eHealth2015 – Health Informatics Meets eHealth
D. Hayn et al. (Eds.)

doi:10.3233/978-1-61499-524-1-81

Evaluation of a Clinical Decision Support Rule-set for Medication Adjustments in mHealth-based Heart Failure Management

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Abstract. Decision-support based medication adjustment in heart failure management. Prospective analysis of clinical decision support in fifteen patients that collected vital parameters and medication intake up to one year within a clinical trial. Correlation of event episodes and medication adjustments with respect to applied rule-sets and medication classes. 713 events were grouped to 195 event episodes. Physicians performed 86 medication adjustments. 30 of them were triggered by event episodes. 35% of all performed medication adjustments occurred between event episodes. 20% of all episodes triggered a medication adjustment. 15% of all episodes triggered the expected medication adjustment. Correlation between episodes and medication adjustment was low. Further analysis needs to be done, to evaluate reasons for low correlation and how the rule-set should be adapted to increase reliability.

Keywords. Decision Support System, Telemedicine, Heart Failure, mHealth, Medication systems

1. Introduction

Telemonitoring is considered an enabler for self-care management and helps physicians to quickly and remotely react on, e.g. cardiorespiratory deteriorations by changing types and doses of prescribed drugs and to continually optimize heart failure (HF) therapy. Although some of the result of previous studies about telemonitoring in heart failure were somewhat ambiguous [1], it was also demonstrated that early detection of deteriorations in vital signs can reduce up to 50% of re-hospitalizations for cardiac decompensation [2].

Although automated telemonitoring related expert systems are a relatively new area of research, the use of expert systems for clinical decision support in general has already been studied extensively [3]. Garg et al. [4] performed a systematic review of the effects of clinical decision support systems (CDSS) and found that CDSS improved practitioner performance in 64 out of 100 controlled trials. These CDSS included diagnostic, reminder, disease management, and drug-dosing or prescribing systems. Similar results were found in the systematic review by Kawamoto et al. [5] of randomized controlled trials, where practitioner performance improved in 68% of the 70 studies reviewed [3].

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The INTENSE-HF telemonitoring study was conducted between 2012 and 2014 in Austria with the aim to evaluate if telemonitoring with a rule-based CDSS helps physicians to treat the patients according to a target medication scheme as derived from the European Society of Cardiology (ESC) HF guideline which addresses four large medication groups of relevance for the management of systolic HF: angiotensin-converting-enzyme inhibitors (ACE-I), angiotensin-receptor-blockers (ARB), beta-blockers (BB) and diuretics. While ACE-I, ARB and BB are advised for managing blood pressure and heart rate, diuretics are used for controlling fluid retention to prevent cardiac decompensations. For ACE-I, ARB and BB the guideline stipulates that the target dose [6] should be reached or – if the target dose cannot be reached – the maximum tolerated dose should be taken. The dose of diuretics should be individually adapted when signs of congestion appear, because the optimal diuretics dose is also influenced by fluid and salt intake.

1.1. Previous and related work

Before starting INTENSE-HF, a retrospective feasibility analysis of the rules used in the CDSS with datasets from previous telemonitoring trials [7] was done. In this preceding analysis, we focused on the absolute number of events generated by the CDSS. Evaluation of existing literature revealed that previous work primarily analyzed user-acceptance of CDSS [8] or described the development process of CDSS [3, 9, 10]. To our best knowledge, up to now, there is no related study, which aimed to evaluate CDSS by using performed medication adjustments as reference annotations.

1.2. Aim

The present paper focusses on the analysis of the performance of the CDSS used in the INTENSE-HF study by evaluating the number and type of generated events in relation to the performed medication adjustments.

2. Methods

Our CDSS algorithm was implemented in Python 2.7 [11] and the generated events were archived to a relational database. Patient demographics, telemonitoring measurements and medication adjustments were also stored to the same database. For preprocessing and analysis we used the KNIME framework [12]. We setup workflows to extract medication changes, to group CDSS events and to perform a combined analysis of the medication changes and the CDSS events.

2.1. Decision support rule-set / algorithm

The rules for the CDSS were derived from the current European Society of Cardiology (ESC) guidelines for HF management and based on knowledge gained from a prior clinical trial [2]. After discussions with a multidisciplinary panel, physiologically reasonable constraints for the algorithm were chosen. A detailed description of the algorithm can be found in [7].

Table 1. Basic rule-set of the CDSS

Rule	Action	Type
Systolic blood pressure > 130 mmHg	Increase dose of ACE-I/ARB	A
Systolic blood pressure < 95 mmHg *	Decrease dose of ACE-I/ARB	A
Heart rate > 70 bpm	Increase dose of betablocker	A
Heart rate < 50 bpm *	Decrease dose of betablocker	A
Weight gain > 2kg in 2 days	Increase dose of diuretics	B
Weight loss > 2kg in 2 days	Decrease dose of diuretics	B

* A decrease of medication is only recommended if the patient additionally reported to feel bad at least once in the previous seven days.

Briefly, the CDSS comprised of six rules (Table 1), which can be divided into two categories (type A and type B). The four type A rules were responsible for long-term medication adjustment, while the two type B rules were responsible for short-term adjustment of diuretics.

Type A rules were defined for adjusting the dose of HF medication for ACE-I, ARB and BB according to guidelines. Type A rules fired when a certain threshold was exceeded for the fifth time in seven consecutive days. For decreasing the dose of medication the patient had to additionally report that he didn't feel well at least once in the previous seven days. The other two rules (type B) generated events depending on body weight gain or body weight loss to indicate early signs of cardiac decompensation.

Whenever monitoring data were transferred to the data center, the CDSS could trigger events only if the following two preconditions were fulfilled:

- a complete set of measurements (blood pressure, heart rate, weight, well-being) were transmitted at that day
- no other event for this rule was triggered that day (to reduce duplicate events).

2.2. Data set

For prospective evaluation of the CDSS we used the data collected during INTENSE-HF randomized clinical trial. Data collected by patients via the mHealth-based system [7] comprised measurements for systolic blood pressure, diastolic blood pressure, heart rate, weight, a subjective measurement of the patient's wellbeing condition (bad, normal, good) and daily medication intake. Date and dose of medication changes performed by the physicians were available in the telemonitoring system and were used for this analysis.

2.3. Preprocessing

We excluded patients who used the telemonitoring system for less than seven days from our analysis. After visual inspection of the event distribution, we implemented an additional algorithm for grouping events. Multiple type A events which belong to the same temporary episode of hypertension, hypotension, tachycardia or bradycardia were grouped into so called "event episodes". An event episode was defined as an arbitrary number of subsequent days where an event of the same type was generated as on the day before.

Table 2. Normalization of medication using target doses

Drug	Target dose [mg]
Enalapril	20
Lisinopril	20
Ramipril	10
Candesartan	32
Valsartan	320
Bisoprolol	10
Carvedilol	50
Metoprolol-Succinat	190
Nebivolol	10

In the telemonitoring system every medication change was documented by the physicians. The list of available medications in the telemonitoring system was taken from the Austrian drug database. Initially, we had to find relevant medication dose changes. Because different products from the same medication group were not equally potent at the same dose level, we had to normalize the dose by using an equivalent dose (Table 2) which was derived from the ESC guidelines for HF management [6].

2.4. Analysis: events with subsequent medication changes

For every medication group a rule was implemented in the CDSS to recommend adjustment of the medication dose. We defined four classes to analyze the performance of the CDSS like a diagnostic test:

- True Positives (TP): monitoring days inside event episodes where recommended medication change was performed (correctly identified situation)
- True Negatives (TN): monitoring days outside event episodes and no medication change was performed (correctly rejected situation)
- False Positives (FP): monitoring days inside event episodes where recommended medication change was not performed (incorrectly identified situation)
- False Negatives (FN): monitoring days outside event episodes and an unexpected medication change was performed (incorrectly rejected situation)

3. Results

Our dataset comprised 4.450 monitoring days for 15 patients. (296.8 +/- 88.8 monitoring days per patient). Table 3 provides a detailed overview of the patient characteristics.

Table 3. Patient characteristics of the analyzed patients

Feature	
Number of patients (male / female)	15 (12 / 3)
Monitoring duration (mean +/- standard deviation)	295.8 +/- 88.8 days
Age (mean +/- standard deviation)	72.1 +/- 9.0 years
Medication adjustments per patient (mean +/- standard deviation)	5.7 +/- 5.3
Event episodes per patient (mean +/- standard deviation)	13.0 +/- 9.4

Table 4. Episodes (E), Medication adjustments (MA) inside and outside event episodes, Episodes with performed medication adjustment following recommendation (EMAFR), Episodes with performed medication adjustment different to recommendation (EMADR)

Rule	E	MA	EMAFR	EMADR
ACE/ARB increase	26	13	6	1
ACE/ARB decrease	9	9	1	0
Beta-blocker increase	81	17	13	5
Beta-blocker decrease	1	3	0	0
Diuretics increase	42	19	1	3
Diuretics decrease	36	25	9	0
∑	195	86	30	9

The CDSS generated a total of 713 raw events. After preprocessing, 195 event episodes remained. The most common episode (81 times) was tachycardia, which triggered the recommendation to raise beta-blocker dosage. Tachycardia recommendations were executed 13 times. The least common episode was bradycardia. Only one bradycardia episode was detected by the CDSS. Details about the total number of episodes, the total number of medication adjustments and the results of the combined analysis of events and medication adjustments are listed in Table 4.

Overall, 39 episodes with medication adjustments were found. In 30 of those episodes the recommended medication adjustment was performed. Dose increase of diuretics, beta-blocker and ACE/ARB sometimes did not follow the recommendations whereas in all cases of decrease of ACE/ARB and diuretics the physicians followed the recommendations.

The results from the diagnostic test are provided in Table 5. On 3857 monitoring days (86.7 %) the patients were outside event episodes and no medication adjustment was performed by the physicians. On 265 monitoring days (5.9 %) the patients were inside event episodes and the medication adjustment was performed. On 314 of the monitoring days (7 %) the patients were inside event episodes and a medication adjustment different to the recommendation was performed. Only on 14 monitoring days (0.3 %) patients were outside event episodes and a medication adjustment has been performed. The results from the test were used for calculating specificity and sensitivity. Sensitivity was 94%, specificity with 92% a bit lower.

Table 5. Diagnostic test evaluating performance of CDSS based on performed medication adjustments

		Medication adjustment	
		+	-
Monitoring days inside / outside event episodes	+	265 (TP)	314 (FP)
	-	14 (FN)	3857 (TN)

Sensitivity = TP / (TP + FN) = 0.94
Specificity = TN / (FP + TN) = 0.92

4. Discussion

Our previous retrospective analysis of telemonitoring data had shown that target values for blood pressure and heart rate as recommended by the ESC guidelines for chronic heart failure management could not be reached for many patients. This resulted in a high number of events for hypertension and tachycardia [7]. For the current analysis, we implemented an additional grouping algorithm, which aggregated events into episodes. Therefore the absolute number of generated events in the present analysis is lower and not directly comparable to previous results as given in [4].

A weakness of the current analysis is that only 15 patients were included in the data analysis and no further data is expected, as the study has been terminated in October 2014.

One of the problems in determining the effectiveness of CDSS is often the lack of reference annotations. This was particularly the case in our retrospective analysis of telemonitoring data, where no CDSS triggered recommendations were given during the treatment of the patients. In those datasets it was not clear whether medication change recommendations were considered or not by the physicians. Results from the present analysis, however, indicate that the CDSS was able to trigger real medication adjustments. We could use the physician decisions as a reference annotation for appropriate medication adjustment recommendations.

Results from Table 4 and 5 show that guideline-based CDSS did indeed trigger medication adjustments, i.e. 579 out of 4450 (13%) of the events were unequivocally related to medication adjustments.

From a clinical point of view it might be of interest whether the usage of the CDSS, finally, results in a better outcome for the patients. Such questions are currently being dealt with, most likely resulting in additional annotations of the clinical courses of both the telemonitoring and the control group. Once these data become available, future work will focus on the comparison of medication doses between the CDSS-guided telemonitoring group and the control group with no CDSS of the INTENSE-HF study.

Subsequently, we will be in a position to analyze if the guideline-based CDSS was able to bring telemonitoring patients closer to a guideline-based medication scheme and, eventually, to elucidate how the rule-set has to be modified to increase the reliability and acceptance of CDSS systems for HF management.

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