Protocol synopsis

Trial: A Pragmatic Trial Comparing Empagliflozin and Dapagliflozin Through Cluster Randomization Embedded in the Electronic Health Record (APPLE TREE)

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Rationale	Sodium-glucose co-transporter 2 (SGLT2) inhibitors are becoming increasingly used due to their therapeutic effectiveness in type 2 diabetes (T2D), heart failure, and chronic kidney disease. The two most commonly used SGLT2-inhibitors, empagliflozin and dapagliflozin, have never been compared in a head-to-head trial. A potential difference in effectiveness and safety may have large public health implications.
Objective	To evaluate comparative effectiveness of dapagliflozin versus empagliflozin on the risk of all-cause mortality, HF hospitalization, myocardial infarction, ischemic stroke, and incident or worsening nephropathy. Furthermore, to evaluate the risks of individual effectiveness and safety outcomes for dapagliflozin vs empagliflozin, and to determine differences in risks for dapagliflozin vs empagliflozin in relevant subgroups.
Main trial endpoints	The primary endpoint will be the 2-year risk of a composite of death from any cause, hospitalization for HF, myocardial infarction, ischemic stroke, and incident or worsening nephropathy.
Secondary endpoints	The secondary endpoints will consist of the individual components of the primary composite endpoint. The following safety endpoints will be evaluated: hospitalization for ketoacidosis, limb amputation, hospitalization for genitourinary infection, and hospitalization for fracture.
Study design	The study will be conducted as a pragmatic, prospective, open-label, multicenter cluster randomized trial where all hospitals in Region Hovedstaden and Region Sjælland will be included. The study will enroll

	patients during a 2-year period and will run for an additional year to ensure an average follow-up of trial participants of 2 years.
Population	A total of 17,600 patients who receive a new prescription for dapagliflozin or empagliflozin during a hospital contact in Region Hovedstaden or Region Sjælland are expected to be included, namely patients with T2D, and/or heart failure, and/or chronic kidney disease. Patients under the age of 18, patients who are incapable of giving consent, and patients who withdraw consent will be excluded.
Interventions	Empagliflozin and dapagliflozin in regular doses will be randomized in the study. The randomization will be done in clusters which will consist of 1-hour time frames. A generic module allows direct cluster randomization through Epic (Sundhedsplatformen). Inclusion and monitoring is automatic through Sundhedsplatformen and national registries, resulting in no harm or detriment to study participants.