Reducing Cardiovascular Medication Complexity in a German University Hospital: Effects of a Structured Pharmaceutical Management Intervention on Adherence

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ABSTRACT

BACKGROUND: Patient adherence is necessary for successful medication therapy. However, highly complex medication regimens may lead to poor adherence, which decreases the effectiveness of treatment and often results in treatment failure, excessive morbidity and mortality, and higher costs.

OBJECTIVE: To examine whether patient adherence can be increased indirectly through reducing medication complexity by (a) pharmaceutical counseling of hospital medical staff and (b) additional information in the discharge letter for the primary care provider (PCP) about the simplified discharge medication.

METHODS: At the Medical Center Hamburg-Eppendorf, a tertiary care university hospital in Germany, 240 chronically ill inpatients with hypertension, diabetes, and/or dyslipidemia were enrolled in this prospective, semirandomized study. For the intervention group, hospital doctors were counseled by a clinical pharmacist on feasible simplifications of cardiovascular and antidiabetic medications. In 1 randomized subgroup, the PCP received additional explanatory information in the discharge letter. Adherence (self-reporting using the Medication Adherence Rating Scale [MARS-D]) and medication complexity (using the Medication Regimen Complexity Index [MRCI-D]) were recorded at admission to the hospital, discharge from the hospital, and 6 weeks after discharge. Patient quality of life (QoL) and satisfaction with information about medications were assessed at admission and after discharge.

RESULTS: At discharge, the medication regimen in the intervention group was significantly less complex than in the comparison group. Yet, 6 weeks after discharge, the complexity of the outpatient medication had increased to values similar to the comparison group, unless the PCP received additional information in the discharge letter. Propensity adjusted complete adherence rates at discharge were slightly, but not significantly, higher in the intervention group than in the comparison group. Yet, 6 weeks after discharge, the complexity of the outpatient medication had increased to values similar to the comparison group. Within the intervention group, complete adherence was more frequent in the subgroup with additional information for the PCP. Patient QoL and satisfaction with information were comparable in both groups.

CONCLUSION: The complexity of cardiovascular and antidiabetic hospital medications can be reduced by counseling the hospital doctors. However, for a sustainable simplification of outpatient medication, the PCPs must receive explicit information about the modifications. Patient adherence was not significantly influenced by this intervention. To verify these results, further research with objective measures of adherence and in patients with other diseases is needed.

What is already known about this subject

• New therapeutic options and an aging population with increasing comorbidities result in highly complex therapeutic medication regimens.
• Previous analyses suggest that complex therapy regimens attribute to poor adherence to long-term medications in chronic diseases. This may lead to suboptimal health outcomes and progressive health care costs.

What this study adds

• The complexity of cardiovascular medications can be significantly reduced in the hospital by switching to long-acting substances, combination drugs, and units that do not need to be split.
• It is essential to inform the primary care provider about the simplifications made when the patients were in hospital care in order to maintain the lower complexity at the transition from hospital to outpatient care.
• Reduced medication complexity alone might not be sufficient to increase patient adherence.

Pharmaco­therapy is one of the most important health care interventions in the treatment of chronic diseases. However, its effectiveness is strongly dependent on patient adherence. Adherence is defined as the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care professional. According to the 2003 World Health Organization report and other investigations, approximately half of patients take their medications as advised by the prescriber, depending on the respective drug class. Several studies have demonstrated that poor adherence is predictive of poor clinical outcomes, future hospitalizations, and high costs. In the United States, direct and indirect costs of drug-related morbidity, including poor adherence, have been estimated to exceed $290 billion annually; approximately 1.7% of health care expenditures in the United States were spent on hospital admissions following nonadherence. Consistent adherence to cardiovascular and/or antidiabetic medication therapy, on the other hand, is associated with better health-related outcomes.
Several methods to assess adherence are available. The indirect method of patient self-reporting is frequently used and is more inexpensive and patient friendly than many other strategies, such as the Medication Event Monitoring Systems, pill counts, or such direct methods as determination of drug concentrations in body fluids. Because patients often overstate their adherence, results gained by self-reporting tend to overestimate adherence. Yet, this bias can be somewhat reduced by stressing the anonymity of the data and by using questionnaires rather than direct interviews.

Adherence is influenced by several issues: social and economic factors, the health care team/system, characteristics of the disease, available therapies, and such patient-related factors as cognitive impairment or attitudes toward treatment. Complexity of medication therapies belongs to therapy-related factors; its inverse association with adherence has been shown by a number of studies. Medication complexity can be defined in several ways. The simplest is to only consider the number of drugs or the dosage frequency. In order to gain a more holistic view on medication complexity, developed and validated an instrument that also includes the dosage form and additional instructions concerning the medication intake: the Medication Regimen Complexity Index (MRCI). It has been translated into different languages and found to be psychometrically sound.

Medication therapy complexity and patient adherence may vary when patients transition from ambulatory to hospital care and back, and data on complexity are incoherent. described a significant increase in the number of medications during hospitalization of drugs at the time of hospital admission and drugs at discharge, while we have shown previously that the number of drugs and the medication complexity remained approximately the same. Adherence was significantly increased during the hospital stay (presumably because of a more controlled medication supply and administration) but returned to baseline values after discharge. Concerning changes in therapy, found that about 50% of the medications used for chronic treatment were changed during hospitalization. Similar results were obtained by (2012), and a marked influence of hospitalization on changes in drug therapy in ambulatory care was shown. investigated the association between changes of medication regimens and adherence following hospital discharge. Nonadherence to at least 1 drug was associated with more extensive medication regimen changes and was more common in patients discharged with prescriptions for 7 or more drugs per day. They concluded that the number of long-term drugs should be reduced in order improve adherence to a medication regimen.

Modification of the discharge medication is frequently necessary because a drug is intended for short-term treatment; the dose titration is completed after discharge; or the brand is switched for financial reasons. However, careful optimization of medication complexity might be short lived when primary care providers (PCPs) are not informed about the background of the treatment modifications. A lack of communication between hospital and community health care providers has frequently been described, and the need for explicit and detailed discharge letters discussed. Nevertheless, information about the real effect of additional information for the PCP with regard to continuity of intentionally modified hospital medication regimens is scarce. To the best of our knowledge, this is the first study that investigated a putative correlation between the reduction of medication complexity and adherence in chronically ill patients across the interfaces of in- and outpatient care.

The purpose of this study was to investigate effects of structured medical management interventions during hospitalization on patient adherence and other outcomes in inpatient and subsequent outpatient care. We examined whether patient adherence can be increased indirectly through reducing medication complexity by (a) pharmaceutical counseling of hospital medical staff and (b) additional information in the discharge letter for the PCP about the simplified discharge medication. Furthermore, we aimed to examine whether these interventions influence health-related quality of life (QoL) and satisfaction of patients.

### Methods

#### Patients and Study Design

This prospective, semirandomized study was conducted at the internal and urologic wards of the Medical Center Hamburg-Eppendorf, a tertiary care university hospital in Germany. All patients who met legal requirements (aged more than 18 years, written informed consent given) and received medications to treat chronic cardiovascular and/or metabolic diseases were enrolled consecutively between March 2010 and October 2011. Patients with reduced cognitive performance or inability to communicate in the German language were excluded. The intervention comprised pharmaceutical counseling for hospital doctors about feasible simplification of cardiovascular and antidiabetic medications (termed “study medication” below). The definition of pharmaceutical counseling in this setting was informing the doctors about the availability of combination drugs, long-acting formulations, and tablet strengths without the need to split tablets, as available on the German market, and patient-individual recommendations of how to simplify the respective medication regimens. If necessary, the doctors were briefed about the half-lives/pharmacokinetics of those drugs. The comparison group was treated as usual. The study design is displayed in Figure 1. Because randomization would have required a parallel design, knowledge bias of the counseled medical staff in the hospital and a resulting “carry-over-effect” would have been inevitable, which means that hospital doctors,
once counseled to decrease complexity, would also apply it to patients in the comparison group. Likewise, block randomization of different wards would have introduced a severe selection bias with the limited number of wards participating in the study. Thus, randomization was waived, and the first cohort of 108 patients was assigned to the comparison group (C), and a subsequent independent cohort of patients was assigned to the intervention group (I). The latter was randomized into 2 subgroups: (I-) received the intervention and was discharged from the hospital with the normal discharge letter for the PCP; (I+) received the intervention and a discharge letter with additional information explaining the background of the simplification and a request to continue the medication unchanged if possible. The randomization of the intervention group was computer assisted, and allocation was concealed from the recruiting pharmacist by using sealed opaque numbered envelopes. The randomization list and the envelopes had been prepared by the trial statistician before recruitment started. After receiving written consent, the envelopes were opened according to their numbering. Neither the patients nor the hospital doctors were aware of the allocation. Patients were enrolled and assigned to their respective groups by the pharmacist conducting the study.

The primary outcome was self-reported patient adherence to the prescribed medications. Secondary outcomes were medication complexity, QoL, and patient satisfaction with the information about medication. Medication complexity was chosen because of its association with medication adherence. QoL and satisfaction were considered to be influenced by increased treatment effectiveness due to adherence.\textsuperscript{36,37}

The study was reviewed and approved by the local ethical review committee.

**Data Collection and Measures**

Data were collected at times of admission (T0), discharge (T1), and 6 weeks after discharge (T2). Data sources in this study were hospital files (T0: clinical and demographic aspects, medication complexity), questionnaires filled out by the patient during hospital stay (T0: sociodemographic data, pre-admission adherence, QoL, satisfaction with information about medicines; T1: in-hospital adherence), the discharge letter (T1: medication complexity), and questionnaires sent to patients and their PCPs after discharge (T2: medication complexity, postdischarge adherence, QoL, satisfaction with information about medicines). The PCPs were further asked about their reasons for acceptance or modifications of the discharge medications.\textsuperscript{29}

Adherence to prescribed drug treatment was measured with pseudonymous questionnaires for patient self-reporting (Medication Adherence Rating Scale [MARS-DI]).\textsuperscript{16,38} Because of the expected strong deviation from a normal distribution as a consequence of strong ceiling effects, sum scores were dichotomized with a cut-off point at 25 as chosen in a previous
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Data Analysis

The evaluation of the effects of pharmaceutical counseling of hospital medical staff (first research question) was based on an observational (compared but not randomized) design. For the comparison at discharge (T1), both intervention subgroups were used (I- and I+), as the additional intervention (detailed discharge letter for the PCP, I+) took effect only after discharge. 

For comparisons of outcomes 6 weeks after discharge (T2), the comparison group was compared only with the standard discharge letter subgroup (I-), in order to avoid confounding with the effects of the discharge letter intervention. This was evaluated separately.

In order to adjust for possible imbalance between the comparison and intervention groups, score stratification was applied. The propensity score matching reduces the confounding effects of covariates and allows differences of responses to be attributed to differences of treatments. Based on propensity scores predicted from demographic and clinical characteristics, as well as from baseline level of outcomes, 5 propensity strata were built. Comparisons between groups were made within these strata, and results were pooled in a fixed-effect model. This was done for the dichotomous outcome (completely vs. incompletely adherent) by logistic regression and for interval-scaled outcomes (scales) by analysis of covariance with inclusion of the stratum as covariate. In each model, the baseline level of the investigated outcome was included, respectively, in order to reduce error variance and increase power.

The evaluation of the effects of additional information on medication in the discharge letter for the PCP (second research question), was performed through the comparison of the 2 randomly allocated groups (I+, I-) 6 weeks after discharge (T2). Analyses were performed as just described, but without propensity score stratification.

Every patient with at least 1 evaluable outcome was included in the analyses. If 1 or more questions of the questionnaire were missing, the questionnaire was still included, and missing values were not substituted. Exceptions were validated tools integrated into the questionnaires, such as the MARS-D, SF-12. Calculations were done according to the respective test instructions. Missing values of the MARS-D and SF-12 were replaced by the average value of the answered questions.

The required sample size was planned to enable the detection of moderate effects (Cohen’s d of 0.40 for metric outcomes). This corresponds to an odds ratio of approximately 2.0 for dichotomous outcomes in two-tailed analyses with a power of 0.80 and a type I error probability of 0.05 in two-group comparisons. This resulted in a required sample size of 100 patients in the comparison cohort (C) and in the two intervention groups (I+ and I-), respectively, yielding a total sample of 300 patients.

All analyses were performed using SPSS 18.0 (IBM Corp., Armonk, NY).

Results

Figure 2 shows the inclusion process. A total of 240 patients were enrolled in the study, with 108 patients in the comparison group (C) and 132 patients in the intervention group (I). Three patients from the intervention group withdrew their consent. The intervention group was further randomized into 2 groups (I-, I+) with initially 64 and 65 patients, respectively. Detailed baseline characteristics of the study population are summarized in Table 1. Mean age was 63.8 years (standard deviation [SD] 13.8 years; range 19-92 years), and 28.1% of the patients were female. The low percentage of female patients partly

study. Patients reaching the maximum sum score (25) were considered completely adherent, and lower scores (<25) were classified as indicators of incomplete adherence.

Complexity was calculated using the German version of the Medication Regimen Complexity Index (MRCI-D) for each patient. The index consists of 3 sections (A, B, C) and incorporates the total number of medications to be taken, the dosage forms, and dosage frequency, as well as additional directives concerning the administration. Each section yields a score for the respective component of complexity. These scores are finally summed up to express the MRCI as a single number. In line with other studies, including the original validation of the MRCI, no cut-off values were defined in our study. Only drugs selected for cardiovascular relevance and oral antidiabetics were included in the analysis of complexity. In cases of discrepancies between the medication lists returned from patients and their PCPs at T2, the information from the PCPs were used for the analysis of complexity.

Patients’ health-related QoL was measured using the 12-item short form health survey (SF-12), an instrument that consists of 2 summary scales (assessing physical function and mental well-being) and developed as a short form of the SF-36. The physical and mental health scores (QoL psychic, QoL somatic) are computed using the scores of the 12 questions and range from 0 to 100. A score of zero indicates the lowest, and 100 indicates the highest level of QoL.

Satisfaction with the amount of information received about prescribed medicines was evaluated with the “Satisfaction with Information about Medicines Scale” in its German version (SIMS-D). This 17-item tool consists of several questions assessing whether patients understand action and usage of their medications (subscore a; items 1-9) and whether they know the potential risks (subscore b; items 10-17). The total score of the scale ranges from 0 to 17, with a high score indicating a high degree of overall satisfaction with the amount of medication information received. The scale has been shown to be valid and reliable and also to correlate with self-reported adherence.

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common illness (88.2%), followed by diabetes mellitus (33.2%) and renal insufficiency (21.8%). At admission, the patients were taking a mean of 7 (SD 4.3) medications (not shown), with 4 (SD 2.2) study medications. Mean length of hospital stay was 7.3 days (SD 5.3).

Adherence

Rates of adherences assessed with the MARS questionnaire are depicted in Tables 1 and 2. Percentage of the patients indicating complete adherence to their prehospital medications was 38.2. Propensity adjusted complete adherence rates at discharge (T1) were slightly higher in the intervention group (74.6%) than in the comparison group (62.4%; however, this difference did not reach statistical significance (odds ratio [OR] = 1.77, 95% confidence interval [CI] 0.81 to 3.85; P = 0.151). The difference in complete adherence rates was statistically not significant between the groups 6 weeks after discharge, either (OR = 0.82, 95% CI 0.27 to 2.52; P = 0.729).

With regard to the second research question, members of the intervention group treated by PCPs who received a detailed discharge letter from the hospital (I+), showed higher complete adherence rates 6 weeks after discharge (56.2%) than the control (I-) group (34.4%). Although this effect was comparatively large (OR = 2.45, 95% CI 0.69 to 8.67), it did not reach statistical significance (P = 0.164).

Complexity

Figure 3 shows the number of medications and the medication regimen complexity for T0, T1, and T2. In Table 2, the values of the complexity are depicted for T1 and T2 for each group. Fifty-one medication lists were returned from the patients and their PCPs at T2, with 25 doublets differing from each other. At discharge, the MRCI score was statistically significantly lower in the intervention than in the comparison group: 3.47 (95% CI 4.84 to 6.09) versus 7.55 (95% CI 6.82 to 8.28), respectively (P = 0.006). At the same time, the number of study medications was reduced from 4.10 (95% CI 3.75 to 4.45) in the comparison group to 3.60 (95% CI 3.30 to 3.90) in the intervention group (P = 0.036). The difference between groups in complexity 6 weeks after discharge was not statistically significant (P = 0.368). Evaluating the effect of additional information for the PCP in the discharge letter for patients in I+, the complexity at T2 was significantly lower for I+ (6.19, 95% CI 5.34 to 7.04) than for I- (7.81, 95% CI 6.96 to 8.66; P = 0.009; Figure 4). The score of subscale B, which is the dosing frequency, was reduced from 5.53 (95% CI 4.92 to 6.14) to 4.30 (95% CI 3.69 to 4.91; P = 0.006), as was the total number of medications in I+ (3.38 vs. 4.36 in I-; P = 0.024).

The PCP responses to the questionnaire about the discharge medications and their reasons for acceptance or modifications are depicted in Figure 5. Approximately 50% of the PCPs contacted via mail returned the questionnaire. In the control
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### TABLE 1 Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Comparison (C)</th>
<th>Intervention (I)</th>
<th>N Analyzed</th>
<th>P Value</th>
<th>Intervention Without Detailed Letter (I-)</th>
<th>Intervention with Detailed Letter (I+)</th>
<th>N Analyzed</th>
<th>P Value</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>108</td>
<td>129</td>
<td>235</td>
<td>&lt; 0.001</td>
<td>28 (43.8%)</td>
<td>20 (31.3%)</td>
<td>128</td>
<td>0.201</td>
<td>66</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>18 (16.8%)</td>
<td>48 (37.5%)</td>
<td>235</td>
<td>&lt; 0.001</td>
<td>28 (43.8%)</td>
<td>20 (31.3%)</td>
<td>128</td>
<td>0.201</td>
<td>66</td>
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<tr>
<td>Age, years (SD)</td>
<td>63.2 (12.0)</td>
<td>64.4 (15.0)</td>
<td>221</td>
<td>0.519</td>
<td>64.8 (13.7)</td>
<td>63.9 (13.7)</td>
<td>129</td>
<td>0.720</td>
<td>63.8</td>
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<td>Family status</td>
<td>182</td>
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<td>99</td>
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<tr>
<td>Single</td>
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<td>16 (16.2%)</td>
<td>8 (17.0%)</td>
<td>8 (15.4%)</td>
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<td>Married</td>
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<td>54 (54.5%)</td>
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<td>Divorced</td>
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<td>5 (5.1%)</td>
<td>3 (6.4%)</td>
<td>2 (3.8%)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Widowed</td>
<td>3 (3.6%)</td>
<td>24 (24.2%)</td>
<td>12 (25.5%)</td>
<td>12 (23.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27</td>
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<tr>
<td>Highest education</td>
<td>187</td>
<td>0.013</td>
<td>100</td>
<td>0.165</td>
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<tr>
<td>None or semiskilled</td>
<td>7 (8.0%)</td>
<td>18 (18.0%)</td>
<td>11 (21.6%)</td>
<td>7 (14.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Professional school</td>
<td>11 (12.6%)</td>
<td>11 (11.0%)</td>
<td>4 (7.8%)</td>
<td>7 (14.3%)</td>
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<td>Apprenticeship</td>
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<td>59 (59.0%)</td>
<td>27 (52.9%)</td>
<td>32 (65.3%)</td>
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<td>College</td>
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<td>12 (12.0%)</td>
<td>9 (17.6%)</td>
<td>3 (6.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Number of diagnoses</td>
<td>7.2 (5.2)</td>
<td>8.7 (5.1)</td>
<td>228</td>
<td>0.027</td>
<td>9.5 (5.0)</td>
<td>7.9 (5.2)</td>
<td>128</td>
<td>0.079</td>
<td>8.0</td>
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<tr>
<td>Hypertension</td>
<td>81 (81%)</td>
<td>121 (93.8%)</td>
<td>59 (92.2%)</td>
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<td>48 (37.2%)</td>
<td>27 (42.2%)</td>
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<td>2 (3.1%)</td>
<td>0 (0%)</td>
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<td></td>
<td>129</td>
<td>0.224</td>
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<tr>
<td>Obesitya</td>
<td>14 (14%)</td>
<td>14 (10.9%)</td>
<td>5 (7.8%)</td>
<td>9 (13.8%)</td>
<td></td>
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<td>30 (23.3%)</td>
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<td>129</td>
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<td>Malignant tumor</td>
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<td>15 (11.6%)</td>
<td>6 (9.4%)</td>
<td>9 (13.8%)</td>
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<td>Ward</td>
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<td>Urology</td>
<td>50 (52.1%)</td>
<td>39 (30.2%)</td>
<td>21 (32.8%)</td>
<td>18 (27.7%)</td>
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<tr>
<td>Nephrology</td>
<td>33 (34.4%)</td>
<td>55 (42.6%)</td>
<td>25 (39.1%)</td>
<td>30 (46.2%)</td>
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<tr>
<td>Endocrinology</td>
<td>13 (13.5%)</td>
<td>35 (27.1%)</td>
<td>18 (28.1%)</td>
<td>17 (26.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48</td>
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<tr>
<td>Length of stay, days, mean (SD)</td>
<td>6.0 (4.4)</td>
<td>8.3 (5.7)</td>
<td>222</td>
<td>0.001</td>
<td>8.8 (5.5)</td>
<td>7.8 (5.9)</td>
<td>127</td>
<td>0.327</td>
<td>73</td>
</tr>
<tr>
<td>Completely adherent (MARS)</td>
<td>35 (39.8%)</td>
<td>38 (36.9%)</td>
<td>191</td>
<td>0.398</td>
<td>22 (42.3%)</td>
<td>16 (31.4%)</td>
<td>103</td>
<td>0.309</td>
<td>73</td>
</tr>
<tr>
<td>Medication complexity,b mean (SD)</td>
<td>3.6 (2.0)</td>
<td>4.3 (2.2)</td>
<td>218</td>
<td>0.662</td>
<td>4.4 (2.0)</td>
<td>4.2 (2.4)</td>
<td>119</td>
<td>0.670</td>
<td>4.0</td>
</tr>
<tr>
<td>Satisfaction, mean (SD)</td>
<td>10.1 (5.0)</td>
<td>10.2 (4.6)</td>
<td>179</td>
<td>0.881</td>
<td>10.1 (4.8)</td>
<td>10.3 (4.5)</td>
<td>93</td>
<td>0.866</td>
<td>10.1</td>
</tr>
<tr>
<td>QoL somatic</td>
<td>6.5 (2.5)</td>
<td>6.7 (2.5)</td>
<td>179</td>
<td>0.551</td>
<td>6.7 (2.6)</td>
<td>6.7 (2.3)</td>
<td>92</td>
<td>0.877</td>
<td>6.6</td>
</tr>
<tr>
<td>QoL psychic</td>
<td>47.4 (11.0)</td>
<td>45.1 (10.3)</td>
<td>176</td>
<td>0.153</td>
<td>44.9 (10.8)</td>
<td>45.4 (9.7)</td>
<td>92</td>
<td>0.827</td>
<td>46.2</td>
</tr>
</tbody>
</table>

*aBMI > 30.

*bOnly study medications included.

BMI = body mass index; MARS = Medication Adherence Report Scale; MRCI = Medication Regimen Complexity Index, MRCI A = Subscale “Dosage form”; MRCI B = Subscale “Dosing frequency”; MRCI C = Subscale "Additional directions"; QoL = quality of life; SIMS = Satisfaction with Information about Medicines Scale; SIMS Sub a = Subscale “Action and usage of medication”; SIMS Sub b = Subscale “Potential problems of medications.”

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5% of the PCPs who commented on the hospital modifications assessed these much better, 27% as better, 19% as inferior, and 49% as equal compared with treatment before the hospital stay. In the intervention group, 10% regarded the medication as much better, 25% as better, 15% as inferior, and 50% as equal to the prior treatment (data not shown).

**Quality of Life/Satisfaction**

Tables 1 and 2 show the QoL measures throughout the study. At T2, the differences between the comparison and intervention groups or I- and I+, respectively, were not statistically significant (P > 0.05).
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The satisfaction with information about medicines at T2 is shown in Table 2. In the intervention group, satisfaction was slightly higher, although it did not reach significance (P=0.126). Subscore a (SIMS Sub a = information about action and usage of medication) showed a statistical tendency to be higher in the intervention group (P=0.097). No statistically significant differences were found between groups I- and I+.

**Discussion**

Our results suggest that the complexity of medication regimens can be reduced temporarily by pharmaceutical counseling of a hospital’s medical staff. This intervention was able to decrease the overall number of cardiovascular/antidiabetic medications, as well as the dosing frequency. While it has been shown before that medication therapies often get more complicated in the hospital, this study showed to what extent therapies can be simplified in this setting. Recently, investigations carried out in Australia analyzed the theoretical potential for simplifications of medication regimens in a hospital setting, as well as the feasibility and barriers of such an intervention. In reviewing 40 discharge medication regimens, 90 simplifications to long-term medications were proposed by clinical pharmacists retrospectively. Eighty-four (93%) of them were rated by a clinical pharmacist as feasible with the same or similar therapeutic outcomes as the complex regimens. These changes, if implemented, could have reduced medication regimen complexity at discharge by an average of 14%. In the second intervention, pharmacists reviewed medication regimen complexity for 173 inpatients and identified 149 potential changes to reduce regimen complexity for 79 of 173 (45.7%) reviewed patients. Ninety-four (63.1%) changes were successfully implemented. The most common reason for not implementing potential changes was lack of time and nonacceptance by the doctor or patient. Still, so far, no study has combined the quantitative assessment of the reduction of medication complexity in the hospital (by using the validated MRCI) with its follow-up in the ambulatory sector and the putative correlation to patient adherence.

In line with our results, Elliott (2012) also identified
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Nevertheless, the reduction of medication complexity was not accompanied by a significantly increased adherence in our study, neither at discharge nor 6 weeks later. This is in contrast to earlier findings that showed a correlation between medication complexity and adherence. In part, that may be due to the heterogeneous definitions of complexity and/or methods to assess adherence. We used the MRCI, which integrates dosage form and specific instructions concerning the medication intake in addition to the number of medications, and the MARS to quantify adherence. Claxton et al. (2001), however, reviewed studies in which complexity was defined as dosing frequency, and adherence was estimated by electronic monitoring systems. Another reason for such discrepancies may be that some studies compared adherence with a single versus a 2-pill regimen. However, in our setting, the patients took a mean of 7.2 drugs at admission, with 4.0 drugs only for the treatment of their hypertension, diabetes, and/or dyslipidemia. The amount of additional medications prescribed might have had a leveling effect on adherence.

Therapeutic adherence is multidimensional, with patient-, physician-, and therapy-related contributing factors. However, the importance and/or effect size of each component for adherence is unknown and variable. In our study, we focused on 1 therapy-related factor (complexity of therapeutic regimens) and 2 physician-related factors (counseling the hospital medical staff and supplying the PCP with additional medication information from the hospital). It seems that addressing only these factors is not sufficient to increase adherence in the long run.

Corresponding with answers on the MARS-D, incomplete adherence was mainly due to forgetfulness concerning the medication intake. Adherence increased during the hospital stay, where the supply of medications was more controlled, the intake was supervised, and the day was scheduled with predetermined mealtimes. Still, adherence did not reach 100% in the hospital. This is in line with a recent investigation, where nonadherence of 23.3% at any time during hospitalization was reported. Being in the hospital does not necessarily mean that

FIGURE 3 Effect of Pharmaceutical Counseling

A. Number of Drugs (Only Study Medications Included)

B. Medication Complexity (Only Study Medications Included)

C = Comparison group; I = Intervention group; MRCI = Medication Regimen Complexity Index; MRCI A = Subscale “Dosage form”; MRCI B = Subscale “Dosing frequency”; MRCI C = Subscale “Additional directions”; T0 = admission; T1 = discharge; T2 = 6 weeks after discharge.

FIGURE 4 Effect of Information Letter

A. Number of Drugs

B. Medication Complexity

I = Intervention group; I+ = Intervention group with detailed discharge letter; MRCI = Medication Regimen Complexity Index; MRCI A = Subscale “Dosage form”; MRCI B = Subscale “Dosing frequency”; MRCI C = Subscale “Additional directions”; T2 = 6 weeks after discharge.
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Reducing complexity means a modification in the medication regimen. A postulated increase in adherence because of a simpler regimen may be outweighed by a decrease in adherence because of the differently named and looking drugs of the new regimen. In line with this, some studies described that changes in drug regimens were significantly associated with nonadherence.31,32

Discharge from the hospital holds a rare chance to simplify complex medication regimens. However, according to our experience gained from this study (although not explicitly predefined as endpoints), several factors limit its potential benefit:

1. Financial reimbursement of hospital care in the diagnosis-related groups system in Germany minimizes the length of stay. Hence, final dose titration and, thus, determination of the availability of suitable combination or extended-release drugs is frequently left to the PCPs.

2. Simplification of medication therapy has so far been a low priority in the hospital compared with controlling clinical parameters due to nondefined clinical benefit.

3. Doctors on the ward rotate frequently, at least in large hospitals, requiring constant reminders from the clinical pharmacist (also in our study) to prescribe medications providing simplification.

4. Hospital pharmacies tend to provide drugs with single active ingredients rather than combination drugs in order to minimize storage costs. The willingness to pay for extra costs arising from a “medication simplification policy” needs to be established.

5. Hospital staff may hesitate to offend PCPs by modifying pre-existing prescriptions.

6. PCPs decide about long-term discontinuation of discharge medications, and their decisions are influenced by different economic conditions than the treatment decisions from hospital staff, at least in Germany and the United States. Higher costs of combination drugs that are not generic yet and a limited number of dosage combinations that complicate the titration of individual components might impede the acceptance of the medication simplifications started in the hospital.

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FIGURE 5  PCP Reasons for Modification/Acceptance of Discharge Medication

C = Comparison group; I = Intervention group; PCP = primary care provider.
Our results show that the reduction of medication complexity achieved for inpatient care was mostly reversed in subsequent ambulatory care, unless the PCP was further informed about the modifications in the discharge letter. This underlines the necessity to involve PCPs in treatment decisions if sustainability and continuity of care are desired, especially since previous analyses have shown PCPs’ partial dissatisfaction with hospital discharge information.\(^\text{33}\) Our study demonstrated that complexity of medication regimens remained significantly lower postdischarge when the PCP received additional information in the discharge letter about the background of medication changes. As mentioned previously, economic issues play a role in the decision by a PCP to continue hospital therapies and may therefore explain reversed simplifications postdischarge. Because some of the new combination drugs are more expensive than available generics, critics fear the use of combination strategies as a technique for “evergreening” an expiring patent to extend the life of a drug brand. Podolsky and Greene (2011) summarize this dilemma as the following: “No one knows how the improvement in adherence resulting from a single expensive pill stacks up against the known adherence benefits of a more affordable regimen of generic medications. This type of comparative effectiveness data would be far more useful in separating hope from hype when it comes to the new combination drugs.”\(^\text{34}\) However, it was not an objective of this study to investigate economic issues of the respective medication therapies or incomplete adherence with all its clinical consequences. So, further research is needed in this area because this is a highly complex issue with diverging views.\(^\text{29}\)

In earlier studies, correlation between medication complexity and health-related QoL has been a controversial subject. While Cardone et al. (2011) did not find a significant relationship between the medication regimen complexity and SF-36 in the setting of nocturnal home dialysis patients,\(^\text{29}\) a higher pill burden was associated with lower QoL for patients with traditional in-center hemo-dialysis.\(^\text{36}\) Our study aimed at increasing adherence by reducing the complexity of medication regimens and indirectly influencing QoL. As we were not able to ameliorate adherence 6 weeks postdischarge, it is not surprising that our intervention failed to improve QoL.

**Limitations**

Our study has various limitations. The comparison and intervention groups were not randomized. This was in order to avoid a “carry-over-effect” on the comparison group because of a knowledge bias of the counseled hospital doctors. The 2 groups differed in various aspects, and even though the analyses for the first research question were adjusted by propensity score stratification, there might still have been differences in unobserved variables. Moreover, we did not reach the aimed sample size of 300 patients that would have allowed an adequately powered analysis of the second research question (if additional information for the PCP had an effect on regimen complexity and adherence).

The method of measuring adherence was by self-report even though the validity of self-reports has been criticized in the past.\(^\text{57,58}\) Nevertheless, compared with the direct measurement of adherence, it is an inexpensive and pragmatic tool for use in clinical practice. To avoid a skewed response distribution and to increase sensitivity in recognizing nonadherent patients, this recommendation was followed for the present study, and a high cut-off of 25 was chosen. The high cut-off and the resulting increase in sensitivity also explain the high incomplete adherence rates (with a rate of 60.2%). When interpreting the results, it has to be kept in mind that even the occasional failure to take the medication as advised is classified by this definition. Hence, the term “incomplete adherence” was chosen rather than absolute “nonadherence.” Nonetheless, this surrogate parameter was used, knowing that it seems impossible to define the precise extent of adherence that is necessary to ensure a given therapeutic benefit.

Our results are limited to cardiovascular and antidiabetic medications and the simplifications described above. Simplifications focused exclusively on the “study medications” and did not include the entire medication regimen of the patient nor the evaluation if medications were really necessary. However, studies have shown that elderly people in particular often receive unnecessary drugs; Hajjar et al. (2005) found that 44% of patients had at least 1 unnecessary drug.\(^\text{59,60}\) Including unnecessary drugs in the intervention could have increased the magnitude of simplifications. Also, medications for noncardiovascular indications might have increased during the hospital stays in our study so that the overall medication complexity would not have been reduced.

The health care system in Germany is different from that in the United States. Still, there are many similarities, such as the costs of medications, the high percentage of nonadherent patients, the division into ambulatory and stationary sectors, and problems at the transition between the interfaces. Thus, the results of this study are also applicable to the United States, and they provide helpful insights in addressing patient adherence and improving outcomes.

**Conclusion**

Pharmacists may be able to reduce the complexity of cardiovascular hospital medications by counseling hospital medical staff about the availability of combination and extended-release medications and patient-individual recommendations of how to simplify subsequent medication regimens. However, the effect is largely leveled in subsequent ambulatory care, reducing the potential of this intervention to ameliorate medication adherence in the long run, unless the PCPs receive an explanation justifying the modifications. Patient adherence was not significantly changed by this intervention. Further
research (e.g., with other indications, including the total medication regimen instead of parts of it, other methods to assess adherence, and other combinations of adherence-directed interventions) is needed to define potential clinical benefits that may justify the increased efforts connected with this intervention. When implementing inpatient interventions, the transition to outpatient care strongly needs to be considered in order to continue sustainability of any possible improvement.

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Reducing Cardiovascular Medication Complexity in a German University Hospital: Effects of a Structured Pharmaceutical Management Intervention on Adherence

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