STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Impact of Clinical Pharmacist-Led Cardiovascular Risk Assessment on Medication Adherence and Quality of Life in Patients With Chronic Kidney Disease: A Randomized Controlled Study

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Sponsor / responsible party	Marmara University, Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Türkiye
Principal investigator	İman Şeyhli, Department of Clinical Pharmacy, Faculty of Pharmacy, Marmara University (imanibraheemal@marun.edu.tr)
Co-investigators	Refik Demirtunç (Haydarpaşa Numune Training and Research Hospital, University of Health Sciences); Mesut Sancar (Department of Clinical Pharmacy, Marmara University)
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PART A — STUDY PROTOCOL

1. Background and rationale

Chronic kidney disease (CKD), defined by a reduced glomerular filtration rate or increased urinary albumin excretion, affects approximately 15–20% of adults worldwide. Cardiovascular disease (CVD) is the leading cause of death in people with CKD [1]. Although clinical guidelines recognise CKD as a cardiovascular risk factor, CKD is not yet fully incorporated into quantitative risk prediction, and disease awareness among patients remains low [2–4].

Patients with CKD typically have multiple comorbidities, most commonly hypertension and type 2 diabetes, and receive complex, frequently adjusted pharmacotherapy. High medication counts, poor adherence and frequent dose changes contribute to drug-related problems and impaired health-related quality of life [14, 19]. Pharmacist-led medication management and patient education have improved outcomes in chronic conditions such as diabetes and hypertension [7, 8], but results in CKD have been variable [9, 10].

This trial evaluates whether a clinical pharmacist-led pharmaceutical care programme that includes structured cardiovascular risk assessment, patient education, medication review and follow-up counselling improves cardiovascular risk, medication adherence and quality of life in hospitalised patients with CKD, compared with standard medical care.

2. Objectives

Primary objective

To compare the change in estimated 10-year cardiovascular risk (Framingham Risk Score) from baseline to 6 months between patients receiving clinical pharmacist-led pharmaceutical care and patients receiving standard care.

Secondary objectives

- To compare medication adherence (4-item Morisky–Green–Levine Medication Adherence Scale) between groups.
- To compare health-related quality of life (SF-12, including physical and mental component summary scores) between groups.
- To describe medication regimen complexity (Medication Regimen Complexity Index, MRCI) at baseline and compare it between groups.
- To compare changes in clinical parameters (blood pressure, eGFR, lipid profile) between groups.
- To explore the association between medication regimen complexity, adherence and quality of life.

3. Study design

Feature	Description
Study type	Interventional
Design	Prospective, randomized, controlled, parallel-group trial
Number of arms	2
Allocation ratio	1:1
Allocation method	Computer-generated simple randomization sequence

Feature	Description
Masking	None (open label); participants and the delivering pharmacist were aware of allocation owing to the nature of the intervention
Primary purpose	Supportive care / health services research
Follow-up duration	6 months (assessments at baseline, 3 months and 6 months)
Phase	Not applicable (non-drug behavioural/educational intervention)

4. Study setting and period

The study is conducted among patients hospitalised in the Internal Medicine Clinic of Haydarpaşa Numune Training and Research Hospital, İstanbul, Türkiye. Recruitment and follow-up are planned between January 2022 and June 2023.

5. Eligibility criteria

Inclusion criteria

- Age 18–74 years.
- Hospitalised in the Internal Medicine Clinic of the study hospital.
- Confirmed diagnosis of chronic kidney disease, including patients receiving dialysis.
- Written informed consent provided.

Exclusion criteria

- Diagnosis of dementia or Alzheimer's disease.
- Inability to provide informed consent.

Sex: all. Healthy volunteers: not accepted.

6. Recruitment, consent and randomization

Eligible patients are identified during hospitalisation. Each patient is informed of the study objectives and of the right to withdraw at any time without any effect on medical care, and enrols after giving written informed consent. Enrolled patients are listed in order of hospitalisation date and assigned 1:1 to the pharmaceutical care (intervention) group or the standard care (control) group using a computer-generated simple randomization sequence.

7. Study arms and interventions

7.1 Control arm — standard medical care (no intervention)

Participants receive routine medical care in the Internal Medicine Clinic without additional pharmacist-led interventions. Demographic and clinical data are taken from medical records and supplemented by information from the patient or caregiver. At 3 and 6 months, kidney function, lipid profile and the calculated cardiovascular risk score are recorded, and medication adherence and quality of life are assessed. Routine laboratory results are reviewed; no additional tests are requested. Clinically significant findings are communicated to the attending physician.

7.2 Intervention arm — clinical pharmacist-led pharmaceutical care (behavioural)

Participants receive the following in addition to standard medical care over 6 months:

- **Baseline (during hospitalisation):** information about kidney disease; comprehensive assessment including eGFR estimation with the CKD-EPI equation, review of routine biochemical results, blood pressure measurement and calculation of cardiovascular risk; medication review. No investigations beyond routine care.

- **Before discharge:** individualised education on CKD, cardiovascular risk factors and risk-reduction strategies, delivered in non-technical language and supported by written materials on healthy lifestyle, nutrition and smoking cessation. Patients who wish to stop smoking are referred to the Turkish Ministry of Health ALO 171 Smoking Cessation Hotline.
- **3 months:** counselling on medication use, treatment adherence and prevention of cardiovascular events; repeat assessment of adherence, quality of life and blood pressure.
- **6 months:** collection of updated clinical data, recalculation of cardiovascular risk, and repeat assessment of adherence, quality of life and blood pressure.

Follow-up visits are conducted in person or by telephone according to patient circumstances and COVID-19 safety protocols. Potentially harmful clinical findings are promptly communicated to the attending physician.

8. Outcome measures

8.1 Primary outcome

Measure	Description	Time frame
Change in estimated 10-year cardiovascular risk	Framingham Risk Score (%), calculated from age, sex, systolic blood pressure, lipid profile, smoking status and diabetes status [24]	Baseline to 6 months

8.2 Secondary outcomes

Measure	Description	Time frame
Medication adherence	4-item Morisky–Green–Levine Medication Adherence Scale (Turkish version) [22]; proportion of adherent patients	Baseline, 3 and 6 months
Health-related quality of life	SF-12 (Turkish version, SF-12-TR) [23]; PCS-12 and MCS-12 scores, 0–100, higher is better	Baseline, 3 and 6 months
Medication regimen complexity	Medication Regimen Complexity Index (Turkish version) [20, 21]	Baseline
Blood pressure	Systolic and diastolic blood pressure (mmHg)	Baseline, 3 and 6 months
Kidney function	eGFR (CKD-EPI equation), mL/min/1.73 m²	Baseline, 3 and 6 months
Lipid profile	Total cholesterol, LDL-C, HDL-C, triglycerides	Baseline, 3 and 6 months

9. Schedule of assessments

Assessment	Baseline	Discharge	3 months	6 months
Eligibility and informed consent	X			
Randomization	X			
Demographics, comorbidities (Patient Profile Record Form)	X			
Medication record (Medication Record Form)	X		X	X
Routine laboratory review (eGFR, lipids)	X		X	X

Assessment	Baseline	Discharge	3 months	6 months
Blood pressure	X		X	X
Framingham cardiovascular risk	X		X*	X
Morisky adherence scale	X		X	X
SF-12 quality of life	X		X	X
MRCI	X			
Education session (intervention arm only)		X		
Counselling (intervention arm only)			X	

*Recorded in the control arm at 3 months as described in section 7.1. Follow-up may be in person or by telephone.

10. Data collection instruments

- **Patient Profile Record Form:** age, sex, education, marital status, smoking (pack-years) and alcohol use, comorbidities, BMI, eGFR, dialysis status, total number of medications.
- **Medication Record Form:** all prescribed and non-prescribed (including over-the-counter) medications.
- **MRCI:** 65 items in three parts — A, dosage forms; B, dosing frequency; C, additional administration instructions. Parts are scored separately and summed. The validated Turkish version is used with permission [21].
- **Morisky–Green–Levine scale:** four yes/no items. No “yes” answers = high adherence; one or two = moderate; three or four = low adherence [22]. For the binary adherence outcome, patients answering “no” to all items are classified as adherent.
- **SF-12-TR:** 12 items across eight subdimensions, summarised as PCS-12 (general health, physical functioning, role-physical, bodily pain) and MCS-12 (social functioning, role-emotional, mental health, vitality), each 0–100 [23].
- **Framingham Risk Score:** points assigned to each risk factor are summed and converted to an estimated 10-year cardiovascular risk percentage [24]. The score is used as an assessment tool and does not replace clinical judgement.

11. Safety reporting and participant protection

The intervention consists of education, medication review and counselling and does not involve administration of an investigational product. No additional diagnostic procedures are performed. Any clinically significant or potentially harmful finding identified by the pharmacist in either arm is communicated promptly to the attending physician, who remains responsible for all treatment decisions.

12. Data management and confidentiality

Data are collected by the clinical pharmacist on structured paper forms and entered into IBM SPSS Statistics. Participants are identified by study codes; identifying information is kept separately and accessible only to the investigators. Datasets are available from the corresponding author on reasonable request.

13. Ethics and dissemination

The study was approved by the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (decision no. HNEAH-KAEK 2021/301-3381, 13 December 2021) and is conducted in accordance with the Declaration of Helsinki. Written

informed consent is obtained from all participants before enrolment. Results will be submitted for publication in a peer-reviewed journal.

PART B — STATISTICAL ANALYSIS PLAN

14. Hypotheses

- **Primary null hypothesis (H0):** there is no difference between the intervention and control groups in the estimated 10-year cardiovascular risk score after 6 months of follow-up.
- **Primary alternative hypothesis (H1):** the cardiovascular risk score after 6 months differs between groups, with an expected reduction of 20% in the intervention group relative to control.
- Secondary hypotheses test for between-group differences in medication adherence, SF-12 scores, baseline MRCI and clinical parameters. All tests are two-sided.

15. Sample size

The sample size was calculated assuming that the intervention would reduce the cardiovascular risk score by 20% compared with the control group after 6 months. With a two-sided significance level of 0.05 and 80% power, a minimum of 58 patients per group (116 in total) is required, using standard methods for comparing means between two independent groups. To allow for loss to follow-up in this high-risk population, 150 patients (75 per group) are to be enrolled.

16. Analysis populations

- **Randomized population:** all patients who give consent and are randomized (planned n = 150).
- **Analysis population (complete case):** randomized patients who complete the 6-month follow-up assessment, analysed in the group to which they were randomized. Patients who die, withdraw or cannot be contacted for the follow-up assessment are excluded from the outcome analyses and reported with reasons in a participant flow diagram.

17. General statistical principles

- Statistical significance: two-sided $p < 0.05$. 95% confidence intervals are reported where appropriate.
- Normality of continuous variables is assessed with the Kolmogorov–Smirnov and Shapiro–Wilk tests.
- Descriptive statistics: mean ± standard deviation for normally distributed variables; median and interquartile range for non-normally distributed variables; frequency and percentage for categorical variables.
- No adjustment for multiplicity is planned for secondary outcomes; these are interpreted as supportive and exploratory.
- No interim analysis is planned.

18. Analysis of baseline characteristics

Demographic and clinical characteristics (age, sex, marital status, smoking status and pack-years, BMI, medication allergy, comorbidities, comorbidity count, dialysis status, medication classes and MRCI) are summarised by group and overall. Between-group comparisons use the independent-samples t-test or Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Baseline differences are reported descriptively and considered in the adjusted analyses (section 21).

19. Analysis of the primary outcome

The Framingham 10-year cardiovascular risk score is summarised by group at baseline and 6 months. Between-group comparisons at each time point use the independent-samples t-test (normal data) or the Mann–Whitney U test (non-normal data). Within-group change from baseline to 6 months is tested with the paired-samples t-test or the Wilcoxon signed-rank test, as appropriate. The mean change and its 95% confidence interval are reported for each group.

20. Analysis of secondary outcomes

Outcome	Type	Between-group test	Within-group test
Medication adherence (adherent vs not)	Binary	Chi-square or Fisher's exact test	McNemar test
Morisky adherence level (high / moderate / low)	Ordinal	Chi-square or Mann–Whitney U	Wilcoxon signed-rank
SF-12 total, PCS-12, MCS-12	Continuous	Independent t-test or Mann–Whitney U	Paired t-test or Wilcoxon signed-rank
MRCI (baseline only)	Continuous	Independent t-test or Mann–Whitney U	—
Systolic / diastolic BP, eGFR, lipids	Continuous	Independent t-test or Mann–Whitney U	Paired t-test or Wilcoxon signed-rank
Dialysis status	Binary	Chi-square or Fisher's exact test	McNemar test

Correlation analyses. Associations between MRCI, medication adherence and SF-12 quality of life are assessed with Pearson's correlation coefficient (normal data) or Spearman's rank correlation coefficient (non-normal data), with the coefficient and p-value reported.

21. Adjusted and sensitivity analyses

To account for any baseline imbalance between groups (for example in age or baseline outcome values), the following adjusted analyses are performed:

- **Quality of life:** analysis of covariance (ANCOVA) with 6-month SF-12 score as the dependent variable, group as the fixed factor, and baseline SF-12 score and age as covariates.
- **Cardiovascular risk:** ANCOVA with 6-month Framingham risk score as the dependent variable, group as the fixed factor, and baseline risk score and age as covariates.
- **Medication adherence:** binary logistic regression with adherence at 6 months as the dependent variable and group allocation and baseline adherence as independent variables; odds ratios with 95% confidence intervals are reported.
- ANCOVA assumptions (homogeneity of regression slopes, homogeneity of variance by Levene's test, normality of residuals) are checked and reported.

Subgroup analyses (for example by smoking status or dialysis status) are exploratory and are reported as such.

22. Missing data and attrition

The primary analysis is a complete-case analysis of participants with 6-month data. No imputation of missing outcome values is planned. The number of patients lost to follow-up in

each group and the reasons (death, withdrawal, unable to contact) are reported, and baseline characteristics of completers and non-completers are compared to assess possible attrition bias.

23. Software

All analyses are performed with IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

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