APT-KIDNEY

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

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Protocol Summary

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At a Glance

Design	Investigator-initiated, pragmatic, randomized, open-label, parallel-group domain of APT-KIDNEY with an event-driven, fixed-sample frequentist design
Population	Adults aged ≥50 years, or ≥18 years with diabetes, with eGFR <30 mL/min/1.73 m^2 for ≥3 months or on maintenance dialysis, without ongoing antithrombotic therapy
Intervention	Aspirin 75 mg once daily, prescribed and dispensed through routine care
Control	No aspirin
Primary outcome	Time to first major adverse cardiovascular event (superiority)
Key safety outcome	Major bleeding, BARC type 3–5
Sample size	631 primary events, approximately 1,900 participants (949 per arm)
Follow-up	Event-driven, planned minimum 24 months, administrative cap 60 months

1 Background and Rationale

Chronic kidney disease (CKD) affects 10–15% of adults worldwide and is projected to become the fifth leading cause of years of life lost by 2040. It is associated with substantial morbidity, impaired quality of life, and excess mortality, and prognosis worsens as kidney function declines.

Cardiovascular disease is the leading cause of death in CKD, and many patients die before reaching kidney failure. The excess risk reflects both traditional risk factors and kidney-specific mechanisms, including altered platelet function, so that patients with CKD are at increased risk of both thromboembolic events and bleeding.

In general populations, low-dose aspirin for primary prevention reduces serious vascular events by approximately 10–20%, mainly through fewer myocardial infarctions, at the cost of more bleeding. Its benefit in CKD is uncertain. International guidelines reserve aspirin for secondary prevention, whereas some national guidelines, including Danish recommendations, support its use in selected high-risk individuals. This divergence reflects genuine clinical equipoise, particularly in advanced CKD, where thrombotic and bleeding risks are both accentuated and randomized evidence is lacking.

2 Objectives

The primary objective of ASPIRE CKD is to determine whether aspirin 75 mg once daily reduces major adverse cardiovascular events compared with no aspirin in adults with advanced CKD. Major bleeding is the key safety outcome.

3 Study Design

ASPIRE CKD is an open-label, parallel-group domain of the APT-KIDNEY platform with an event-driven, fixed-sample frequentist design without adaptive features.

4 Study Population

Adults with advanced CKD are recruited from outpatient clinics and dialysis units at participating APT-KIDNEY sites. Participants must meet the core APT-KIDNEY criteria and the domain-specific criteria below.

Inclusion criteria	Exclusion criteria
• eGFR <30 mL/min/1.73 m^2 for ≥3 months or kidney failure on maintenance hemodialysis or peritoneal dialysis • Age ≥50 years, or ≥18 years with diabetes	• Ongoing antiplatelet or anticoagulant therapy • Intracranial hemorrhage <6 months • Major gastrointestinal bleeding <3 months • Active bleeding • Platelet count <100×10^9/L • Hemoglobin <4.6 mmol/L • Severe liver disease or coagulopathy (INR >1.5) • Known intolerance or hypersensitivity to aspirin • Planned kidney transplantation within 3 months

Kidney transplant recipients who meet the domain criteria, including the absence of ongoing antiplatelet or anticoagulant therapy, are eligible.

5 Interventions

Participants are randomized 1:1 to aspirin 75 mg once daily or no aspirin. The allocated strategy is started as soon as feasible after randomization and continued until the end of the domain or death, with an administrative cap of 60 months. Aspirin is prescribed by the site and dispensed by community pharmacies through standard Danish prescription procedures. Participants pay the usual co-payment (approximately DKK 325 per year before subsidy), which the trial does not reimburse. Concomitant medication, including proton pump inhibitors, is at the discretion of the treating physician. Aspirin may be interrupted or stopped when clinically indicated, and antithrombotic therapy may be started in the control arm for a new clinical indication.

6 Study Procedures and Data Collection

Trained site staff record efficacy and safety outcomes in the eCRF from source documentation at four-monthly timepoints, with register data used for verification where available. Participants complete the EQ-5D-5L at baseline and every four months. Follow-up takes place during routine outpatient and dialysis contacts, and no additional study visits or blood samples are required.

7 Statistical Analysis

All analyses follow the intention-to-treat principle. Time to first MACE is compared between arms with a Cox proportional hazards model stratified by site, with absolute risks reported at 36 months. Major bleeding is analyzed with a cause-specific Cox model, and the EQ-5D-5L index is compared at prespecified timepoints with linear models adjusted for baseline and site, with a mixed model for repeated measures as a supportive analysis. Only the primary outcome is confirmatory. The domain is event-driven, and 631 primary events provide 80% power to detect a hazard ratio of 0.80 at a two-sided α of 0.05. With accrual over five years, a minimum follow-up of 24 months, and an administrative cap of 60 months, this corresponds to approximately 1,900 participants (949 per arm).

8 Study Outcomes

Level	Outcome	Definition and analysis
Primary (superiority)	Major adverse cardiovascular events	Time to first cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke. Hazard ratio from a Cox model.
Secondary (key safety)	Major bleeding	Time to first BARC type 3–5 bleeding. Hazard ratio from a cause-specific Cox model, reported regardless of the primary result.
Tertiary (exploratory)	Mortality and MACE components	All-cause mortality, cardiovascular death, and the individual MACE components.
	Bleeding	Hemorrhagic stroke, intracranial hemorrhage, and major gastrointestinal bleeding (BARC type 3–5).
	Net clinical benefit	Composites of MACE and major bleeding, with and without all-cause mortality.
	Health-related quality of life	EQ-5D-5L index at each four-monthly timepoint, with non-survivors assigned a utility of 0.
	Register-derived outcomes	Transient ischemic attack, heart-failure hospitalization, and urgent coronary revascularization, derived from register linkage.

9 Safety Monitoring

Safety management follows the APT-KIDNEY risk-proportionate framework for risk level 1 domains. Major bleeding (BARC 3–5) and all-cause mortality are registered in the eCRF as prespecified safety outcomes, and an independent data and safety monitoring committee (IDSMC) reviews safety by arm at regular intervals, assessing bleeding independently of any efficacy trend. Suspected unexpected serious adverse reactions are reported to EudraVigilance, and safety data are included in the annual safety report submitted via CTIS.

10 Governance and Organization

ASPIRE CKD is conducted as a domain of the APT-KIDNEY platform, with Nicholas Carlson, MD PhD, as sponsor and domain lead. The domain is overseen by the APT-KIDNEY Platform Steering Committee, managed by a domain steering committee, and advised on safety by its IDSMC. Each participating site appoints a principal investigator.

11 Ethics and Dissemination

ASPIRE CKD is conducted in accordance with the APT-KIDNEY core protocol, Regulation (EU) No 536/2014, the Declaration of Helsinki, ICH-GCP, the GDPR, and applicable national legislation. Results will be published irrespective of outcome, and a summary of results, including a summary for laypersons, will be submitted to CTIS within one year of the primary analysis data cut.

12 Funding and Conflicts of Interest

Funding has been applied for from Sundhedsdonationer. Declarations of interests from the sponsor and members of the steering committees are collected, and a summary is published on the APT-KIDNEY website.