REMOTE MONITORING FOR THE EARLY DETECTION OF CHANGES IN PATIENT STATUS
USING THE HOME MONITORING TECHNOLOGY

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Aims: To perform the analysis of adverse events (AE) rate and trends of physiologically meaningful parameters in
patients with cardiac implantable electronic devices (CIEDs) with the mobile remote monitoring option.

Methods: In 9 clinical centers of the Russian Federation and 2 clinical centers of the Republic of Kazakhstan, 126
patients with an implantable cardioverter-defibrillator (ICD) or a pacemaker (PM) equipped with the Home Monitoring
(HM) technology (BIOTRONIK, Berlin, Germany) were enrolled. Based on the daily data transmission, all alarm alerts,
all HM options changes and all AE were recorded with dated alert content and undertaken measures.

Results: The study patients, followed up at least for one year, experienced 42 adverse events (AE), of which 26 were
serious AE (SAE) and 3 SAE were defined as device-related (SAED). ICD patients (N=90) with concomitant coronary
artery disease (CAD) had a statistically significantly higher SAE prevalence (p=0.0249). Patients with CRT-D had a lower
SAE rate than patients with dual- or single-chamber ICD (p=0.046). Downloads of Home Monitoring parameters for
retrospective mathematical analysis were available for 60 ICD patients, of which 47 had episodes of ventricular tachycar-
dia (VT), ventricular fibrillation (VF) and/or atrial tachyarrhythmia (AT). Machine learning analysis of the trends of the
physiologically meaningful parameters revealed correlations between changes and arrhythmia episodes, with the random
forest and gradient boosting methods demonstrating the random effect of the results.

Conclusion: Home Monitoring of CIED patients enables the evaluation of different devices applications and their
clinical advantages. This might implement the prevention of adverse events and iatrogenic effects of pacing. Based on daily
transmission of physiologically meaningful Home Monitoring parameters, the study results demonstrate the feasibility of
developing a prediction algorithm for adverse events.

Key words: electrotherapy of heart; Home Monitoring; adverse events; trends of physiological parameters

Conflict of Interests: nothing to declare
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Remote monitoring (RM) of patients with cardiac implantable electronic devices (CIEDs) has been in use for more
than 20 years [1]. Currently, RM is recommended for patients with pacemakers (PMs), implantable cardioverter-defbribilla-
tors (ICDs) and systems for cardiac resynchronization therapy (CRT) as a part of standard follow-up (FU) strategies [2, 3].

Numerous clinical trials as well as randomized, have been performed with the Biotronik Home Monitoring (HM)
systems. The TRUST study [4] has demonstrated statistically that relevant clinical events can be revealed in patients fol-
lowed-up by RM much earlier than for patients, followed-up only by ambulatory visits. Clinical outcome can be improved

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through early diagnostics of important cardiac events, prone to serious complications (e.g. stroke as a consequence of persistent atrial fibrillation) [4-6], better patients’ compliance [7] and satisfaction of therapy procedures [8].

On one hand, the COMPAS [6] and OEDIPE [9] clinical trials have shown that RM can significantly shorten time to necessary physician’s intervention and, on the other hand, reduce greatly the number of unnecessary FUs, approximately 50% of patients not needing a scheduled FU [10] as no changes in their therapy or their implant’s program are necessary [11]. According to the “TRUST” [4] and “COMPAS” [6] trials, the related clinical burden can be reduced, both for physicians and patients, by 45% and 56%, respectively.

The “ECOST” study showed [12] that HM can reduce the number of inadequate shocks by 52% and the number of related hospitalizations - by 72%. The appropriate implant reprogramming enabled for reduction of the number of shock charges by 76%, and of delivered shock discharges - by 71%, with a significant positive effect on the battery longevity.

The most important clinical result have been reported in the “IN-TIME” trial [13], with a more than two-fold reduction of the overall and cardiovascular mortality in congestive heart failure (CHF) patients monitored remotely, in comparison to patients, followed-up only by scheduled ambulatory FUs.

The Russian Scientific Society of Arrhythmology, Electrophysiology and Cardiac Pacing has sponsored the “ReHoming” (Registry Home Monitoring) clinical trial with the goal to evaluate the clinical results of patient’s remote monitoring FU in the Russian Federation and the Republic of Kazakhstan. The Home Monitoring generated alerts of relevant clinical events have been recorded in case report forms (CRF). Trends of physiologically meaningful parameters have been used by physicians to decide whether to intervene with an unscheduled FU. Serious adverse events including hospitalizations and cardiovascular complications have been recorded, as well as undertaken measures, like therapy or implant program changes.

METHODS

Patient enrollment and study protocol

Patients of both sexes older than 18 years were eligible to enroll in the study if they had an ICD or a PM with the mobile RM option (Home Monitoring BIOTRONIK, Germany). Exclusion criteria were:

• Post cardiac surgery or post infarction < 1 month,
• More than two cardioversion shocks within last 6 months (for ICD patients),
• Lead dislodgement, and/or impedance, threshold, or sensing failure, loss of capture and inadequate ICD therapy,
• Implant-related infection,
• Inability to handle the “Home Monitoring” system correctly,
• Participation in another clinical study,
• Insufficient GSM coverage at patient’s home,
• Pregnancy or nursing.

Study design

The Rehoming trial was designed as an open, multi-center and observational study. In addition to an ICD or a PM the enrolled patients received (or already had) a RM transmitting device (Cardiomessenger II-S, BIOTRONIK) with both the patient and the transmitter registered at the Home Monitoring Service Center (HMSC).

Regular patient’s FUs were scheduled by the study investigators according to the guidelines intervals starting from the enrollment procedure: 3 months for ICD patients, and 6 months for PM patients (Fig. 1).

All FU results were documented in the patient’s health record and then entered into the CRF. Russian Internet platform rehoming.dicoming.com was developed [14], with the downloaded Home Monitoring data, offering a possibility to fill in the CRF protocols online.

Study parameters

Continuous patient RM was aimed to register all alarming HM alerts with the "red" (urgent) and with the
"yellow" (attention) status, and to register all resultant changes of the HM options. If necessary, based on the physician’s decision and/or patient’s need and in view of received HM alert, FU was scheduled, to prevent an anticipated a serious adverse event (SAE). An EchoCG was recommended in case of the following patient’s status changes: dramatic increase of atrial arrhythmia burden, dramatic increase of the ventricular paced events ratio Vp, rapid worsening of the Heart Failure Monitor (HFM, Biotronik) parameters.

Ambulatory FUs of patients with ICDs or CRT-D systems were scheduled 3, 6, 9 and 12 months after enrollment, and the following data were recorded:

- Implant printout of device parameters and statistical data (paroxysms of atrial tachyarrhythmia - AT, ventricular tachycardia - VT, mean ventricular rhythm, also, at rest, patient activity, number of ventricular extrasystoles (VES) per hour);

- Necessity of the EchoCG procedure;
- Implant reprogramming;
- Changes of drug therapy;
- Events revealed by Home Monitoring.

### Statistical Analysis

Study were analyzed with the SAS software package (SAS Institute, USA), version 9.4. Mean value and standard square deviation (SD) are stated for parameter sets with normal distribution, median and quartiles for the other parameters. For categorical data, absolute and relative frequencies are given.

Metric study parameter sets were compared using the Student’s t-test or the Wilcoxon-Mann-Whitney test (if the parametric test assumption was not fulfilled). Binary and categorical parameters were analyzed using the χ²-test and the Fisher exact test. Critical double-sided level of significance for all tests was 0.05.

### Internet platform

Besides the HMSC portal, investigators were offered to use the ReHoming portal [14] developed as a part of the universal HELTERBOOK™ [15] Internet platform. The portal enabled for comprehensive HM data mirroring and continuous study monitoring. Automatic options of statistical analysis were available with different filtering parameters, allowing analysis of study data in different patient sampling groups.

### Study endpoints

The primary endpoint was the occurrence of a serious adverse event (SAE), including patient’s death or hospitalization, complications from cardiovascular disease and the implanted device failure.

Secondary endpoints were the efficiency of the “Home Monitoring” technology to reveal the AEs and the clinical benefit of RM application within the country healthcare structure.

### Retrospective analysis of the Home Monitoring database

To reveal possible correlation between the changes of the daily RM parameters and the probability of certain arrhythmia events, the trends of the physiologically meaningful parameters that could be used to develop a predictor of patient’s status worsening were retrospectively analyzed [16]:

- Mean heart rate (HR) over 24 hours,
- HR at rest,
- Patients activity,
- VES per hour averaged over 24 hours,
- HR variability (HRV),
- Right ventricle lead impedance,
- Shock lead impedance,
- Ratio of atrial paced events Ap.

To evaluate the feasibility to develop a predictor algorithm, the events that are automatically recorded by Home Monitoring for ICD were chosen (i.e. episodes of AT, VT and ventricular fibrillation (VF)).

### RESULTS

#### Patient population

In 9 research centers of the Russian Federation and 2 research center of the Republic of Kazakhstan, 126 patients were enrolled, 114 of which completed the trial and 12 - dropping out. The database contains the complete data...
of 119 patients, included in the study efficacy analysis population: 89 patients with ICDs, 30 with PM. Data for ICD patient were partly available and used for appropriate results analysis. Therefore, the total population size was 120 patients and the ICD population size was 90 patients.

For the total population of 119 patients, 88 (73.9%) were male and, for the ICD population (n=89), 69 (77.5%) were male. Mean ages were 57.5±11.4 and 56.8±11.4, respectively. The main comorbidities were cardiovascular disease (mostly CHF) and diabetes mellitus (Table 1).

The majority of patients, 111 (93.3%) and 85 (95.5%) of the total and the ICD groups, respectively, received cardiovascular medications (Table 2). 59 patients of the total population (49.6%) and 48 patients of the ICD population (53.9%) were surgically treated due to coronary artery disease (CAD), congenital (CHD) or valvular heart disease (VHD), or arrhythmias. 30 patients of the ICD population (n=89) had an ICD for cardiac resynchronization therapy (CRT-D systems).

Ventricular arrhythmia was the indication for the ICD or the CRT-D implantation in all ICD patients (n=89), mostly for primary SCD prophylaxis - 59 patients, 66.3% (Table 3).

Safety analysis included 120 patients with a total 42 adverse events (AE), of which 4 were evidently related to the implantable device (AED) and 2 - possibly related. In total, 26 serious AE (SAE) were reported, of which 3 were SAED (related or probably related to the device). During the course of the study there were 2 patient deaths not related to the implant. The other 24 SAE included patient hospitalizations due to different reasons: CHF worsening (n=8, 19.0% of all AE), VT (n=7, 17%), CAD (n=2), gastritis (n=2), acute myocardial infarction (n=1), ischemic stroke (n=1), permanent atrial fibrillation (n=1), cardiac transplant rejection (n=1) and lead dislodgement (n=1).

Fisher exact double-sided test of ICD patients’ data (n=90) demonstrated statistically significant differences in SAE rate for patients with and without CAD, p=0.0249 (Table 4).

For some other cardiac diseases, no statistically significant differences were observed other than a trend for higher SAE rate was seen: for VHD - p=0.1473, and for diabetes mellitus (DM) - p=0.2151.

Fisher exact double-sided test demonstrated a statistically significant lower SAE rate in patients with CRT-D than in patients with dual-chamber ICD, p=0.046 (Table 4).

Study efficacy analysis

Upon CIED implantation and RM activation, 120 patients were followed-up according to the study protocol for an average of 28.3±10.1 months (2±43 months). Mean annual number of HM messages was 43.6±35.6 messages per year for the total population (n=120), (5±221). Home Monitoring of the ICD population (n=90) documented ventricular arrhythmias in 52 patients: VF episodes - in 43, and VT - in 21 (Table 5).

Thirty four ICD patients (n=89) received on the average 4 [1;11.5] defibrillation shocks per patient (maximum - 127), with an efficiency of 100[60.7;100]% in the VT zone (n=29) and of 54.5 [14.3;99] % in the VF zone (n=30).

Of clinical interest was to reveal any correlation between the disease etiology and the rate of arrhythmias, registered by the implant. The most significant correlation in the ICD population (n=90) was VT prevalence in patients with supraventricular tachycardia (SVT), p = 0.0107. VT episodes rates were statistically significantly lower in ICD patients with CHF in anamnesis (Fisher test p=0.0320), and with comorbidity of CHF and VHD, p = 0.0327 (Table 6). CAD did not increase in a statistically significantly manner the rate of VT detection, p = 0.6706.

Clinical patient load

According to the study protocol, investigators recorded different aspects of the clinical load related to patients’ FU and also based on VT presence (Table 7). The total number of patients’ visits to clinic was 240 for an average of 0.97±0.56 per patient per year. Medical care was requested by 41 patients. Patients with VT needed emergency help twice more often than patients without VT, while the mean number of hospitalization and unproductive days per year were approximately the same for both subgroups.

Clinical load was analyzed based on patients’ etiology. Among the ICD population (n=90), CHD patients created higher clinical load than VHD patients: days to first therapy - 213 and 354 days, unproductive days - 8.9 and 8.3, hospitalization days - 6.8 and 5.7, respectively. Efficacy of different ICD therapy types for CHD and VHD patients showed non significant statistical trends: ATP in VF zone (56.6% vs 52.3%) and cardioversion shocks (81.7% vs 75.0%) were more efficient in CHD patients, but ATP in

| Study efficacy analysis |

| Implantable device type | Total (n) Mean* Total (n) Mean* |
|-------------------------|-----------------------------|
| ICD                     | 14                          | 42                          |
| CRT-D                   | 2                           | 28                          |
| Total                   | 16                          | 70                          |

| Number of episodes |

| Number |
|---------|
| VA      |
| VT      |
| VF      |
| PS      |

* - per patient, VA - ventricular arrhythmias, PS - patient sample
the VT zone was more efficient in VHD patients (47.9% vs 41.9%).

In accordance with the study protocol, investigators rated different aspects of the Home Monitoring technology for patients' FU with a 5-point scale (5 - highest rating). The mean ratings were: HMSC performance - 4.7, “traffic light” concept - 4.7, “IEGM online” option - 4.7 and sufficiency of HM data - 4.6.

Analysis of physiological parameters' trends

For 60 ICD patients, long-term trends of daily recorded parameters were downloaded from the HMSC portal. Data for retrospective mathematical analysis were chosen according to the criteria of possible correlation analysis between the RM parameters' trends and the event onset probability. Therefore, the episodes with monitoring data available for at least 7 days and with no more than 2 successive blank days were selected. After trends review, 47 patients with events of the VT, VF and SVT type were selected. In order to build analytical models on the available dataset, we selected the following number of independent events: SVT - 200, VT - 27, VF - 38.

We used the cross validation technique to evaluate accuracy of possible correlations [17]:
- The dataset was randomly divided into five subgroups so that the number of records with and without the specific event were approximately similar in different subgroups;
- The data of four subgroups were used to determine which correlations (training sets) could predict the onset of a specific event;
- The models were validated on the retained data of the fifth subgroup.

To evaluate the models quality, a ROC-analysis (Receiver Operating Characteristic) was performed with the ROC_AUC (area under the curve) metrics [18]. The choice was due to the relatively low number of specific events in the dataset (VF, VT) and large time intervals with no events. The ROC_AUC metric does not depend on the number of specific events and, in general, reflects the ratio of truly classified cases of event occurring or not, with 1 meaning ideally correct prediction, and 0.5 - a random guess.

Search for correlations and predictor modelling

The search for correlations was performed with the following algorithms of machine learning:
- Decision tree - random forest classifier (search of parameters' values that could be the symptoms of the target event and splitting data trends in groups according to the parameters' values) [19];
- Support-vector networks with linear and radial kernels (values separation by hyperplanes in multi-dimensional space of parameters) [20];
- Nearest neighbors algorithm [21];
- Logistic regression (based on correlation of events and parameters) [22];
- Gradient boosting method [23].

These algorithms revealed significant deviations of ROC-curves from the diagonal demonstrating the possibility of the available parameters' set to predict specific events with a probability, significantly exceeding a random guess.

The best result for AT (with the largest dataset) was shown by the gradient boosting method with a ROC_AUC = 0.79624, min = 0.73510. Overall, owing to the relatively large number of samples, this event type was the best predicted. The following parameters were the most relevant for the modelled predictors (in order of importance): mean heart rate (HR), HR at rest, impedance of the right ventricular (RV) lead, mean number of ventricular extrasystoles (VES) per hour and patient activity.

Comparatively good intermediate results for VF (38 event samples) were achieved by the random forest (ROC_AUC = 0.71819, min = 0.55398) and gradient boosting methods (ROC_AUC = 0.66753, min = 0.53420576). Even the worst case result was exceeding a random guess (though much weaker than for the AT event type). The

| VT detection | Yes | No | Total |
|--------------|-----|----|-------|
| Total        |     |    | 90    |
| Supraventricular tachycardia |
| Yes          | 31  | 12 | 43    |
| No           | 21  | 26 | 47    |
| Total        | 52  | 38 | 90    |
| Congestive HF |
| Yes          | 23  | 26 | 49    |
| No           | 29  | 12 | 41    |
| Total        | 52  | 38 | 90    |
| Congestive HF & valvular heart disease |
| Yes          | 23  | 19 | 42    |
| No           | 33  | 15 | 48    |
| Total        | 56  | 34 | 90    |

Table 6. Rate of VT detection in ICD patients (n=90) and comorbidities: SVT, CHF and VHD

| VT detection | Yes (n=54) | No (n=36) | Total (n=90) |
|--------------|------------|-----------|--------------|
| Number of messages* | 17.3 [11.2; 30.7] | 10.6 [6.7; 14.5] | 14.9 [8.4; 29.4] |
| Days to first therapy | 199 [61; 485] | - | 199 [61; 485] |
| Number of patients with inability days* | 12 (22.2%) | 8 (22.2%) | 20 (22.2%) |
| Number of patients with emergency help* | 9 (16.7%) | 3 (8.3%) | 12 (13.3%) |
| Days of hospitalization* | 0 [0; 8.5] | 0 [0; 7.9] | 0 [0; 8.6] |

Table 7. Clinical load for ICD patients in dependence on VT presence

* - per year
most relevant parameters for the modelled predictor were as follow: PP-interval variability (HRV), RV-lead impedance, shock lead impedance, mean HR, number of high HRV intervals, ratio of cardiac cycles with atrial pacing Ap, patient activity, mean VES per hour and number of «mode switchings» per day.

For the VT events (27 event samples), we were not able to define statistically reliable correlations though the result of the gradient boosting method were found to be slightly better than a random guess (ROC_AUC = 0.68984, min = 0.51504). The most relevant parameters for the modelled predictors were as follow: mean HR, RV-lead impedance, presence of blanking monitoring data and mean atrial rate.

**DISCUSSION**

During the course of the ReHoming study we have developed a Russian portal to conduct remote follow-up of patients with CIEDs. As opposed to other similar portal, and in addition to the CIED compiled data, our portal also enables us to record other clinical data for their processing. The integrated automatic system for statistical analysis of the data allows for the processing of all recorded patients' data as well as specific groups pooling according to different clinical feature of the investigator’s choice (e.g. ICD or PM patients, CAD patients, etc.). These options give unlimited possibilities for research and management of clinical studies of any scale.

The newly developed study RM center has proven its efficacy and advantages that could be used in the future as an additional service to gather RM of patients of different clinics. It could be especially relevant for medical institutions with small number of patients, where additional personnel workload would be not cost-effective.

Strengthening the preventive aspect of this medical service is one of the priorities of healthcare development. Intervventional arrhythmology and, especially CIED therapy, are currently leading innovative fields in the broad use of the RM technology. The “ReHoming” project is an example of the “Home Monitoring” technology localization in the healthcare structure that facilitates the development of guidelines for patients’ FU with mobile RM. This clinical study demonstrates the potential of medical data integration and the machine learning methods for complex data analysis of large population cohorts to develop a predictor of patient’s status worsening.

It must be outlined that the predictor models, presented in this paper use essentially nonlinear methods, and therefore, there is no direct linear relationship between the parameters’ values and the probability of the event onset. Importantly, the implants record automatically both the parameters’ trends and the predictable events, without any physician’s or patient’s intervention. This will become an important factor as the data volume will increase due to greater patient and physiological parameters number.

**STUDY LIMITATIONS**

Results of the ReHoming study are largely aligned with other studies on remote monitoring of CIED patients. However, our study is a registry with no control group for comparative analysis. It is advisable to organize a larger national trial including a control group in order to reveal the influence of the specific national healthcare system, and to verify statistically the clinical and economic advantages of CIED patients’ remote monitoring.

**CONCLUSION**

Follow-up of the CIED patients with the RM technology enabled the evaluation of the clinical aspects of different implants’ use and how to avoid iatrogenic pacing effects. The SAE rate was significantly lower in CRT-D patients than in patients with single- and dual-chamber ICDs.

Comparative analysis of the arrhythmias rate based on the diseases etiology showed statistically significant correlations between the VT number and SVT, CHF and VHD comorbidity.

Despite the limitations due to the small amount of statistical data, the study results demonstrate the possibility to develop a predictor of disease complications based on daily transmission of trends of physiologically meaningful parameters recorded by the implant. Machine learning algorithms, such as the random forest and gradient boosting methods, revealed results that were strongly exceeding a random guess.

The Internet portal developed in the context of the ReHoming project and the built-in automatic system of data statistical analysis provide a framework for the implementation of machine learning methods. CIED therapy has therefore become one of the clinically relevant fields of artificial intelligence development and application.

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