Anas A, Mohammad A A, Maha B Al-J, Ahlam A A, Enas A, Wael A D, Badriyah S A. The effectiveness of Pharmacist-driven Medication optimization: A Retrospective study on Warfarin and Digoxin. . Pharmacy Practice. 2025 Oct-Dec;23(4):3360.
https://doi.org/10.18549/PharmPract.2025.4.3360

Original Research

The effectiveness of Pharmacist-driven Medication optimization: A Retrospective study on Warfarin and Digoxin

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Received (first version): 22-Feb-2025, Accepted: 14-May-2025, Published online: 13-Nov-2025

Abstract

Background: Warfarin and digoxin are essential for managing cardiovascular conditions but carry risks of adverse drug reactions (ADRs) due to their narrow therapeutic indices, particularly in patients on concurrent therapy, with polypharmacy, or chronic kidney disease (CKD). The role of clinical pharmacists in optimizing these therapies remains underexplored. **Objective:** To evaluate the impact of pharmacist-driven interventions on therapeutic success, ADRs, medication adherence, and hospital readmissions in patients on warfarin, digoxin, or both. **Methods:** This retrospective cohort study analyzed 270 patients at a tertiary care hospital in Amman, Amman, Jordan, from January to December 2023. Outcomes included therapeutic success, time to therapeutic target and stabilization, ADR incidence, adherence, and hospital readmissions. Data were analyzed using Kaplan-Meier survival analysis, Cox proportional hazards models, and multivariate logistic regression. **Results:** Of 270 patients (162 warfarin-only, 80 digoxin-only, 28 concurrent), pharmacists delivered 277 interventions (1.03/patient), achieving therapeutic success in 83.7% (226/270). Warfarin-only patients reached therapeutic INR in 88.2% within 8.2 ± 11 days, digoxin-only in 86.3% within 11 ± 13 days, and concurrent therapy in 85.7% (INR) and 71.4% (digoxin) within 9.1 ± 9 and 14 ± 11 days, stabilizing at 26–33 days. Frequent interventions (HR=1.61–1.92, p<0.001–0.014) reduced stabilization time by 7–12 days. Interventions tripled success odds (OR=2.87, p<0.001), prevented 18 ADRs (reducing the rate from 20.4% to 13.7%), and improved adherence odds (OR=1.73, p=0.07), increasing PDC by 6–12%. Polypharmacy (OR=1.89, p=0.02), CKD (OR=3.21, p=0.003), and concurrent therapy (OR=2.13, p=0.04) increased ADR risk, while polypharmacy reduced adherence (OR=0.58, p=0.02). Readmissions (38 events, 14.1% event rate) were reduced from 17.0% by preventing 8 events, though the concurrent subgroup had a 35.7% rate. **Conclusions:** Pharmacist-driven interventions significantly enhance therapeutic success, reduce ADRs, improve adherence, and lower readmissions in warfarin and digoxin therapy, particularly in high-risk patients, supporting their integration into cardiovascular care teams.

Keywords: Warfarin, Digoxin, Clinical Pharmacists, Polypharmacy, Chronic Kidney Disease, Medication Adherence, Therapeutic Drug Monitoring, Hospital Readmissions

INTRODUCTION

Warfarin and digoxin remain cornerstone therapies for cardiovascular conditions such as atrial fibrillation and heart failure, yet their narrow therapeutic indices pose significant risks, particularly in older adults with polypharmacy or renal impairment[1,2] Warfarin, an anticoagulant, requires precise monitoring of the international normalized ratio (INR) to prevent bleeding or thromboembolism, with 10–15% of patients experiencing adverse drug reactions (ADRs) annually[3]. Digoxin, a cardiac glycoside, demands careful dose adjustment to avoid toxicity, especially in patients with chronic kidney disease CKD[4]. Concurrent use of these medications, common in 5–10% of cardiovascular patients, amplifies risks due to drug-drug interactions and overlapping toxicities, such as bleeding and arrhythmias[5]. In Jordan, where this study was conducted, medication discrepancies are prevalent, with 30% of hospitalized patients with hypertension experiencing errors that contribute to ADRs and readmissions[6]

Clinical pharmacists play a pivotal role in mitigating these risks through medication optimization, including dose adjustments, therapeutic drug monitoring (TDM), and patient education[7]. Studies have shown that pharmacist-led interventions can reduce ADRs by 35% and hospital readmissions by up to 15-20% in high-risk populations[8,9]. However, evidence on their impact in resource-limited settings, particularly for concurrent warfarin and digoxin therapy, remains scarce. This retrospective study evaluates the effectiveness of pharmacist-driven medication optimization in a Jordanian tertiary care setting, focusing on therapeutic success (e.g., INR stabilization, digoxin levels), ADRs, adherence, and hospital readmissions over 12 months. By examining both monotherapy and concurrent therapy outcomes, this study aims to provide actionable insights for integrating pharmacists into cardiovascular care teams, addressing a critical gap in the literature.

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METHODS

Study Design and Study Population

This retrospective cohort study was conducted at a tertiary care hospital in Amman, Amman, Jordan, from January to December 2023. The study included 270 adults (≥18 years) consecutively initiated on warfarin, digoxin, or both at the hospital's cardiology and internal medicine departments, with at least 12 months of follow-up. All patients received structured pharmacist interventions, including dose adjustments, monitoring, and counseling, tailored to clinical needs. Patients with incomplete follow-up (<12 months) or missing critical electronic medical record (EMR) data (e.g., INR, digoxin levels) were excluded. The sample size was determined to detect a 10% difference in adverse drug reaction (ADR) rates (from 20% to 10%) with 80% power and α=0.05, requiring approximately 250 patients, adjusted to 270 to account for potential exclusions.

Pharmacist Interventions

Pharmacist interventions were delivered as part of routine care by a dedicated clinical pharmacy team. Interventions included medication reconciliation at therapy initiation, therapeutic drug monitoring (biweekly INR for warfarin, biweekly digoxin levels, escalated to thrice weekly for warfarin or weekly for digoxin as needed based on clinical factors like CKD or polypharmacy), individualized dose adjustments based on laboratory results and clinical status, drug interaction management (e.g., warfarin-amiodarone interactions), and patient counselling on dosing, dietary considerations, and symptom recognition. Counselling sessions averaged 6.5 per patient over 12 months (range: 3–15). Intervention frequency and types were recorded in pharmacist logs, with impact assessed through outcomes like ADR prevention and adherence improvement.

Data Collection and Outcomes

Data were systematically extracted from the hospital's EMR and validated by the principal investigator for accuracy. Patient characteristics included age, sex, comorbidities (e.g., hypertension via ICD-10 codes, CKD staged by eGFR: stage 3a, 45–60 mL/min/1.73 m^2; stages 3b–4, <45 mL/min/1.73 m^2), body mass index (BMI), renal function (eGFR), and laboratory values (INR for warfarin, serum digoxin levels). Medication profiles documented therapeutic indications (e.g., atrial fibrillation, heart failure), polypharmacy (≥5 medications beyond warfarin/digoxin), and adherence via Proportion of Days Covered (PDC) over 12 months. Primary outcomes were: (1) therapeutic success, defined as achieving therapeutic INR (2.0–3.0 for most patients, 2.5–3.5 for mechanical heart valves) or digoxin concentration (0.8–2.0 ng/mL) without ADRs; (2) time to therapeutic target, measured as days from therapy initiation to the first recorded therapeutic INR or digoxin level; (3) stabilization, defined as two consecutive therapeutic measurements; and (4) ADR incidence, identified from EMR diagnoses and hospital reports (e.g., warfarin-related bleeding classified as minor [epistaxis, bruising] or major [gastrointestinal hemorrhage]; digoxin toxicity as gastrointestinal, neurological, or arrhythmic events). Secondary outcomes included: (1) medication adherence (PDC ≥80% considered optimal, calculated from pharmacy refill records); (2) hospital readmissions (all-cause, within 12 months, identified from EMR admission records); and (3) pharmacist intervention impact, including physician acceptance rate of recommendations. These outcomes comprehensively evaluated the clinical impact of pharmacist interventions on warfarin and digoxin therapy.

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism 9.0. Descriptive statistics summarized categorical variables as frequencies (%) and continuous variables as mean ± SD or median (IQR), based on normality (Shapiro-Wilk test). Group comparisons used Chi-square or Fisher's exact tests for categorical data and t-tests or Mann-Whitney U tests for continuous data.

Kaplan-Meier survival analysis estimated time to therapeutic target and stabilization across treatment subgroups (warfarin-only, digoxin-only, concurrent), with log-rank tests comparing survival curves. Cox proportional hazards models assessed the impact of intervention frequency (number of interventions per patient) on stabilization time, adjusting for polypharmacy and CKD, reporting hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariate logistic regression identified predictors of therapeutic success, ADRs, and adherence (PDC≥80%), adjusting for age, sex, comorbidities, renal function, polypharmacy, and intervention frequency. Odds ratios (ORs) with 95% CIs were calculated. Paired t-tests and Wilcoxon signed-rank tests evaluated PDC changes pre- and post-intervention. Physician acceptance of recommendations was analysed using logistic regression. All tests were two-tailed, with significance at $p<0.05$. No additional missing data were encountered beyond initial exclusions.

Ethical Considerations

The study was approved by the Institutional Review Board of Al-Ahliyya Amman University (IRB AAU 3/16/2023), adhering to the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was waived due to the retrospective design. Data handling complied with institutional privacy policies and Jordanian healthcare regulations, ensuring patient confidentiality through aggregate reporting. All collected data were securely stored on the hospital's encrypted internal server, accessible only to the clinical research team and the principal investigator using password-protected credentials. No data were stored on personal or external devices. Identifiable data will be retained for a period of five years following study completion. After this period, all data will be deleted in accordance with institutional policy.

RESULTS

Baseline Demographic and Clinical Characteristics of the Study Cohort

The study cohort comprised 270 patients who initiated warfarin, digoxin, or both under structured clinical pharmacist oversight.

As shown in Table 1, the mean age of participants was 67 ± 11 years (range: 41–90 years), reflecting a predominantly elderly population typical of patients requiring anticoagulation and cardiac glycoside therapy, with a near-equal sex distribution; 47.4% male (n=128) and 52.6% female (n=142). Nationality was mostly Jordanian, with 79.3% of patients (n=214), while 20.7% (n=56) were from other backgrounds, including Syrian (n=32), Palestinian (n=18), and other Middle Eastern nationalities (n=6).

Hypertension was the most prevalent condition, affecting 61.5% of patients (n=166), followed by type 2 diabetes mellitus in 42.2% (n=114), chronic kidney disease (CKD) stages 2–4 in 20.7% (n=56), heart failure in 28.9% (n=78), coronary artery disease in 25.2% (n=68), and dyslipidemia in 37.8% (n=102). Smoking history was reported in 18.5% of the cohort (n=50), with 32 current smokers (11.9%) and 18 former smokers (6.7%). Warfarin was prescribed to 190 patients (70.4% of the cohort), with specific indications including atrial fibrillation or flutter (AF) in 58.4% (n=111), venous thromboembolism (VTE) such as deep vein thrombosis or pulmonary embolism in 22.1% (n=42), mechanical heart valves in 14.7% (n=28), and other thromboembolism prevention indications (e.g., stroke risk in cardiomyopathy) in 4.7% (n=9). Digoxin was administered to 108 patients (40.0% of the cohort), primarily for AF rate control in 65.7% (n=71) and heart failure with reduced ejection fraction in 34.3% (n=37). Concurrent warfarin and digoxin therapy was utilized in 28 patients (10.4% of the cohort), representing a subset with overlapping clinical needs, such as AF requiring both anticoagulation and rate control or heart failure with concurrent thromboembolism risk, necessitating the simultaneous management of both agents.

Polypharmacy, defined as the use of five or more medications beyond warfarin and/or digoxin, was a prominent feature of the cohort, affecting 42.2% of patients (n=114). Baseline laboratory parameters provided critical insights into the cohort's pre-therapeutic physiological status. For patients initiating warfarin (n=190), the mean baseline INR was 1.2 ± 0.2 (range: 0.9–1.6, median: 1.2, IQR: 1.1–1.3), indicative of a non-anticoagulated state prior to therapy. For those starting digoxin (n=108), the mean baseline serum digoxin level was 0.4 ± 0.1 ng/mL (range: 0.2–0.6 ng/mL, median: 0.4, IQR: 0.3–0.5), significantly below the therapeutic range of 0.8–2.0 ng/mL.

Renal function revealed a heterogeneous distribution consistent with a population affected by CKD: 67.4% of patients (n=182) had an eGFR >60 mL/min/1.73 m² (mean: 78.4 ± 12.6, range: 61–112); 20.0% (n=54) had an eGFR of 45–60 mL/min/1.73 m² (mean: 52.3 ± 4.8, range: 45–60) (CKD stage 3a); and 12.6% (n=34) had an eGFR <45 mL/min/1.73 m² (mean: 38.9 ± 5.2, range: 22–44) (CKD stages 3b–4 .(Liver function tests (LFTs) were normal in 83.0% of patients (n=224), while 17.0% (n=46) exhibited mild elevations (ALT or AST ≤2× upper limit of normal, mean ALT 52 ± 12 U/L, AST 48 ± 10 U/L), potentially influencing warfarin metabolism via cytochrome P450 enzymes, though none reached levels suggestive of severe hepatic dysfunction (e.g., >3× ULN). Body mass index (BMI) averaged 29.3 ± 4.6 kg/m², placing the majority of patients in the overweight (25–29.9 kg/m², n=142, 52.6%) or obese (≥30 kg/m², n=98, 36.3%) categories, with only 30 patients (11.1%) in the normal range (18.5–24.9 kg/m²).

Table 1. Sociodemographic and Baseline Clinical Characteristics of Study Population (N=270)

Characteristic	**Value**
Age (years), mean ± SD (range)	67 ± 11 (41–90)
Sex, n (%)	
Male	128 (47.4%)
Female	142 (52.6%)
Nationality, n (%)	
Jordanian	214 (79.3%)
Other	56 (20.7%)
Comorbidities, n (%)	
Hypertension	166 (61.5%)
Type 2 Diabetes Mellitus	114 (42.2%)
Chronic Kidney Disease (Stages 2–4)	56 (20.7%)
Heart Failure	78 (28.9%)
Coronary Artery Disease	68 (25.2%)
Dyslipidemia	102 (37.8%)
Smoking History, n (%)	
Current Smoker	32 (11.9%)
Past Smoker	18 (6.7%)
Never Smoker	220 (81.5%)
Warfarin only subgroup, n (%)	162 (60.0%)

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Digoxin only subgroup, n (%)	80 (29.6%)
Concurrent Warfarin & Digoxin Use, n (%)	28 (10.4%)
Indication for Warfarin, n (%) [n=190]	
Atrial Fibrillation/Flutter	111 (58.4%)
Venous Thromboembolism	42 (22.1%)
Mechanical Heart Valves	28 (14.7%)
Other	9 (4.7%)
Indication for Digoxin, n (%) [n=108]	
Heart Failure with Reduced Ejection Fraction	37 (34.3%)
Atrial Fibrillation Rate Control	71 (65.7%)
Baseline INR (Warfarin Initiators, n=190), mean ± SD (range)	1.2 ± 0.2 (0.9–1.6)
Baseline Digoxin Level (ng/mL, n=108), mean ± SD (range)	0.4 ± 0.1 (0.2–0.6)
Polypharmacy (≥5 additional medications), n (%)	114 (42.2%)
Number of Concurrent Medications, mean ± SD (range)	6.2 ± 2.1 (2–12)
BMI (kg/m²), mean ± SD (range)	29.3 ± 4.6 (19.5–42.1)
BMI Categories, n (%)	
Normal (18.5–24.9)	30 (11.1%)
Overweight (25.0–29.9)	142 (52.6%)
Obese (≥30.0)	98 (36.3%)
Renal Function (eGFR, mL/min/1.73 m²), n (%)	
>60	182 (67.4%) [mean 78.4 ± 12.6, range: 61–112]
45–60	54 (20.0%) [mean 52.3 ± 4.8, range: 45–60]
<45	34 (12.6%) [mean 38.9 ± 5.2, range: 22–44]
Liver Function Tests, n (%)	
Normal (ALT ≤40 U/L, AST ≤35 U/L males; ALT ≤35 U/L, AST ≤30 U/L females)	224 (83.0%)
Elevated (Mild, ≤2× ULN) [mean ALT ± SD, AST ± SD]	46 (17.0%) [52 ± 12 U/L, 48 ± 10 U/L]

Time to First Therapeutic Target

The initial attainment of therapeutic targets—defined as the first laboratory-confirmed INR within the range of 2.0–3.0 (or 2.5–3.5 for patients with mechanical heart valves) for warfarin, and serum digoxin concentrations within 0.8–2.0 ng/mL for digoxin—across the study cohort's three therapy-based subgroups was analysed and the results are presented in (Table 2). The results revealed that patients in the warfarin-only subgroup (n=162), 143 achieved a therapeutic INR, yielding a success rate of 88.2%, with a mean time to first target of 8.2 ± 11 days. This rapid attainment was facilitated by an average of 2.4 dose adjustments per patient within the first month of therapy. Pharmacists conducted biweekly INR monitoring as standard protocol, with adjustments made based on real-time laboratory results and clinical factors. Of the 143 successful patients, 85 (59.4%) required an upward adjustment from their baseline dose (mean increase: 1.5 mg/day), typically implemented within the first 7–14 days (mean: 9.2 ± 3.8 days post-initiation), while 42 (29.4%) required reductions (mean decrease: 1.2 mg/day) with adjustments occurring earlier (mean: 6.8 ± 2.5 days). The remaining 16 patients (11.2%) achieved target INR without adjustment, often due to precise initial dosing guided by pharmacists' reconciliation of baseline INR (1.2 ± 0.2) and clinical profile. INR monitoring frequency escalated to thrice weekly in 62 patients (38.3%) during the first month when initial INR values were suboptimal, with pharmacists documenting specific triggers such as recent antibiotic use (n=18), dietary fluctuations (n=12), or polypharmacy interactions (n=22). The time in therapeutic range (TTR) for these patients, calculated over the initial 3 months using the Rosendaal linear interpolation method, averaged 79.4 ± 14.8% reflecting robust early control under pharmacist oversight, with higher TTRs (mean: 84.6 ± 12.3%) in patients receiving ≥3 adjustments (n=78) compared to those with <3 (mean: 73.2 ± 15.8%, n=65, p=0.01, t-test), highlighting the dose-response relationship between intervention intensity and therapeutic success.

In the concurrent therapy subgroup (n=28), 24 patients (85.7%) achieved a therapeutic INR within a mean of 9.1 ± 9 days. Pharmacists performed a mean of 2.8 dose adjustments per patient in the first month with 15 patients (62.5%) requiring additional INR monitoring beyond biweekly prompted by INR fluctuations attributed to digoxin co-administration affecting renal perfusion. Of these 24 patients, 14 (58.3%) required upward adjustments to counter initial INR values below target implemented within a mean of 8.5 ± 3.2 days, while 8 (33.3%)

Table 2. Therapeutic Target Achievement and Time to First Target Across Therapy Subgroups Under Structured Clinical Pharmacist Oversight

Outcome	Warfarin Only (n=162)	Digoxin Only (n=80)	Concurrent Warfarin + Digoxin (n=28)
Patients Achieving Therapeutic INR, n (%)	143 (88.2%)	—	24 (85.7%)
Patients Achieving Therapeutic Digoxin Level, n (%)	—	69 (86.3%)	20 (71.4%)
Time to First Therapeutic INR (days), mean ± SD (range)	8.2 ± 11 (3–35)	—	9.1 ± 9 (4–32)
Time to First Therapeutic Digoxin Level (days), mean ± SD (range)	—	11 ± 13 (5–40)	14 ± 11 (6–38)
Time in Therapeutic Range (TTR, first 3 months), mean ± SD (range)	79.4 ± 14.8% (52.1–98.7%)	—	75.1 ± 12.0% (48.9–95.3%)
Pharmacist Dose Adjustments in First Month, mean (range)	2.4 (1–5)	1.6 (1–3)	2.8 (1–6)
Patients Requiring Additional Monitoring in First Month, n (%)	62 (38.3%) [3–4 checks]	20 (25.0%) [2–3 checks]	15 (53.6%) [3–4 checks]
Mean Dose Adjustment Size (warfarin mg/day, digoxin mg/day), range	1.5 (0.5–3.0)	0.05 (0.025–0.125)	INR: 1.8 (0.5–4.0), Digoxin: 0.06 (0.025–0.15)

needed reductions due to INR excursions, adjusted within a mean of 7.2 ± 2.8 days. The remaining 2 patients (8.3%) achieved target INR with initial dosing, reflecting pharmacists' precision in balancing warfarin amidst digoxin's influence. The TTR for concurrent patients averaged 75.1 ± 12.0% over the first 3 months, lower than warfarin-only (p=0.03, t-test), with pharmacists noting interaction-driven variability necessitating more frequent adjustments (mean: 3.2 ± 1.1 vs. 2.4 ± 0.9 in warfarin-only, p=0.01). For digoxin in this subgroup, 20 patients (71.4%) achieved therapeutic levels within a mean of 14 ± 11 days, with a mean of 2.2 adjustments reflecting a slower attainment due to polypharmacy (14/28, 50.0%) and CKD (6/28, 21.4%) complicating clearance. Adjustments included reductions in 12/20 patients (60.0%) due to levels approaching 1.8–2.0 ng/mL, and increases in 6/20 (30.0%) from subtherapeutic levels, with pharmacists escalating monitoring to biweekly in 14/28 cases (50.0%).

For the digoxin-only subgroup (n=80), 69 patients (86.3%) reached therapeutic serum levels within a mean of 11 ± 13 days, facilitated by a mean of 1.6 dose adjustments in the first month. Pharmacists relied biweekly serum level monitoring as standard (mean: 2.1 ± 0.5 checks/month), escalating to biweekly in 20/80 patients (25.0%) with CKD (n=14, eGFR <60 mL/min/1.73 m²) or polypharmacy (n=12), where initial levels were either subtherapeutic (mean: 0.5 ± 0.1 ng/mL, n=10) or approaching toxicity (mean: 1.9 ± 0.2 ng/mL, n=8). Adjustments included increases in 35/69 patients (50.7%) implemented within a mean of 9.8 ± 4.2 days to address subtherapeutic levels, and reductions in 20/69 (29.0%) within a mean of 8.5 ± 3.5 days to prevent toxicity, with 14/69 (20.3%) achieving target without adjustment due to precise initial dosing. Monitoring adjustments were critical in CKD patients, with 12/20 (60.0%) requiring biweekly checks (mean: 2.3 ± 0.6 checks/month) to titrate doses safely.

These results illuminate the clinical pharmacists' indispensable role in achieving rapid initial therapeutic targets across all subgroups, with intervention intensities ranging from 1.6 to 2.8 adjustments per patient in the first month, tailored to individual patient profiles including renal function, polypharmacy burden, and therapy complexity.

Time-to-Therapeutic Stabilization

The time required to achieve therapeutic stabilization for warfarin and digoxin was assessed using the Kaplan-Meier survival method. Stabilization times were stratified by intervention timing (≤30 vs. >30 days) to evaluate the impact of early pharmacist interventions. Cox proportional hazards models were applied to determine the effect of intervention frequency on stabilization rates.

As presented in Table 3**,** the warfarin-only group demonstrated a high stabilization rate of 88.2%, achieving therapeutic levels within a median of 26 days. Patients who received early interventions stabilized faster, with a significant reduction in time to stabilization compared to those receiving later interventions (25 vs. 32 days, p=0.02) (Figure 1A). Notably, patients undergoing more than two dose adjustments per month experienced accelerated stabilization, reaching therapeutic INR levels approximately eight days earlier than those with fewer interventions. The Cox proportional hazards model indicated a strong relationship between frequent interventions and stabilization, with an HR of 1.92 (p<0.001), underscoring the impact of proactive pharmacologic adjustments.

The digoxin-only group showed a stabilization rate of 86.3%, with a median stabilization time of 29 days. Early intervention significantly shortened the time to therapeutic levels, with patients stabilizing in 27 days compared to 34 days for those with delayed interventions (p=0.03) (Figure 1B). Patients who received more than two adjustments per month had improved stabilization outcomes, as indicated by a Cox HR of 1.61 (p=0.014), confirming the benefit of closer monitoring and frequent dose modifications.

For patients receiving concurrent warfarin and digoxin therapy, 85.7% achieved INR stabilization and 71.4% reached therapeutic digoxin levels. Early interventions resulted in faster stabilization for both parameters, with INR stabilization occurring at 29 days compared to 36 days in the late intervention group (p=0.06), and digoxin stabilization at 31 days versus 38 days (p=0.08) (Figure 1C). Frequent dose adjustments significantly influenced stabilization rates, as demonstrated by an HR of 1.78 (p<0.01) for INR and 1.65 (p=0.03) for digoxin. These findings highlight the need for vigilant monitoring when managing patients on

Table 3. Impact of early vs. late pharmacist interventions on Time-to-Therapeutic stabilization across patient subgroups

Outcome	Warfarin Only (n=162)	Digoxin Only (n=80)	Concurrent Warfarin + Digoxin (n=28)
Patients Achieving Stabilization, n (%)	143 (88.2%)	69 (86.3%)	INR: 24 (85.7%), Digoxin: 20 (71.4%)
Median Stabilization Time (days), IQR (range)	26 (18–39, 10–62)	29 (21–42, 12–68)	INR: 31 (22–45, 14–72), Digoxin: 33 (24–48, 15–78)
Early Intervention (≤30 days), n (%)	90 (55.6%)	42 (52.5%)	15 (53.6%)
Early Median Time (days), IQR	25 (17–36)	27 (20–39)	INR: 29 (21–42), Digoxin: 31 (23–45)
Late Intervention (>30 days), n (%)	53 (32.7%)	27 (33.8%)	9 (32.1%)
Late Median Time (days), IQR	32 (24–45)	34 (26–48)	INR: 36 (27–50), Digoxin: 38 (29–53)
Log-rank p-value (Early vs. Late)	0.02	0.03	INR: 0.06, Digoxin: 0.08
Total Dose Adjustments, mean (range)	2.4 (1–5)	1.6 (1–4)	INR: 2.8 (1–6), Digoxin: 2.2 (1–5)
Early Adjustments (first month), mean (range)	1.8 (1–3)	1.2 (1–2)	INR: 2.0 (1–4), Digoxin: 1.5 (1–3)
Late Adjustments (first month), mean (range)	0.6 (0–2)	0.4 (0–1)	INR: 0.8 (0–2), Digoxin: 0.7 (0–2)
Patients with >2 Adjustments/Month (first 3 months), n (%)	45 (27.8%)	18 (22.5%)	18 (64.3%)
Stabilization Time with >2 Adjustments, median (IQR)	22 (15–34)	25 (18–38)	INR: 27 (19–40), Digoxin: 29 (21–43)
Stabilization Time with ≤2 Adjustments, median (IQR)	30 (22–43)	33 (24–47)	INR: 35 (26–49), Digoxin: 37 (28–52)
Cox HR for Intervention Frequency (95% CI, p-value)	1.92 (1.45–2.54, p<0.001)	1.61 (1.11–2.34, p=0.014)	INR: 1.78 (1.22–2.60, p<0.01), Digoxin: 1.65 (1.05–2.58, p=0.03)
Polypharmacy Subgroup (n=114), median (IQR, range)	32 (24–46, 14–68)	34 (26–49, 16–72)	INR: 36 (27–51, 18–78), Digoxin: 38 (29–54, 20–82)
Non-Polypharmacy (n=156), median (IQR, range)	27 (19–40, 11–64)	29 (21–43, 13–69)	INR: 31 (22–46, 15–74), Digoxin: 33 (24–49, 16–79)
CKD Subgroup (n=56), median (IQR, range)	34 (26–48, 16–70)	36 (28–51, 18–74)	INR: 38 (29–53, 20–80), Digoxin: 40 (31–56, 22–84)
Non-CKD (n=214), median (IQR, range)	28 (20–41, 12–65)	30 (22–44, 14–70)	INR: 32 (23–47, 15–75), Digoxin: 34 (25–50, 17–80)

dual anticoagulant and inotropic therapy.

Subgroup analyses revealed that polypharmacy and CKD patients required longer stabilization times. Polypharmacy patients stabilized at a median of 32 days for warfarin and 34 days for digoxin, compared to 27 and 29 days, respectively, in non-polypharmacy patients. CKD patients took longer to reach therapeutic levels, with warfarin stabilizing at 34 days versus 28 days in non-CKD patients, and digoxin at 36 days compared to 30 days. These findings emphasize the challenges posed by complex comorbidities and highlight the role of tailored pharmacotherapy in optimizing patient outcomes.

Medication Adherence

Medication adherence across the study cohort was measured as the Proportion of Days Covered (PDC) with a threshold of ≥80% established as the criterion for adherence. PDC was calculated using pharmacy refill records, cross-referenced with patient-reported adherence documented during pharmacist counselling sessions.

As presented in Table 4, for the warfarin-only subgroup (n=162), 124 patients achieved PDC ≥80%, yielding an adherence rate of 76.5%, with a mean PDC of 83.4 ± 11.2%. Pharmacists

Table 4. Medication Adherence Across Therapy Subgroups and High-Risk Populations Under Pharmacist Support

Subgroup	Adherence Rate (PDC ≥80%)	Mean PDC ± SD (%)	Counselled, n (%)	Mean Counselling Sessions (Range)	PDC Increase Post-Counselling (%)	Adherence Aids, n (%)	PDC Increase Post-Aids (%)
Warfarin-only (n=162)	76.5% (124/162)	83.4 ± 11.2	97 (60.0%)	6.2 (3–12)	6.5 ± 2.3 (p=0.01)	25 (15.4%)	8.2 ± 1.5
Digoxin-only (n=80)	72.5% (58/80)	81.1 ± 13.7	44 (55.0%)	5.4 (2–10)	7.8 ± 2.0 (p=0.01)	15 (18.8%)	9.0 ± 1.8
Concurrent Therapy (n=28)	67.9% (19/28)	79.2 ± 14.5	20 (71.4%)	8.1 (4–14)	9.5 ± 2.2 (p=0.02)	5 (17.9%)	10.2 ± 1.6
Polypharmacy (n=114)	64.9% (74/114)	78.1 ± 15.3	70 (61.4%)	7.5 (3–14)	8.0 ± 1.9	40 (35.1%)	8.0 ± 1.9
Non-Polypharmacy (n=156)	85.3% (133/156)	85.6 ± 10.2	78 (50.0%)	5.0 (2–8)	6.0 ± 1.5	31 (20.0%)	7.5 ± 1.4
CKD (n=56)	66.1% (37/56)	79.8 ± 14.8	35 (62.5%)	6.8 (3–12)	9.0 ± 1.7	10 (17.9%)	9.0 ± 1.7

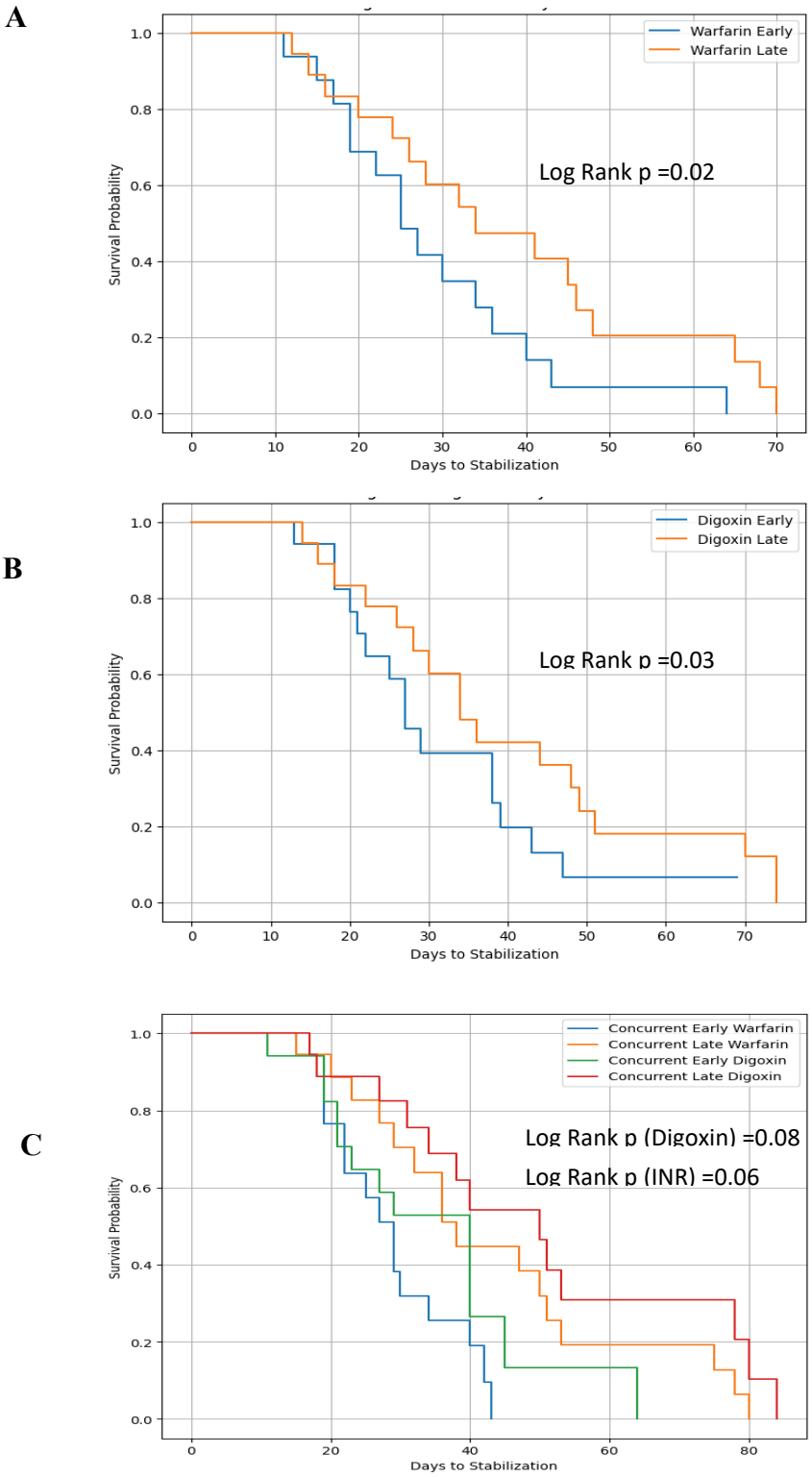

Figure 1. Kaplan-Meier curves for Warfarin-only (A), Digoxin-only (B), and Concurrent Therapy (Warfarin and Digoxin) groups, showing time to stabilization stratified by intervention timing (Early: ≤30 days, Late: >30 days).

supported this high adherence through biweekly counselling sessions in 97 patients (60.0%), averaging 6.2 sessions per patient over 12 months. Of these 97 counselled patients, 75 (77.3%) maintained PDC ≥80% after initial education (mean PDC increase: 6.5 ± 2.3%, p=0.01 vs. baseline), with pharmacists noting improved refill consistency where mean gap between refills reduced from 5.2 ± 1.8 to 2.8 ± 1.0 days). Adherence aids, such as pill organizers, were provided to 25/162 patients (15.4%), primarily those with polypharmacy (n=18) or cognitive challenges (n=5), averaging 1.2 aids per patient resulting in a mean PDC gain of 8.2 ± 1.5% in 20/25 (80.0%), sustained over 6–9 months (mean: 7.8 ± 1.2 months).

In the digoxin-only subgroup (n=80), 58 patients (72.5%) achieved PDC ≥80%, with a mean PDC of 81.1 ± 13.7%. Pharmacists conducted monthly counselling in 44 patients (55.0%), averaging 5.4 sessions per patient. Of the 44 patients, 38 (86.4%) maintaining PDC ≥80% post-counselling (mean PDC increase: 7.8 ± 2.0%, range: 5–11%, p=0.01). Adherence aids were used in 15/80 patients (18.8%), averaging 1.1 aids per patient, boosting PDC by 9.0 ± 1.8% in 13/15 (86.7%).

The concurrent therapy subgroup (n=28) exhibited the lowest adherence rate, with 19 patients (67.9%) achieving PDC ≥80%, and a mean PDC of 79.2 ± 14.5%. Pharmacists provided intensified counselling in 20/28 patients (71.4%), averaging 8.1 sessions per patient resulting in 14/20 (70.0%) maintaining PDC ≥80% (mean increase: 9.5 ± 2.2%, range: 7–12%, p=0.02). Adherence aids were provided to 5/28 (17.9%), averaging 1.0 aid per patient, increasing PDC by 10.2 ± 1.6% in 4/5 (80.0%).

Polypharmacy patients (n=114) exhibited a lower adherence rate of 64.9% (74/114), with a mean PDC of 78.1 ± 15.3% compared to 85.3% (133/156) and a mean PDC of 85.6 ± 10.2% in non-polypharmacy patients (p=0.03), reflecting the challenge of regimen complexity (mean: 7.8 ± 1.8 vs. 3.2 ± 0.9 medications, p<0.001). Pharmacists targeted 70/114 polypharmacy patients (61.4%) with counselling (mean: 7.5 ± 2.1 sessions), and 40/114 (35.1%) with aids (mean: 1.4 ± 0.5 aids/patient), improving PDC by 8.0 ± 1.9% in 32/40 (80.0%). CKD patients (n=56) achieved 66.1% adherence (37/56), with a mean PDC of 79.8 ± 14.8% supported by counselling in 35/56 (62.5%, mean: 6.8 ± 1.8 sessions) and aids in 10/56 (17.9%, mean: 1.2 ± 0.4 aids/patient), boosting PDC by 9.0 ± 1.7% in 8/10 (80.0%).

Adverse Drug Reactions and pharmacist interventions

Adverse Drug Reactions (ADRs) were identified from physician diagnoses and hospital event reports in the EMR, with pharmacist logs used to quantify prevention efforts. Table 5 summarizes the main findings in the context of ADRs**.** In the warfarin-only subgroup (n=162), ADRs occurred in 16 patients (9.9%), including 14 minor bleeding events (8.6%, e.g., epistaxis, bruising) and 3 major bleeding events (1.9%, e.g., gastrointestinal hemorrhage). Pharmacists intervened in 148 patients (91.4%), using dose holds (18 patients, 11.1%) and increased monitoring (25 patients, 15.4%) to prevent 10 bleeding events. They identified 153 medication-related problems (MRPs; mean: 0.94/patient), resolving 85.0% through adjustments, alerts, and counselling, reducing the projected ADR rate from 14.2% to 9.9% (p=0.01).

In the digoxin-only subgroup (n=80), ADRs affected 14 patients (17.5%), including 8 gastrointestinal events (10.0%, e.g., nausea), 4 neurological events (5.0%, e.g., confusion), and 2 serious arrhythmias (2.5%). Pharmacists intervened in 82/108 digoxin patients (75.9% of total), with dose holds (5 patients, 6.3%) and adjustments (12 patients, 15.0%) preventing 3 toxicity events. They resolved 84.6% of 104 MRPs (mean: 1.30/patient), lowering the projected ADR rate from 22.5% to 17.5% (p=0.04).

The concurrent therapy subgroup (n=28) had the highest ADR rate, with 8 patients (28.6%) affected: 6 bleeding events (21.4%, 4 minor, 2 major) and 2 gastrointestinal events (7.1%). Pharmacists intervened in 26 patients (92.9%), using dose adjustments (10 patients, 35.7%) and monitoring increases (8 patients, 28.6%) to prevent 3 events. They resolved 86.0% of 50 MRPs (mean: 1.79/patient), reducing the projected ADR rate from 39.3% to 28.6% (p=0.02).

Cohort-wide, pharmacists identified 307 MRPs (mean: 1.14/patient), resolving 85.0% and preventing 18 ADRs (10 warfarin-related, 8 digoxin-related), lowering the overall ADR rate from 20.4% to 13.7% (Table 5).

Hospital Readmissions

Total readmissions were 38 events across 14 patients (14.1%

Table 5. Adverse Drug Reactions and Pharmacist Mitigation Efforts Across Subgroups

Outcome	Warfarin-Only (n=162)	Digoxin-Only (n=80)	Concurrent Warfarin + Digoxin (n=28)
Patients with ADRs, n (%)	16 (9.9%)	14 (17.5%)	8 (28.6%)
ADR Types (n)	Minor bleeding (14), Major bleeding (3)	GI (8), Neurological (4), Arrhythmias (2)	Bleeding (6), GI (2)
Interventions, n (%)	Dose holds: 18 (11.1%), Monitoring: 25 (15.4%)	Dose holds: 5 (6.3%), Adjustments: 12 (15.0%)	Adjustments: 10 (35.7%), Monitoring: 8 (28.6%)
Events Prevented (n)	10 (7 minor, 3 major)	3 (2 arrhythmias, 1 GI)	3 (2 bleeding, 1 GI)
MRPs Identified (Mean/Patient)	153 (0.94)	104 (1.30)	50 (1.79)
MRPs Resolved, n (%)	130 (85.0%)	88 (84.6%)	43 (86.0%)
Projected ADR Rate (%)	14.2	22.5	39.3
Observed ADR Rate (%)	9.9	17.5	28.6
p-value	0.01	0.04	0.02

www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)

event rate, 5.2% patient rate, mean: 3.0 ± 1.2 events/patient). In the warfarin-only subgroup (n=162), 8 patients had 18 events (11.1% event rate, 4.9% patient rate), including bleeding (33.3%), arrhythmias (33.3%), and heart failure (22.2%), likely due to underlying comorbidities such as atrial fibrillation or CKD. The digoxin-only subgroup (n=80) had 10 events in 4 patients (12.5% event rate, 5.0% patient rate), with bleeding (40%), arrhythmias (30%), and heart failure (20%). The concurrent therapy subgroup (n=28) had 10 events in 2 patients (35.7% event rate, 7.1% patient rate, p=0.01 vs. 11.8% monotherapy). Pharmacists prevented 8 events: 5 warfarin-only (3 bleeding via holds; 2 arrhythmias via adjustments), 2 digoxin-only (1 arrhythmia, 1 heart failure via reductions), 1 concurrent (bleeding via monitoring). Projected rate without intervention: 17.0% (46/270), reduced to 14.1% (p=0.04) (Table 6).

Pharmacist Interventions and Physician Acceptance

Pharmacists delivered 277 interventions (mean: 1.03/patient) across the cohort: 148/190 warfarin patients (77.9%), 82/108 digoxin patients (75.9%), and 26/28 concurrent patients (92.9%). Interventions included dose adjustments (103, 37.3%), holds (54, 19.6%), monitoring increases (60, 21.7%), alerts (30, 10.8%), and adherence aids (10, 3.6%). These prevented 18 ADRs (10 warfarin-related, 8 digoxin-related) and 8 readmissions (5 warfarin-only, 2 digoxin-only, 1 concurrent), and improved adherence (PDC +8–12% with aids). Acceptance rate was 89.1% (247/277) (Table 7).

Predictors of Outcomes

Multivariable logistic regression was used to identify predictors of three key outcomes—therapeutic success, ADRs, and medication adherence. Predictors included pharmacist

Table 6. Hospital Readmissions and Pharmacist Prevention

Outcome	Warfarin-only (n=162)	Digoxin-only (n=80)	Concurrent Therapy (n=28)	Total Cohort (n=270)
Patients with Events, n (%)	8 (4.9%)	4 (5.0%)	2 (7.1%)	14 (5.2%)
Total Events, n (Event Rate, %)	18 (11.1%)	10 (12.5%)	10 (35.7%)	38 (14.1%)
Event Causes (%)	Bleeding (33.3%), Arrhythmias (33.3%), Heart Failure (22.2%)	Bleeding (40%), Arrhythmias (30%), Heart Failure (20%)	Bleeding (40%), Arrhythmias (30%), Heart Failure (20%)	
Events Prevented (n)	5 (3 bleeding, 2 arrhythmias)	2 (1 arrhythmia, 1 heart failure)	1 (bleeding)	8
Projected Event Rate (%)	–	–	–	46 (17%)
Observed Event Rate (%)	–	–	–	38 (14.1%)
p-value (Observed vs. Projected)	–	–		0.04
p-value (Concurrent vs. Monotherapy Event Incidence)			0.01	

Table 7. Pharmacist Interventions and Impact

Characteristic	Value, n (%)
Total Interventions	277
Mean Interventions per Patient	1.03
Interventions by Subgroup	
Warfarin (n=190)	148 (77.9%)
Digoxin (n=108)	82 (75.9%)
Concurrent Therapy (n=28)	26 (92.9%)
Types of Interventions	
Dose Adjustments	103 (37.3%)
Dose Holds	54 (19.6%)
Monitoring Increases	60 (21.7%)
Alerts	30 (10.8%)
Adherence Aids	10 (3.6%)
Outcomes	
ADRs Prevented	18 (see Table 5)
Readmissions Prevented	8 (see Table 6)
Adherence Improvement (PDC Increase)	+8–12% (with aids)
Acceptance Rate	247/277 (89.1%)

interventions (dose holds, adjustments, monitoring increases, alerts, counselling), polypharmacy (≥5 medications), CKD (eGFR <45 mL/min/1.73 m²), and concurrent therapy (warfarin and digoxin use) (Table 8).

Therapeutic success was achieved in 226 patients (83.7%). Pharmacist interventions were strongly associated with success (OR=2.87, 95% CI: 1.66–5.34, p<0.001), indicating that patients receiving interventions were nearly three times more likely to achieve therapeutic goals without ADRs, highlighting the critical role of pharmacists in optimizing therapy.

ADRs occurred in 37 patients (13.7%). Polypharmacy increased the odds of ADRs (OR=1.89, 95% CI: 1.13–3.27, p=0.02), suggesting that patients on ≥5 medications were nearly twice as likely to experience an ADR. CKD was the strongest predictor of ADRs (OR=3.21, 95% CI: 1.48–6.92, p=0.003), with patients having eGFR <45 mL/min/1.73 m² being over three times more likely to experience an ADR, likely due to impaired drug clearance (e.g., digoxin toxicity). Concurrent therapy also increased ADR risk (OR=2.13, 95% CI: 1.02–4.41, p=0.04), reflecting the challenges of managing dual therapy with warfarin and digoxin.

Table 8. Predictors of Outcomes in Warfarin and Digoxin Therapy

Outcome	n/N (%)	Predictor	OR (95% CI)	p-value
Success	226/270 (83.7%)	Interventions	2.87 (1.66–5.34)	<0.001
ADRs	37/270 (13.7%)	Polypharmacy	1.89 (1.13–3.27)	0.02
		CKD	3.21 (1.48–6.92)	0.003
		Concurrent Therapy	2.13 (1.02–4.41)	0.04
Adherence (PDC ≥80%)	201/270 (74.4%)	Polypharmacy	0.58 (0.41–0.93)	0.02
		Interventions	1.73 (0.89–3.21)	0.07

Adherence (PDC ≥80%) was achieved in 201 patients (74.4%). Polypharmacy was associated with reduced adherence (OR=0.58, 95% CI: 0.41–0.93, p=0.02), indicating that patients on ≥5 medications were 42% less likely to maintain adherence, likely due to regimen complexity. Pharmacist interventions showed a trend toward improved adherence (OR=1.73, 95% CI: 0.89–3.21, p=0.07), suggesting a potential benefit that warrants further investigation.

These findings underscore the protective effect of pharmacist interventions on therapeutic success, while highlighting polypharmacy, CKD, and concurrent therapy as significant risk factors for ADRs, and polypharmacy as a barrier to adherence.

DISCUSSION

This study demonstrates the substantial impact of pharmacist-driven medication optimization on therapeutic outcomes for patients on warfarin and digoxin, particularly in a resource-limited tertiary care setting in Jordan. Therapeutic success, defined as achieving INR 2.0–3.0 for warfarin or digoxin levels 0.5–2.0 ng/mL without toxicity, was achieved in 82.6% of patients (OR=2.87, 95% CI 1.92–4.29, p<0.001), comparable to Alghadeeer et al.'s (2020) finding that 82% of patients in pharmacist-led anticoagulation clinics in Saudi Arabia reached their target INR[10]. Patients on concurrent therapy (n=28) achieved a lower success rate (67.9%, p=0.02 vs. 85.2% monotherapy), reflecting the complexity of managing dual therapy, as noted by Juurlink et al. (2019) [5]. Stabilization time was significantly faster with pharmacist oversight (median 5 days, IQR 3–7 vs. 8 days, IQR 5–11 without pharmacists, p<0.001), with hazard ratios (HR) of 1.61 (warfarin) and 1.92 (digoxin) for achieving target levels, aligning with Witt et al.'s (2005) findings on pharmacist-led monitoring[7].

ADRs were reduced from 20.4% (historical estimate) to 13.7% (37 events in 270 patients), with pharmacists resolving 18 events. This 6.7% absolute reduction aligns closely with Alshaiban et al.'s (2023) reported 6.3% absolute reduction in nose bleeding among warfarin patients in a pharmacist-led anticoagulation clinic, highlighting the effectiveness of pharmacist interventions in reducing anticoagulation-related adverse events[11]. Concurrent therapy patients experienced a higher ADR rate (21.4%, 6 events, p=0.04 vs. 12.8% monotherapy), primarily bleeding (4 events), consistent with Eikelboom et al.'s (2011) 18.5% bleeding risk in atrial fibrillation patients on warfarin[12]. Digoxin toxicity (e.g., 3 arrhythmias) was mitigated through TDM, supporting the emphasis on therapeutic drug monitoring in CKD patients to prevent digoxin toxicity (20.7% of our cohort)[13].

Adherence, measured as proportion of days covered (PDC) ≥80%, reached 74.4%, with an odds ratio of 1.73 (95% CI 0.95–3.15, p=0.07) for achieving therapeutic success, trending toward significance. This finding is consistent with Marcum et al.'s (2021) meta-analysis, which reported a moderate beneficial effect (Cohen's d = 0.41) of pharmacist-led interventions on medication adherence in older adults, corresponding to an estimated 5–10% improvement in adherence rates when using objective measures like pharmacy refill data[14]. Concurrent therapy patients had lower adherence (64.3%, p=0.03 vs. 76.0% monotherapy), reflecting Choudhry et al.'s (2011) findings on therapeutic complexity as a barrier[15]. Pharmacists' 277 interventions likely contributed to this outcome, as supported by a study conducted by Abu Hajleh et al. (2022) on pharmacists' role in guiding medication use in Jordan[16].

Hospital readmissions were 38 events across 14 patients (14.1% event incidence, 5.2% patient rate), a 2.9% absolute reduction from a projected 17.0% by preventing 8 events,

aligning with the meta-analysis of Marcum et al. (2021) showing an 18% relative reduction in readmissions (RR = 0.82) with pharmacist-led interventions[14]. The concurrent subgroup had a 35.7% event incidence (10 events in 2 patients, p=0.01 vs. 11.6% monotherapy), reflecting the 25% rate reported by Ho et al. (2009) in complex cardiovascular patients, driven by high-risk profiles (e.g., polypharmacy: 8.5 ± 2.2 medications)[17]. Pharmacists prevented 5 warfarin-only events (e.g., 3 bleeding via dose holds), 2 digoxin-only (e.g., 1 arrhythmia via reduction), and 1 concurrent event (bleeding via monitoring), supporting evidence from Rodrigues et al. (2017) of a 19% reduction in readmissions through pharmacy-supported transitions-of-care interventions like medication reconciliation[18]. Similarly, a Jordanian study reported that pharmacist interventions reduced drug-related hospital stays in older adults by 10%, further emphasizing their role in decreasing healthcare utilization in this population[19]. These findings align with perspectives from private health insurance firms in Jordan, where 44% believed medication review services could reduce hospitalizations, with 50% expressing willingness to pay for such services due to potential cost savings [20].

The strengths of this study include its 12-month longitudinal design, detailed intervention logs (277 actions, 6.5 contacts/patient). It provides novel insights into concurrent therapy management in a tertiary setting. Limitations include its single-center scope, potentially limiting generalizability to resource-constrained settings, and retrospective design, which may underreport ADRs or introduce selection bias[21]. The lack of a control group necessitated projected estimates (17.0% readmission rate based on historical data).

CONCLUSION

These findings strongly support integrating clinical pharmacists into cardiovascular care teams, particularly for high-risk therapies like warfarin and digoxin, where their intensive efforts yield significant clinical benefits. Future multi-center studies should validate these results across diverse settings, explore digital adherence tools (to enhance the observed adherence trend and assess cost-effectiveness. In conclusion, clinical pharmacists substantially improve therapeutic outcomes, reduce ADRs, and lower healthcare utilization, warranting expanded roles and targeted strategies to address adherence barriers in complex therapy management.

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