i.e. not imputed as VAS=0.

8.3 Overview of analyses including secondary and sensitivity analyses

8.3.1 Primary analyses (3-point MACE)

The primary analysis will estimate the effect of aspirin versus no aspirin on time to first 3-point MACE in the intention-to-treat population using a Cox proportional hazards model with treatment as the explanatory variable, stratified by site to allow site-specific baseline hazards. A covariate-adjusted Cox model including age, sex, diabetes, and dialysis status will be reported as supportive, retaining site stratification. If site stratification is not feasible due to sparse events within sites, site will be modeled using fixed effects (or an alternative prespecified approach) as detailed in the SAP. Cardiovascular death is included as a MACE event; deaths not classified as cardiovascular death will be censored at the date of death. Proportional hazards will be assessed using standard diagnostics, including Schoenfeld residuals. If proportional hazards are not supported, restricted mean event-free survival time through 36 months (and secondarily through 60 months) will be reported as an alternative summary, with exploration of time-varying effects in sensitivity analyses.

8.3.2 Secondary analysis (Major bleeding: BARC 3-5)

The key secondary analysis will evaluate safety based on the treatment effect of aspirin versus no aspirin on time to first major bleeding (BARC 3–5) using a cause-specific Cox proportional hazards model including treatment and site (the randomization stratification factor), with participants analyzed as randomized in the intention-to-treat population. Participants who die without prior major bleeding will be censored at death in the cause-specific analysis. A supportive covariate-adjusted analysis will include age, sex, diabetes, and dialysis status, retaining site handling as above, with further specification in the SAP. Supportive summaries will include model-based absolute risks and risk differences at 36 months (and secondarily 60 months). A competing-risk sensitivity analysis i.e. Fine–Gray may be reported, and handling of censoring and treatment modifications will follow prespecified SAP methods.

8.3.3 Subgroup analyses

Exploratory subgroup analyses will be conducted for the prespecified subgroups below. Treatment effects will be summarized with hazard ratios and two-sided 95% confidence intervals, and heterogeneity assessed using treatment-by-subgroup interaction terms in Cox models.

- Dialysis status (non-dialysis, maintenance dialysis)
- Age (<60; 60–80; >80 years)
- Sex (male vs female)
- Diabetes (yes vs no)
- Proton-pump inhibitor use (yes vs no)
- Prior peptic ulcer disease (yes vs no)
- Prior cardiovascular disease (yes vs no)
- History of major bleeding and/or prior gastrointestinal bleeding (yes vs no)
- Prior kidney transplantation (yes vs no)

Prior peptic ulcer or gastrointestinal bleeding and baseline proton pump inhibitor use are derived by register linkage (core protocol Section 8.7.3).

8.3.4 Sensitivity analyses

Sensitivity analyses will assess robustness of the primary (3-point MACE) and key safety (major bleeding) results and will include: (i) alternative Cox specifications (unadjusted and covariate-adjusted; site handled by stratification where feasible or fixed effects if needed), (ii) competing-risk sensitivity analyses where relevant i.e. Fine–Gray for non-cardiovascular death for the primary endpoint, and for death as a competing event for bleeding), and (iii) supportive per-protocol/as-treated analyses addressing discontinuation and cross-over based on documented antithrombotic changes and prescription redemptions, as specified in the SAP. Additional sensitivity analyses i.e. follow-up truncation, endpoint-definition checks, transplantation handling, and PRO sensitivity analyses.

Participants who receive a kidney transplant during follow-up will remain in the primary ITT analysis regardless of post-transplant aspirin status. A prespecified sensitivity analysis will censor participants at the date of transplantation to assess the impact on the primary and key safety endpoints.

For patient-reported outcomes, mandatory sensitivity analyses will include (i) analyses adjusting for collection method and (ii) analyses assessing the impact of differential missing data between arms, in accordance with core protocol Sections 8.6.2.2 and 9.6, with further specification in the SAP.

8.4 Sample Size Determination

8.4.1 Sample size assumptions for the primary endpoint (3-point MACE)

Superiority will be assessed on the hazard-ratio (HR) scale for time to first three-point MACE using Cox proportional hazards model with log-rank test. With a design target HR = 0.80, two-sided $\alpha = 0.05$, 80% power, and 1:1 allocation, the required number of primary endpoint events is estimated using the Schoenfeld approximation:

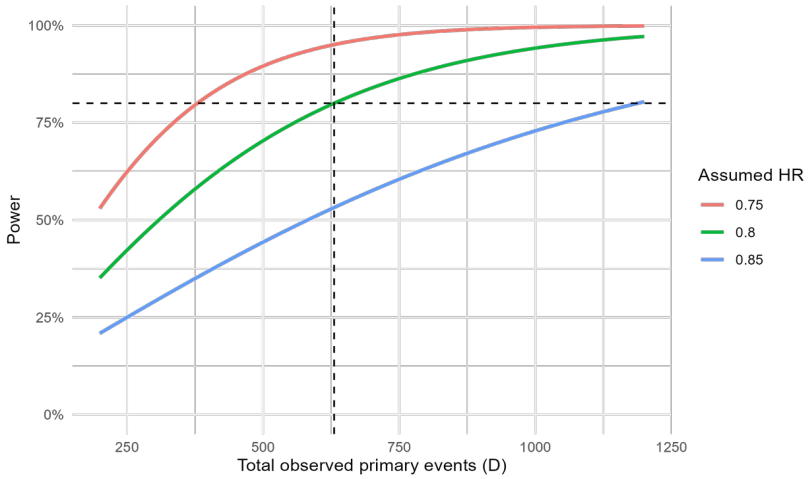
$$D = ((z_{1-\alpha/2} + z_{1-\beta})^2) / ([\ln(HR)]^2 \times p \times (1-p)), \quad p = 0.5$$

Using $z_{1-\alpha/2} = 1.96$, $z_{1-\beta} = 0.842$, and HR = 0.80 gives $D \approx 631$ primary events.

Planning event rates were informed by observational data from eligible patients identified in the Danish National Patient Registers, with event rates estimated from piecewise constants between prespecified timepoints until five years. Cause-specific cumulative hazards for (i) three-point MACE and (ii) all-cause death were used to account for death as a competing event when translating the required number of events into a required sample size. Under the planning follow-up structure (uniform accrual over 5 years, minimum follow-up 24 months, administrative cap 60 months, with minimal additional censoring), the expected probability of observing a primary MACE event is approximately 0.332 overall. The implied total sample size is therefore:

$$N \approx D / \Pr(\text{observed MACE}) \approx 631 / 0.332 \approx 1{,}897$$

corresponding to ~1,897 participants i.e. ~949 per arm. For operational planning, a small buffer may be applied, giving an enrollment target of approximately 2,000 participants. An overview of sample size and power relative to the design hazard ratio is shown in the figure below:



The domain is event driven. Enrollment will continue until the prespecified primary-event target is accrued or projected to be accrued with enrolled participants, and the final sample size and enrollment duration will depend on observed event rates. Sample size calculations will be implemented in validated, version-controlled R code, with software versions and scripts archived and referenced in the final SAP.

The sample size calculation assumes full adherence and no cross-over. In practice, non-adherence in the aspirin arm and low-level contamination in the control arm (including intermittent OTC use) will attenuate the observed treatment effect. The intention-to-treat design accepts this dilution as reflective of the pragmatic estimand; per-protocol and as-treated sensitivity analyses addressing adherence and cross-over are prespecified in Section 8.3.4.

8.4.2 Sample size assumptions for the secondary endpoint (major bleeding; BARC 3–5)

The key secondary safety endpoint is time to first major bleeding (BARC 3–5)**.** The domain is powered for the primary efficacy endpoint (3-point MACE); major bleeding does not drive the enrollment target and is presented to contextualize the amount of safety information expected at the planned sample size.

Under the planned total sample size implied by the primary event target (approximately 1,897 participants; ~949 per arm), the detectable treatment effect for major bleeding depends on the underlying bleeding incidence. Assuming two-sided α=0.05, 80% power, 1:1 allocation, and approximately constant hazards for planning, the corresponding detectable hazard ratio (aspirin vs no aspirin) is approximately 1.3–1.4, depending on the absolute major bleeding rate (e.g., detectable HR ≈ 1.46 at 4%/year, 1.37 at 6%/year, and 1.32 at 8%/year). At the detectable boundary this translates to roughly a 7–8% absolute increase in 60-month major bleeding risk (administrative cap 60 months; key absolute-risk summaries will be reported at 36 months, with 60-month summaries presented secondarily/supportively), depending on baseline risk.

Only the primary 3-point MACE endpoint is confirmatory and tested at two-sided α=0.05. Consequently, major bleeding is not alpha-controlled, and p-values are nominal, with effects reported primarily as hazard ratios and model-based absolute risks/risk differences as prespecified in the SAP.

8.5 Event accrual, enrollment stop, and analysis trigger

8.5.1 Primary event definition

Primary events are first-occurring three-point MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke) occurring after randomization. Events contribute to the primary event target if they occur before the prespecified domain database cut-off date (administrative censoring at 60 months after randomization).

8.5.2 Enrollment stop rule

Enrollment will cease upon confirmation from a locked extract of the trial database that the pooled cumulative number of primary events is ≥ 631.

8.5.3 Analysis trigger

The primary analysis will be performed using a database cut-off date corresponding to the next scheduled nominal 4-month platform assessment window after the primary event target is reached.

9 Ethics and Dissemination

ASPIRE CKD is an IMP domain of the APT-KIDNEY platform trial and is conducted in accordance with Regulation (EU) No 536/2014 (core protocol Section 7.2), the Declaration of Helsinki, ICH-GCP, the GDPR, and applicable national legislation, with safety reporting as described in Section 3.2.3.

Results will be disseminated irrespective of outcome through conference presentations and peer-reviewed publications, following the publication and authorship principles described in the core protocol.

Patient and public perspective. Where feasible, patient representatives and/or relevant patient organizations may be invited to comment on participant-facing materials and the acceptability of follow-up procedures and study burden, and patient-facing dissemination including plain-language summaries will be considered.

10 Study Assessment and Monitoring

Study assessments and procedures are described in the APT-KIDNEY core protocol. Any additional domain-specific assessments and procedures for ASPIRE CKD are summarized in the schedule of appointments.

10.1 Monitoring plan

Monitoring by the GCP unit and central monitoring will be performed in accordance with the APT-KIDNEY core protocol, using a risk-based quality management approach focusing on critical-to-quality data and trial processes, consistent with the domain's low-intervention design.

10.2 Protocol deviations and serious breaches

Protocol deviations, violations, and serious breaches will be handled as described in the APT-KIDNEY core protocol.

10.3 Independent Data and Safety Monitoring Committee (IDSMC)

An independent Data and Safety Monitoring Committee (IDSMC) will oversee participant safety, trial conduct, and the overall benefit–risk balance for the ASPIRE CKD domain and provide independent recommendations to the domain and platform steering committees in alignment with the APT-KIDNEY core protocol. No formal interim analyses for efficacy or futility are planned; IDSMC reviews are for safety and conduct oversight. Any unblinded comparative summaries will be used for oversight and participant protection only.

10.3.1 IDSMC membership and independence

IDSMC composition and independence requirements follow the APT-KIDNEY core protocol. In brief, the IDSMC is multidisciplinary, independent of sponsor/investigators, and members must have no relevant conflicts of interest. The domain IDSMC will be appointed prior to first inclusion (Section 1.2.4).

10.3.2 IDSMC meetings and reports

The IDSMC will schedule meetings as appropriate for domain progress and will meet periodically (and at least annually), with additional ad hoc meetings as needed. Meetings will follow the core protocol structure, including an open session (operational updates and aggregate data) followed by a closed session with participation limited to the IDSMC and designated unblinded methodological/statistical support, permitting review of unblinded comparative summaries. Open and closed reports will be prepared and shared according to the core protocol.

10.3.3 IDSMC responsibilities

The IDSMC's core responsibilities are to protect participant safety and identify emerging safety concerns, to monitor trial conduct and integrity (including recruitment, adherence and discontinuation/cross-over patterns, and protocol deviations), and to advise whether risk-mitigating changes to trial conduct are warranted.

Key clinical outcomes for safety monitoring in ASPIRE CKD include:

- All-cause mortality
- Major bleeding (BARC 3–5)
- Other domain-specific safety outcomes as defined in Section 3.2.2

Consistent with evidence that antithrombotic therapy in advanced CKD may increase bleeding before or in the absence of cardiovascular benefit, the IDSMC will assess the bleeding signal independently of any efficacy trend, and an unfavorable bleeding profile may itself prompt a recommendation to modify or stop the domain, notwithstanding the absence of planned formal interim efficacy or futility analyses. Aggregate adherence data (including PDC summaries and cross-over rates by arm) will be provided to the IDSMC at scheduled reviews to support assessment of trial integrity, irrespective of the 12-monthly formal adherence assessment schedule.

10.3.4 Unblinding, confidentiality, and communication

ASPIRE CKD is open-label i.e. participants and treating teams know the assigned aspirin strategy. Interim comparative results (between-group summaries) are confidential and restricted to the IDSMC and designated unblinded support staff. Communications to the sponsor/ principal investigator (PI), investigators, and steering committees will be framed as

recommendations (e.g., “continue” / “modify” / “pause”), without sharing interim comparative estimates unless urgent participant-safety actions require disclosure.

10.3.5 Interpreting signals and recommendations (harm-focused; non-binding)

Consistent with the core protocol, the IDSMC may recommend continuing, modifying, pausing, or stopping the domain (or an arm) if observed differences in safety outcomes are concerning, even without prespecified statistical rules. The IDSMC will consider the totality of evidence, including magnitude and consistency across mortality and serious safety outcomes, clinical plausibility, timing and severity of events, data quality, and operational factors (including adherence and cross-over). All recommendations are advisory.

10.3.6 IDSMC documentation

IDSMC procedures—including meeting cadence, report templates, confidentiality, documentation of deliberations, and urgent communication pathways—will be documented prior to first inclusion and maintained as part of domain and platform governance. An IDSMC Charter will be finalized prior to inclusion of the first participant. Any changes to monitoring procedures will be prospectively documented and archived.

10.4 End-point classification

Endpoint events are registered by site staff from source documentation against the definitions below, with verification against national registers where available; cause of death is classified as described in core protocol Section 8.9.2. Central blinded adjudication is not performed (core protocol Section 8.9.2).

10.4.1 End-point definitions

1) **All-cause mortality:** Death from any cause during follow-up.
2) **Cardiovascular death:** Death due to myocardial infarction, stroke, sudden cardiac death, or heart failure, assigned when a cardiovascular cause is supported, and non-cardiovascular causes are reasonably excluded.
3) **Non-fatal myocardial infarction (MI):** MI consistent with the Fourth Universal Definition of MI (myocardial injury with clinical evidence of acute myocardial ischemia), including type 1–2 MI. Peri-procedural MI (types 4/5) is excluded, unless occurring in the setting of acute coronary syndrome.
4) **Non-fatal ischemic stroke:** Acute ischemic stroke causing a new focal neurological deficit lasting ≥24 hours, or <24 hours with imaging evidence of acute infarction. Intracerebral, subarachnoid, and subdural hemorrhage are excluded. TIA is not counted as stroke.
5) **Major bleeding (BARC 3–5):** BARC type 3, 4, or 5 bleeding (including intracranial hemorrhage) classified according to prespecified BARC definitions.

11 Organizational and financial aspects

11.1 Conflicts of interest

Declarations of interests are handled as described in core protocol Section 11.3.

11.2 Funders, supporters, and roles

The domain is conducted under the platform sponsor (core protocol Section 3.1). Funding has been applied for from Sundhedsdonationer; funders have no role in design, conduct, analysis, or publication decisions.

11.3 Compensations

Sites may receive per-patient payments for screening, randomization, and follow-up visits. No participant reimbursement is planned. Participant compensation for trial-related injury is provided at platform level as specified in core protocol Section 11.4.2.

11.4 Publication and authorship considerations

Publication and authorship considerations will be in accordance with core protocol considerations.

11.5 Estimated timeline

First sites are expected to open in Q3–Q4 2027. Enrollment is planned over approximately five years (planning rate approximately 400 participants per year), with a minimum follow-up of 24 months and an administrative cap of 60 months after randomization. The primary analysis is event-driven and takes place at the first platform timepoint after 631 primary events have accrued (Section 8.5).

12 Supporting Documentation

Appendix 1: Flowchart of study inclusion

Appendix 2: Schedule of appointments

13 References

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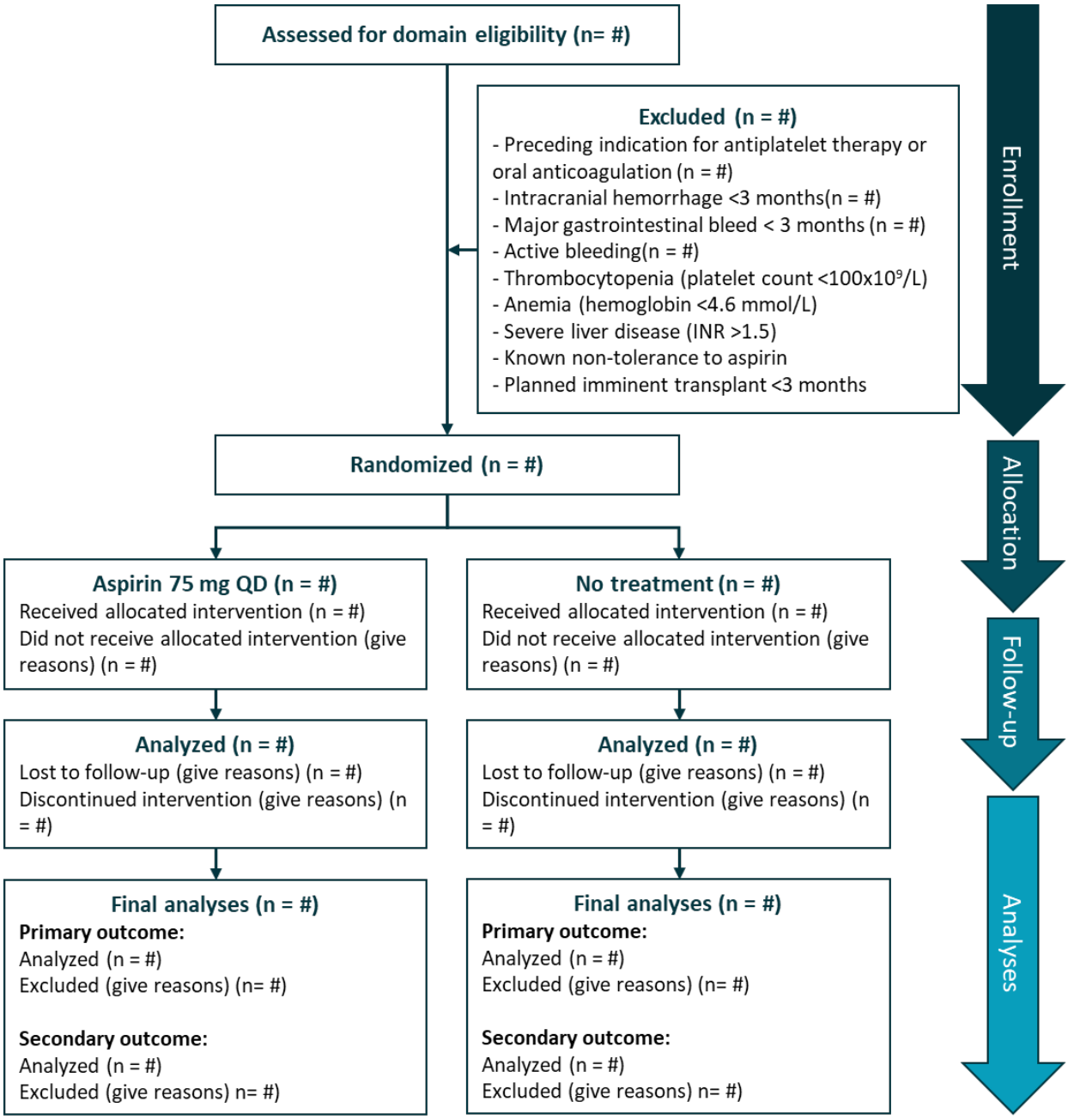
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14 Appendix 1: Flowchart of study inclusion



15 Appendix 2: Schedule of Appointments

	Screening	Inclusion (Day 0)	Every 4 months	Every 12 months	End of study
Informed consent	⊗				
Eligibility check (inclusion/exclusion)	⊗				
Baseline data		⊗			
Primary outcomes[1]			⊗		⊗
Safety outcomes[2]			⊗		⊗
HRQoL[3]		⊗	⊗		⊗
Discontinued allocation			⊗		⊗
Adherence[4]				⊗	⊗
Register linkage[5]				(⊗)	⊗

[1]Primary outcomes: Major adverse cardiovascular events
[2]Safety outcomes: Major bleeding (BARC 3-5) and all-cause mortality
[3]Health-related quality of life (HRQoL): assessed by EQ-5D-5L and/or EQ-VAS
[4]Adherence to aspirin: PDC based on redemption of prescriptions from pharmacies
[5]Linkage to Danish national health registers, where approved, for verification of outcomes and key covariates

The listed 4-monthly assessments follow the platform timepoints counted from the participant's first platform randomization (core protocol Section 8.9.1.1), throughout the full follow-up period with administrative censoring at 60 months after ASPIRE CKD randomization.

16 Appendix 3: ASPIRE CKD Design card

Paradigm: Frequentist, fixed-sample

Primary outcome: 3-point MACE (time-to-event, event-driven)

Guiding outcome for adaptation: Not applicable (no adaptive features)

Randomization: Fixed 1:1, permuted blocks, stratified by site and diabetes

Interim efficacy/futility analyses: None

Adaptive stopping/arm-dropping: None

Response-adaptive randomization: None

Decision rules: Not applicable

Maximum planned information: 631 primary events

IDSMC role: Safety and conduct oversight only