Telemonitoring in heart failure patients with clinical decision support to optimize medication doses based on guidelines

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***Abstract*— The European Society of Cardiology guidelines for heart failure management are based on strong evidence that adherence to optimal medication is beneficial for heart failure patients. Telemonitoring with integrated clinical decision support enables physicians to adapt medication dose based on up to date vital parameters and reduces the number of hospital visits needed solely for up-titration of heart failure medication. Although keeping track of weight and blood pressure changes is recommended during unstable phases, e.g. post-discharge and during up-titration of medication, guidelines are rather vague regarding telehealth aspects. In this paper, we focus on the evaluation of a clinical decision support system for adaption of heart failure medication and for detecting early deteriorations through monitoring of blood pressure, heart rate and weight changes. This clinical decision support system is currently used in INTENSE-HF, a large scale telemonitoring trial with heart failure patients. The aim of this paper was to apply the decision support algorithm to an existing telemonitoring dataset, to assess the ability of the decision support concept to adhere to the guidelines and to discuss its limitations and potential improvements.**

I. INTRODUCTION

Heart failure affects about 20-30% of individuals older than 70 years and is described and characterized as a major health problem and a burden of epidemic proportion. It is also associated with high re-admission and mortality rates [1-3]. The re-admission rate of patients with HF is between 30-45% within six months after their initial admission. Forty percent of the patients that are admitted for HF die or are re-admitted within one year. About 50% of the patients die within five years after the diagnosis [4].

There is strong evidence that adherence to guidelines and optimal medication leads to better outcomes and reduces mortality and the need for re-hospitalizations [5]. The European Society of Cardiology (ESC) guideline for HF management [5] provides a pathway for optimizing HF medication dosages. However, a number of difficulties exist related to the development and interpretation of the content of a guideline: the exact meaning of terms is not always defined, recommendations are not always clearly articulated and sometimes vague wording is used [6]. The ESC guideline for HF management mentions 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 loop diuretics. While ACE-I, ARB and BB are advised for managing blood pressure and heart rate, loop diuretics are used for controlling fluid retention to prevent cardiac decompensations. For ACE-I, ARB and BB the guideline stipulates that the target dose [5, Table 14] should be reached or – if the target dose cannot be reached – the maximal tolerated dose should be taken. The dose of loop diuretics should be individually adapted when signs of congestion appear (e.g. sudden weight gain).

Telemonitoring has the potential to enhance patients' self-care capabilities and - in combination with a clinical decision support system (CDSS) - medication adaption according to the ESC guidelines for HF management can be facilitated. Although the current guideline does not give a clear recommendation for telemonitoring, some studies have shown positive effects and state that through early detection of deteriorations in vital signs up to 50% of re-hospitalizations can be prevented [7].

The INTENSE-HF study [8] started at the end of 2012. It is one of the first randomized controlled trials (RCT) where telemonitoring with an integrated CDSS enables physicians to quickly and remotely react on cardiorespiratory deteriorations (e.g. by changing types and doses of prescribed drugs) and to continually optimize HF therapy according to guidelines. The exploratory endpoint of INTENSE-HF focuses on evaluating for which portion of patients the recommended dose from the guideline can be reached, using the CDSS.

The present paper aims to evaluate this CDSS algorithm, which has been developed specifically for and is currently used in the INTENSE-HF study [8]. We focus on applying the algorithm to an existing dataset and describe the number and distribution of generated events. Our analysis is going to address the following questions:

- How is the number of events distributed across all patients?
    - Are there patients without events?
    - Are there patients who have events very often?
- How is the number of events distributed across all rules?

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- Are there rules which are never fulfilled?
- Are there rules which are fulfilled very often?

TABLE I. RULE SET USED IN CDSS

#	Rule	Action	Type
R1	Systolic blood pressure > 130 mmHg	Increase dose of ACE-I/ARB	A
R2	Systolic blood pressure < 95 mmHg AND patient reports feeling unwell	Decrease dose of ACE-I/ARB	A
R3	Heart rate > 70 bpm	Increase dose of betablocker	A
R4	Heart rate < 50 bpm AND patient reports feeling unwell	Decrease dose of betablocker	A
R5	Weight gain > two kg in two days	Increase dose of diuretics	B
R6	Weight loss > two kg in two days	Decrease dose of diuretics	B

II. METHODS

A. Decision support rule set / algorithm

We derived the rules for the CDSS from the current ESC guidelines for HF management and experiences gained from a prior clinical trial [7]. From the ESC guidelines we essentially used the *How to use?* section from their Web Table 11, 12, 14 and 15. In case the guideline did not provide accurate definitions, physiologically reasonable constraints for the algorithm were chosen after discussions in a multidisciplinary panel, as described in the following.

A.1 Rule categories

We defined six rules (Table 1), which can be divided into two categories. Four rules (type A) were responsible for adapting the dose of HF medication for ACE-I, ARB and BB according to guidelines. Type B rules generated events depending on sudden body weight gains or losses (greater than two kg in two days) to indicate early signs of fluid retention, which could be an early sign for cardiac decompensation. This rule was derived from Web Table 12 of the ESC guidelines of HF management [5].

A.2 Low pass filtering

ESC guidelines are primarily intended to be used by physicians. Therefore, doses adaptions are based on the measurements that are taken when the patient visits the physician. However, during remote monitoring, vital parameters are available more frequently. Therefore, events for type A rules were generated when five values in seven days exceeded a physiologically reasonable threshold, which was defined by the medical experts. The five out of seven approach is basically a moving-average-filter and was chosen from a pragmatic medical point of view to smooth out short-term fluctuations and highlight longer-term trends or cycles.

Advanced heart failure is a rather unstable disease with frequent changes e.g. increase of body weight. This reflects fluid retention and blazes the trail for deterioration. Not surprisingly, physicians are eager to react on these measurements with adjustments of treatment. It was presumed that vital parameters within one week are most relevant for further dosage adaption. Short outliers (less than five days) of abnormal vital parameters were also considered to be not yet relevant to trigger medication adaption recommendations.

For decreasing the dose of ACE-I, ARB and BB an additional constraint was included. Only if the patient reported that he/she feels unwell, a suggestion to decrease medication dose was generated.

A.3 Presented events / muted events

To avoid the presentation of multiple events for the same episode of type A events (increase or decrease of ACE/ARB/BB) we decided to cluster events into two categories:

• *Presented* event: event generated by the CDSS and presented to the physician in order to initiate a medication adaption

• *Muted* event: event generated by the CDSS, but not presented to physician, because an event of the same type was generated within the previous n days (for INTENSE-HF: n=7 days). This feature was implemented to avoid multiple medication recommendations for the same episode of high or low blood pressure or heart rate.

A.4 Handling of multiple measurements per day

The used dataset comprised several patients for which multiple measurements of the same type (for instance blood pressure) were available per day. Multiple measurements can appear for four different reasons:

a) patient wanted to correct a erroneously submitted measurement;

b) patients were instructed to measure off-protocol (e.g.in unstable phases)

c) patients took additional measurement of their own accord (e.g. subjective discomfort, technical problems)

d) measurements were taken by someone else (e.g. relatives)

To handle multiple measurements in INTENSE-HF patients were instructed to measure vital parameters at the same time every day under standardized conditions, preferably in the morning and after emptying the bladder. Since this is known to be the most stable measurement available, only this first measurement of the day is considered by the CDSS. However, to give patients the possibility to correct measurements (for example that have been recorded under non-standard conditions), a correction time window of one hour was defined. The correction window of one hour was set arbitrarily in order to allow on-time processing of data for the treating physician. The on-time processing of data allows the physician an early response on values that go out of range. If e.g. a second blood pressure value was submitted within one hour after the first one, the second one was used by the CDSS. We defined these values to be *correctional values*. Measurements that were taken more than one hour after the first measurement are known to vary significantly depending on nutritional and physical behavior. Therefore, such measurements were defined to be *supplemental values* and were not considered by the algorithm.

A.5 Handling of missing data

Monitoring episodes with missing data did not trigger medication adaptions. Nevertheless patients with missing

data should not be ignored by the physician, as missing data could be a hint, that somethings wrong with the patient which might require special attention of the physician. To recognize episodes of missing data, a "missing data" rule was introduced, which checks for complete datasets and notifies the physician in case a patient does not submit his vital parameters as instructed.

B. *Analysis framework / assessment of algorithm*

For assessment of the CDSS algorithm we used MATLAB (The MathWorks, Inc., Natick, MA, USA) as analysis framework.

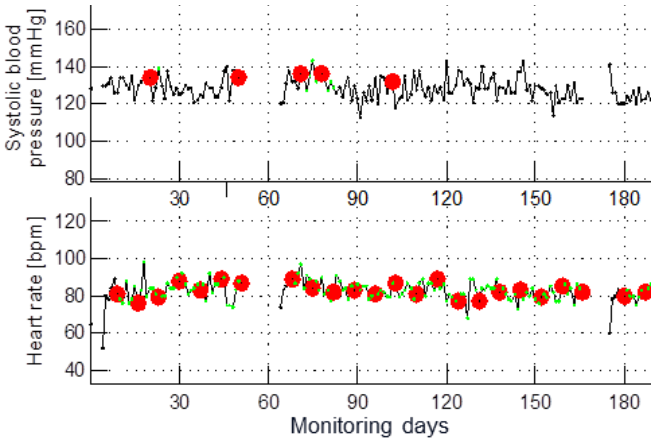

Figure 1. Time series figure with generated events for visual analysis. Larger red dots indicate events *presented* to physician. Smaller green dots indicate *muted* events, not presented to physicians.

We applied the algorithm to the dataset resulting in a particular number and type of events for each patient. For visual inspection we created time-series-plots (Fig. 1). For further analysis and for answering our research questions an output file with a detailed list of the circumstances for all generated events was created.

C. *Dataset(s)*

To increase the size and diversity for the assessment of the rule set we merged the data sets from two telemonitoring applications, which were used previously to collect measurements from chronic HF patients. Both systems used the same underlying telemonitoring platform. A detailed description of this platform is given in [1]. Data had been collected during the course of a randomized controlled trial

(MOBITEL [7]) and from a routinely applied telemonitoring systems in the HF department of an Austrian hospital (ELICARD [9, 10]). Detailed demographics for both patient cohorts are provided in the enlisted references. Basically, in both systems patients were equipped with a blood pressure meter, a weight scale and a smartphone. They were instructed to submit daily measurements for systolic blood pressure, diastolic blood pressure, heart rate, weight and a subjective assessment of their wellbeing (bad, normal, good). The merged dataset comprised of 34.071 monitoring days for 101 patients (median: 187 days, interquartile range: 584 days).

TABLE II. NUMBER OF EVENTS GENERATED BY CDSS ALGORITHM DURING 34.071 MONITORING DAYS

Event	Presented	Muted
R1	712	3.061
R2	24	74
R3	1.611	9.028
R4	1	3
R5	398	-
R6	435	-
No decision possible because of missing data	7.460	-
Multiple measurements per day available	2.822	-

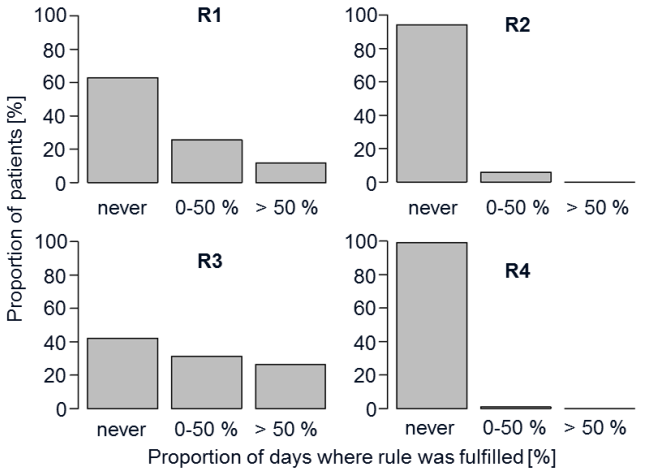

Figure 2. Proportion of days on which medication adaption alerts are generated for patients (classification is based on thresholds which were selected by visual inspection of the event distribution)

III. RESULTS

Table 2 shows the number of generated events for type A rules when applying the algorithm to the merged dataset.

Based on visual inspection of the distribution of generated events we defined cut-offs and assigned patients to cohorts:

- Patients, for whom a given rule is never fulfilled
- Patients, for whom a given rule is fulfilled between 0 and 50% of all monitoring days
- Patients, for whom a given rule is fulfilled more than 50% of all monitoring days

Results of the classification are depicted in Fig. 2.

IV. DISCUSSION

Published guidelines represent a distillation of the best evidence and should help to improve the management of HF [11]. However, for telemonitoring situations, there is a lack of knowledge on how to transform guidelines into rules, which can be processed by a CDSS. As far as we know, up to now there has been just one RCT [4], which has examined the impact of a CDSS in combination with telemonitoring for HF management. This particular RCT was not able to show a significant outcome improvement for telemonitoring with integrated decision support in their primary endpoint. One reason for this might be that patients in the control group were also enrolled in a comprehensive disease management

program, where HF medication dosages have been optimized by special trained HF nurses. However, they could show that patients who were enrolled in the telemonitoring group of the study had to visit the HF clinics less often than patients enrolled in the control group.

Our retrospective analysis with the existing telemonitoring datasets revealed that our current rule implementation tends to advice to increase the dose of HF medication. On the one hand, this was to be expected since the goal of our CDSS was to increase the dose of HF medication to reach the target dose. On the other hand, our analysis also revealed that rules for decreasing ACE/ARB/BB were hardly ever fulfilled (for R4, only a single event for 34.071 monitoring days). The reason for this rather low numbers of events for R2 and R4 as compared to R1 and R3 is the additional symptom based constraint. Patients needed to report that they don't feel well at least once in the previous seven days to fulfill the prerequisites for these rules, which overall happened in just 2% of all monitoring days (680 times out of 34.071 monitoring days).

In general, target values for blood pressure and heart rate recommended from the ESC guideline for chronic HF management were not reached in a number of patients and, as a consequence, led to a high number of events for R1 and R3. Most likely, current guidelines were designed without considering the high sampling rate of measurements that are typically done in telehealth scenarios - if measurements are taken every day, preprocessing and filtering of the data before applying a CDSS is absolutely needed.

A limitation of our retrospective analysis and one explanation for the high number of events is that medication adaption – which would follow after an event – had not been performed according to the guidelines in the available datasets. Therefore – a prospective study, like INTENSE-HF [7], is necessary to see what the impact of therapy changes with a long-term effect (ACE-I, ARB and BB) on the number of generated events is.

One key problem in validating telemonitoring with integrated CDSS is the lack of a "ground truth". Although we do have data on the interventions that were performed in the previous telemonitoring groups, these interventions were based on alarms triggered by different algorithms (e.g. for [7] and [9]). Therefore those interventions were biased and should not be used to evaluate the performance of our current algorithm which has been designed to be more closely aligned with the ESC guidelines.

From an engineering point of view, the subject of our evaluation is the control dynamics of a closed-loop system. An "open-loop" control group, who does telemonitoring but is not subject to any kind of feedback or interventions based on their submitted vital signs, would be of some help. Nevertheless, it could be difficult to find significant differences with respect to the closed-loop group in a reasonably sized control group. Therefore, we cannot reliably predict the performance of our decision support algorithm before the results of the ongoing prospective INTENSE-HF clinical trial will be available. These results are expected to reveal the clinical utility of telemonitoring with integrated decision support for medication adaptation in patients with systolic HF and provide data needed to further optimize the parameters of our algorithm.

However, the use of fixed thresholds for generating events for medication adaptions was found to be inappropriate in some patients. For example, in patients with cardiac pacemakers, fixed thresholds for the heart rate were always exceeded, and, as a consequence a large number of events were generated. Dynamic thresholds could be the solution to get rid of those useless events.

In conclusion, transforming guidelines to formal decision support rules is not a trivial process. The guidelines are currently not designed for frequent measurements as available when patients are enrolled in telemonitoring programs. This has to be taken into account when designing an algorithm for a CDSS. For values that are measured every day, a *filter* needs to be designed, to aggregate values of several days. The results from our study indicate that the 5-out-of-7 filter implemented for type A rules may need to be substituted by an optimized filter design in the future.

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