APT-KIDNEY

INITIATE - Incremental hemodialysis in incident patients with end-stage 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 within 90 days of starting maintenance hemodialysis with residual urine output ≥1,000 mL/24 h
Intervention	Twice-weekly hemodialysis with protocol-defined escalation
Control	Conventional thrice-weekly hemodialysis
Primary outcome	All-cause mortality within 12 months, non-inferiority margin for the hazard ratio 1.30
Sample size	114 deaths, approximately 492 participants (246 per arm)
Follow-up	12 months, at four-monthly platform timepoints

Background and Rationale

Chronic kidney disease affects 10–15% of adults worldwide and is projected to become the fifth leading cause of death by 2040. It is associated with substantial morbidity, excess mortality, and impaired quality of life, and prognosis is poorest in kidney failure, where annual mortality among patients receiving dialysis exceeds 20%.

Since the 1970s, hemodialysis has conventionally been prescribed as three four-hour in-center sessions per week. This standard was adopted without prospective evidence that took residual kidney function, patient preference, or clinical and biochemical symptom control into account, and the *one-size-fits-all* approach is increasingly being questioned in favor of individualized strategies such as incremental dialysis.

Incremental dialysis matches dialysis frequency to residual kidney function and intensifies treatment as that function declines. Observational studies and small randomized trials suggest that twice-weekly initiation may be non-inferior to thrice-weekly treatment, with potential benefits for quality of life, preservation of residual kidney function, and the environmental footprint of dialysis. Feasibility has been established, but no adequately powered pragmatic trial has yet determined whether less frequent initiation with protocolized escalation is non-inferior with respect to survival.

Objectives

The primary objective of INITIATE is to determine whether initiating hemodialysis twice weekly is non-inferior to conventional thrice-weekly hemodialysis with respect to all-cause mortality within 12 months. The key secondary objective is to determine whether twice-weekly initiation improves health-related quality of life.

Study Design

INITIATE is an investigator-initiated, pragmatic, randomized, parallel-group, open-label domain of the APT-KIDNEY platform comparing twice-weekly with thrice-weekly initiation of hemodialysis. The domain uses an event-driven, fixed-sample frequentist design without adaptive features.

Study Population

Adults who have started maintenance hemodialysis within the preceding 90 days at participating APT-KIDNEY sites are eligible if they meet the core APT-KIDNEY criteria and the domain-specific criteria below.

Inclusion criteria	Exclusion criteria
• Maintenance hemodialysis ≤90 days • Residual urine output ≥1,000 mL/24 h	• Life expectancy <3 months • Documented plan to change kidney replacement therapy within 3 months • Peritoneal dialysis for >3 months

Study Interventions

Participants are randomized 1:1 to incremental or conventional hemodialysis.

Incremental dialysis (intervention)

Hemodialysis is prescribed twice weekly. Session duration, dialysate composition, and concomitant medication may be adjusted, and monitoring follows routine clinical practice. Escalation to thrice-weekly treatment is recommended if residual urine output falls below 500 mL/24 h or symptoms of inadequate dialysis persist despite optimization, and immediate escalation is indicated for urgent complications such as severe hyperkalemia or volume overload. Temporary escalation, for example during hospitalization, is permitted.

Conventional dialysis (control)

Hemodialysis is prescribed thrice weekly according to standard practice, and session duration and other treatment may be adjusted as clinically indicated.

Study Procedures and Data Collection

The allocated strategy is started as soon as feasible after randomization and continued for 12 months. Trained site staff register outcomes and safety outcomes in the eCRF from source documentation at four-monthly timepoints. Participants complete the EQ-5D-5L at baseline and at 4, 8, and 12 months and a 24-hour urine collection at 4, 8, and 12 months, using a clinical collection where one is available. Follow-up takes place during routine dialysis sessions, and no additional study visits are required.

Statistical Analysis

All analyses follow the intention-to-treat principle. Non-inferiority for all-cause mortality is assessed with a Cox proportional hazards model and is concluded if the upper bound of the two-sided 95% confidence interval for the hazard ratio is ≤1.30. The EQ-5D-5L index at 12 months is compared between arms, supported by a mixed model for repeated measures, and is tested for superiority only if non-inferiority for mortality is demonstrated. Tertiary outcomes are analyzed with survival and count models. The domain is event-driven, and 114 deaths provide 80%

power to demonstrate non-inferiority at a one-sided α of 0.025 if the true hazard ratio is 1.0. With an expected 12-month mortality of 25.5% in the control arm, this corresponds to approximately 492 participants (246 per arm).

Study outcomes

Level	Outcome	Definition and analysis
Primary (non-inferiority)	All-cause mortality	Time to death within 12 months. Hazard ratio from a Cox model, non-inferiority margin 1.30.
Secondary (superiority)	Health-related quality of life	EQ-5D-5L index at 12 months, with non-survivors assigned a utility of 0.
Tertiary (exploratory)	Cardiovascular events	MACE (non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular death), its components, and non-fatal hemorrhagic stroke.
	Residual kidney function	Time to loss of residual kidney function, defined as urine output below 400 mL/24 h.
	Hospitalization	First and recurrent all-cause hospitalization, hospitalization for serious infection, and days alive out of hospital, derived from register linkage.
	Treatment adherence	Proportion of follow-up on the allocated dialysis frequency.

Safety Monitoring

Hemodialysis is delivered in specialized units with close clinical and biochemical monitoring, and the additional trial procedures (timed urine collections and questionnaires) are non-invasive. The domain is classified as risk level 1. Predefined safety outcomes are registered at each four-monthly timepoint, escalation follows protocol-defined criteria, and an independent data and safety monitoring committee (IDSMC) reviews safety by arm at regular intervals. Unexpected events affecting the benefit-risk balance are notified via CTIS, and safety data are included in the annual safety report.

Governance and Organization

INITIATE 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.

Ethics and Dissemination

INITIATE is conducted in accordance with the APT-KIDNEY core protocol, 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.

Funding and Conflicts of Interest

Funding has been applied for from Sundhedsdonationer and Danske Regioners Medicin- og behandlingspulje, and the domain will open only once funding is secured. Declarations of interests from the sponsor and members of the steering committees are collected, and a summary is published on the APT-KIDNEY website.