Remote monitoring: Doomed to let down or an attractive promise?

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ABSTRACT

Device interrogation and management are time consuming, representing a relevant burden for pacing centers. In several situations, patients' management requires additional follow up visits.

Remote Monitoring (RM) allows an optimal recall management and a rapid diagnosis of device or lead failure, without the need of additional in office visits. Further it allows a significant delay reduction between the adverse event and the reaction to the alarm, shortening the time needed to make a clinical decision. A role in risk-predicting patient-related outcomes has also been shown. RM permits detection of the arrhythmia from 1 to 5 months in advance compared to in-office visits. Importantly, by using specific algorithms with multiparametric analysis, RM has been studied as a potential instrument to identify early patients on risk of worsening HF using specific algorithms. Although the use of RM in HF setting remains controversial, it has been proposed to improve HF clinical outcomes and survival in clinical trials. In this sense, RM success could require a standardization of process within a management model, that may involve different health care professionals. In this review, we examine recent advances of RM providing an update of this tool through different clinical scenarios.

1. Introduction

In the last decade, the implantations of pacemaker (PMK), defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices (Cardiac Implantable Electronic Devices - CIED) have significantly increased [1–3]. Clinical and device follow-up is usually scheduled every 3–12 months according to the type of the CIED and patient's clinical status. It represents a fundamental step in the management of patients with devices [4]. However, device interrogation and management are time consuming, representing a relevant burden for pacing centers, especially due to technologically advanced algorithms and patients' clinical complexity.

In several situations, such as a depleting battery, recall for malfunction, and urgent clinical or technical issues, patient management appears more complex than usual requiring additional follow up visits [5].

The description of different RM functions has been described and standardized in the ISHNE/EHRA consensus [6]. Remote follow-up consists of scheduled automatic device interrogation, using wireless technology, aiming at assessing device function while decreasing scheduled visits. RM, instead, consists of automatic unscheduled transmission of data based on prespecified alerts related to device functionality and clinical parameters which provides a rapid detection of a potentially dangerous event such as arrhythmias, device/lead malfunction, and battery depletion, so that the patient will be called in case of trouble for a nonscheduled follow-up, since remote programming is still not available.

However, this success has not yet been equally achieved across different clinical settings, especially in HF its role remains controversial.

The aim of this review is to explore the state-of-art of RM with an emphasis on randomized trials and to examine the recent advances and future directions through different clinical scenarios.

2. Lead and device surveillance

Heart Rhythm Society (HRS) recommendations [7] suggest the use of RM as a lead surveillance tool and battery lifespan optimization. The implantation center has the responsibility to control device performances. RM provides a continuous surveillance of device integrity through automatic alerts which assess any variations in leads impedance, burden and duration of atrial fibrillation, stimulation modality change, atrial or ventricular amplitude variation, ventricular arrhythmia or noise signals. Moreover, the continuous monitoring of battery lifespan allows to plan the device replacement when it is at the end of life, avoiding closer follow-up visits and increasing device longevity, with several economic and clinical advantages [8]. The aforementioned benefits have been widely demonstrated in large randomized trial such as TRUST (Lumos-T Safely Reduces Routine Office Device Follow-up) [9]. Specifically, in TRUST [9] trial there was a reduction of 50% of the number of scheduled and unplanned in-office follow-ups. In this regard, other studies have demonstrated a reduction of in-office follow-up visits [10–14]. The REFORM Trial [10] (Remote Follow-Up for ICD-Therapy in Patients Meeting MADIT II Criteria) showed a reduction of unplanned follow-up visits in 63.2% of patients followed with RM. Similar results were achieved in the COMPAS [11] and the EVOLVO studies [12], which enrolled patients with PMK and ICD respectively. These studies showed a significant reduction of unplanned follow-up visits in the RM group compared to the control group.

In line with these observations, real world registries such as ALTITUDE [13] and MERLIN [14], have demonstrated reduction of in office visits secondary to device malfunction and survival benefits. ALTITUDE registry demonstrated that patients with ICDs followed with RM showed a better outcome in terms of survival compared to patients followed in office. Similarly, MERLIN registry confirmed that RM is associated with improved survival, irrespective of device type, according to the level of adherence.

3. Reduction of event-reaction time of each center and arrhythmia management

The reduction of the delay between the adverse event (i.e. arrhythmias, malfunctions etc.) and the reaction to the alarm received by the pacing center, is a significant advantage of RM compared to the traditional follow-up, showing a shorter time to make the clinical decision [9–15]. The Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision (CONNECT) study evidenced a reduction of the median time from the clinical event to clinical decision from 22 days in the in-office patients to 4.6 days in the remote patients ($p < 0.01$) [15].

In TRUST [9] study, the delay between arrhythmic event and the medical diagnosis and treatment was reduced from 36 days to 1 day for ventricular fibrillation and from 28 days to 1 day for ventricular tachycardia. In several cases, a slow incessant VT may precipitate into decompensated HF or repetitive non-sustained VT could precede the development of an electrical storm. Hence, the early detection of these arrhythmias may change the clinical course of patients.

The immediate evaluation of the effective and appropriate delivered therapy may allow to reprogram the device if the detection was incorrect (magnetic interferences, T wave oversensing, non-ventricular arrhythmia etc.) or if the therapy was not considered useful [7]. Using this personalized approach, clinicians may consider to modify the detection rate or program an anti-tachycardia pacing instead of shock, which may result painful and uncomfortable, in case of slow ventricular tachycardia, hemodynamically stable or recurrent but non-sustained VT.

Beyond the optimization of device programming, physicians could prescribe drug therapy or consider ablation of arrhythmias [16,17]. These advantages have been confirmed in the ECOST [18] study which demonstrated a 52% rate reduction of inappropriate shock and a 76% rate reduction of capacitor charge in ICD patients, compared to in-office follow-up, with a consequent longer battery lifespan and a 72% rate reduction of hospitalizations related to inappropriate shock. Another prospective randomized study [19] confirmed these results with a rate of inappropriate shock of 4.7% in the RM group compared to 7.7% in the control group ($p < 0,005$).

RM is recommended for arrhythmic burden quantification [6,7] and for the early detection of asymptomatic atrial fibrillation (AF) [20]. RM may early identify both symptomatic and asymptomatic AF episodes with a sensitivity of 95% [21,22].

Data from the ASSERT [23] study showed that subclinical atrial tachyarrhythmias were frequently detected in CIED patients and were associated with a significantly higher risk of ischemic stroke or systemic embolism. Despite the higher risk of thromboembolic events, a temporal relationship between subclinical AF and systemic or cerebral embolic event was not confirmed in a subsequent study [24].

Since RM can detect AF from 1 to 5 months in advance compared to in-office visits, it may allow an early anticoagulant therapy according to the thromboembolic risk and the duration of atrial fibrillation episode. Moreover, it helps to assess the need of cardioversion, device reprogramming, biventricular pacing rate optimization and the identification of others associated arrhythmias [25,26]. The impact of RM to reduce the hospitalization secondary to atrial or ventricular arrhythmias has been assessed in the COMPAS [11] study. Patients with RM experienced less hospitalization with a prevalence of 2.4%, compared to 7.3% in the control group. Although there were few ischemic events, the study also showed a reduction of ischemic stroke (0.8% in RM group vs 3.3% in the control group). Similarly TRUST [9] study demonstrated a significant reduction in time to AF diagnosis in patients followed with RM compared to the control group (5.5 vs 40 days). Although the aforementioned studies demonstrated a benefit of RM, the IMPACT study did not show any benefit in thromboembolism prevention and bleeding associated with an early initiation and interruption of anticoagulation based on remotely atrial tachyarrhythmias detection [27]. The lack of benefit in the IMPACT study may be related to a lower thromboembolic risk in patients with atrial high-rate episodes

(AHRE) compared to patients with documented AF [23]. Moreover, the utility of anticoagulant therapy in patients with AHRE lasting <24 h is still under investigation and further study, such as ARTESIA and NOAH, are ongoing to understand the best treatment in this setting [28,29].

4. Heart failure and RM

HF is the major and growing public health issue, characterized by steep morbidity and mortality rates, and high costs [30] and it has become a leading cause of hospital admission worldwide. In this regard the EVOLVO study [12] showed a reduction of 35% in urgent admissions and 21% in urgent follow-up visits for worsening heart failure (HF) in the RM arm, even though this study was not powered to demonstrate clinical benefit (because it enrolled only 200 patients).

A substantial proportion of this poor outcome appears to be mainly related to HF progression [31]. As such, an early detection of precipitating factors leading to worsening HF may help to prevent death from HF progression, and facilitate the identification of the best strategies for these patients.

In this regard, RM may be a useful tool to identify patients at risk of worsening HF by using specific algorithms to detect early signs of HF decompensation [32–34]. Despite several algorithms have been developed to identify an early worsening HF, the generalizability, incremental value, and cost-effectiveness of device algorithms continue to be questionable [34] and the RM role remains challenged.

In this sense, RCT have reported controversial data. Specifically, the PARTNERS HF study [35], which enrolled chronic HF patients with CRT-D equipped with intrathoracic impendence monitoring, showed that RM was an effective tool to identify patients at risk of HF hospitalization at 30 days. Similarly, CONNECT [15] study has demonstrated a shorter from clinical event to clinical decision, along with a significant reduction of mean length cardiovascular in-hospital stay in the RM patients. Importantly, the IN-TIME study [36] assessed the role of RM to reduce mortality in 664 HF patients with left ventricular ejection fraction no >35%, NYHA class II/III and dual chambers or biventricular ICD. Over a follow-up of 12 months, RM was associated with a significant lower mortality compared to no-RM arm (3.0 vs 8.2%; HR 0.36, IC 95% 0.17–0.74; $p = 0.004$). As confirm of RM effectiveness on hard endpoints, a recent meta-analysis of TRUST, ECOST, and IN-TIME, highlighted the positive role of RM to reduce all-cause mortality and the composite end-point of all-cause mortality or hospitalization for worsening HF, even though the benefit appeared to be mainly driven by the prevention of worsening HF [37].

Conversely, the MORE-CARE study [38], which randomized HF patients with CRT-D to RM VS in office-follow-up visits, failed to show a reduction of mortality, cardiovascular or device-related hospitalization in the RM arm. Of note, patients enrolled in this study, had a more advanced HF (NYHA class III/IV).

In line with the MORE-CARE results, in similar populations (1002 patients with ICD or CRT-D and history of HF) OPTILINK-HF failed to demonstrate a reduction of mortality and HF hospitalizations using the remotely transmission of fluid status alerts [39].

Ongoing, REM-HF demonstrated no benefit of RM in HF setting irrespective of the device implanted. Indeed, after a median follow up of 2.8 years, RM strategy using weekly downloads and a formalized follow up approach, failed to improve survival and cardiovascular hospitalizations rate in HF patients with CIED [40].

Thus, all the aforementioned studies have led to question the usefulness of RM in HF setting. However, these studies were heterogeneous in methodological quality, sample size, population, intervention, and control group care [34]. An important difference about the characteristics of the enrolled population should be noted.

Particularly, the MORE-CARE study included patients with more advanced HF, compared to patients enrolled IN-TIME trial [36]. Further it should be underlined that in the IN-TIME study RM management was standardized and a multiparametric approach was used, whereas the MORE-CARE study managed the RM according to local clinical practice.

Notably, a multiparametric approach has been also adopted in MONIC [41], HOMEGUIDE [21], Primary Nursing [22], IN-TIME mixed [36] studies, proving its effectiveness on different outcomes. Thus, the use of a multiparametric approach in selected symptomatic HF patients with reduced left ventricular ejection fraction (LVEF ≤ 35%) appears a reasonable approach.

Based on benefit of multiparametric approach, the most recent guidelines highlighted this strategy as an important tool for RM management in a HF setting [3].

However, the identification of several parameters and multiparametric scores able to predict an adverse outcome and the understanding on how to integrate RM in multidisciplinary models still represent an important goal. In this sense, MULTISENSE trial proposes a multiparametric score [42]. Specifically, the authors analyzed several parameters related to HF exacerbations such as first and third cardiac tone, their ratio, respiratory rate, heart rate, level of daily physical activity and thoracic impedance. These parameters integrated into the Heart Logic index were able to detect gradual HF worsening. The effectiveness of multiparametric evaluation of HF exacerbation is also emerged in the SELENE study [43].

Hence, the identification of the best multiparametric approach appears to be one of the most important aims in the future to raise the benefit of RM management in a HF setting.

5. Economic analysis of remote monitoring of cardiac implantable electronic devices

Three recent trials (CHAMPION [44], REM-HF and MORE-CARE) analyzed cost-effectiveness of RM. However, an appropriate economic comparison across the studies is challenging, due to differences in study design and the local variability in the socioeconomic context and the health system structure. Also, some inequalities appear across different countries, in the financing, organization, access, delivery, quality and effectiveness of cardiac care, thus all cost-saving results are reliable only in the context in which they have been analyzed [45]. The use of RM seems associated to a reduction in staff time and costs compared with standard care. Therefore, in the MORE-CARE, the RM showed a significant 38% reduction of the composite endpoint of healthcare resources utilization (i.e. cardiovascular hospitalizations, emergency department admissions for cardiovascular causes and in office follow ups), mainly driven by reduction of in office visits [38].

Furthermore, the CHAMPION study [44] analyzed cost-effectiveness data on RM. According to the results of the study, greater advantage has been found in HF patients with LVEF >40%.

However, REM-HF [40] did not demonstrated any benefit in terms of cost-effectiveness associated with RM. Finally, in a recent registry study (TARIFF) [46] an economic analysis of RM of CIED has been performed, confirming that RM is useful from both perspective of health care system and patients. Therefore, the overall mean annual cost per patient was significantly lower in the RM group than in the standard care group (respectively, €482.87 ± €2488.10 vs €1044.89 ± €1990.47; $p < 0.0001$), with a reduction of 53.87% achieved in the RM group, mainly driven by the cost of cardiovascular hospitalizations. Although the quality of life was not significantly different between groups, the number of in-office follow-ups was lowered by 58.78% in the RM group. Authors concluded that an introduction of an appropriate reimbursement could encourage a widespread adoption of RM [46].

6. Clinical management

The management of in office-follow-up needs significant reassessment after the spread of RM. Every nurse and physician should accurately define assignment and responsibilities [47]. Every patient should be assigned to a referring nurse and a supervising physician.

The referring nurse should be an expert in cardiac pacing and device follow-up. The principal tasks of the nurse are patient education, website data introduction, alert revision, data screening, revision of critical cases with the supervising physician, and monitoring of patient compliance. Conversely, the physician should obtain the informed consent, control and supervise the organization, evaluate the critical clinical cases, contact the general physician and other specialists and monitor the security of recorded data. The reaction to the alert should be performed after a pre-defined time, because it represents a critical variable of service quality according to the possibilities of the hospital. The referring nurse should have a dedicated e-mail address to receive alerts and reports. A daily connection with website should be performed to evaluate received alerts. Despite alerts, a periodical revision of data from every patient should be realized to identify false negatives and verify the proper programming of alerts. The daily check of a potentially threatening alert is the main advantage of RM compared to the traditional in office follow-up. In the aforementioned paragraphs the significant reduction of the delay between arrhythmic event and the medical diagnosis and treatment was widely analyzed (i.e. in TRUST [9] study, the delay was reduced from 36 days to 1 day for ventricular fibrillation and from 28 days to 1 day for ventricular tachycardia) (Table 1). Every center must define a written decision algorithm in order to standardize process of alerts. According to the protocol, the referring nurse must discuss critical cases with the supervising physician to have a clinical evaluation. In case of an interruption of the transmission, patient should be called to verify the integrity of the transmission system and if necessary, an unscheduled visit should be programmed to change the transmission unit [48]. After device implantation, a first in office follow-up must be done to verify system stability and to program the device. A yearly in office-follow-up should be performed in order to realize a complete clinical evaluation.

In recent years there has been a growing concern about the emerging issue related to legal aspects of RM, such as the confidentiality of the data, privacy of the patient and medical liability for omitting RM alerts or neglecting transmission revision, including the maximum reaction time. Nowadays, this topic remains unclear because it has not been adequately clarified by any specific legislation appropriately addressing emerging challenges. The patient must be warned that RM cannot be used for remote programming and nor should the remote system be considered an emergency tool although it could be useful to enhance device surveillance and patient management. Patients have to be aware of scheduling for alert and transmission revision by signing an informed consent document so that general rules for patient RM can be defined.

Table 1

HM: home monitoring; ICD: implantable, cardioverter defibrillator; PMK: pacemaker; RM: remote monitoring; CRT-D: cardiac resynchronization therapy, defibrillator; LVEF: left ventricular ejection fraction; HF: heart failure; FU: follow up; NHYA: New York Heart Association.

Clinical evidence of remote monitoring						
Study	Year	Type of study	Number of patients	Inclusion criteria	FU months	Results
TRUST [9]	2010	Multicentric, prospective, randomized	1339	Biotronik HM ICD single/dual chambers, non-PMK dependent	12.0	- Reduction of in office follow up from 3.8 patients/year in control group to 2.1 patients/year in RM, $p < 0.001$ - Non-inferiority in adverse events (10.4% in both groups at 12 months, $p = 0.005$) - decrease in the delay event-detection >30 days in RM group, $p < 0.001$
EVOLVO [12]	2012	Multicentric, prospective, randomized	200	Medtronic ICD or CRT-D LVEF ≤ 35%	16.0	-number of events: 0.59 in RM vs 0.93 in office per patient/year, $p = 0.005$ - Reduction of emergency admission of urgent follow up for HF, arrhythmia or ICD related events. 4.4 in RM group vs 5.7 in control group, $p < 0.001$ -Decrease in the delay event-detection from 1.4 days in RM group vs 24.8 days in control group, $p < 0.001$
REFORM [10]	2013	Randomized, parallel	155	ICD implanted according to MADIT II criteria	24	-Reduction of in office FU of 58% ($p < 0.001$). -trend of reduction of unscheduled FU (0.27 in RM vs 0.64 in control group, $p = 0.03$) - No differences on mortality
COMPAS [11]	2011	Multicentric, randomized	538	Biotronik PM DDD, non-PMK dependent	18	- Reduction of major adverse events 17.3% in RM vs 19.1% in control group ($p < 0.01$ for non-inferiority) - Decrease of hospitalizations due to PMK complications in RM (0.4% RM vs 2.8% in control group, $p < 0.05$) - Reduction of 56% in unscheduled follow up in RM ($p < 0,001$)
CONNECT [15]	2011	Multicentric, prospective, randomized	1997	Medtronic ICD or CRT-D	12.0	- decrease in the delay event-detection from 22 days (in-office group) vs 4.6 days (RM group) $p < 0.001$ - Reduction of mean hospitalization duration (3.2 days in RM vs 4.3 days in control group, $p = 0.002$)
ECOST [18]	2012	Multicentric, prospective, randomized	433	ICD single and dual chamber except NYHA class IV	24.2	- Reduction of major adverse events 40.3% in RM vs 43.3% in control group ($p < 0.05$ for non-inferiority) -Decrease of hospitalizations due to PMK complications in RM (0.4% RM vs 2.8% control, $p < 0.05$) - Reduction of 71% in appropriate and inappropriate shocks in RM ($p < 0.05$) Increase of battery lifespan in RM ($p < 0.02$)
EVATEL [19]	2012	Multicentric, prospective, randomized	1.501	ICD single and dual chamber in primary or secondary prevention	12.0	- Significant reduction of inappropriate shocks - No mortality differences
IN TIME [36]	2014	Multicentric, parallel, randomized	716	ICD or CRT-D, LVEF ≤ 35% Class NYHA II -III, HF history >3 months	12.0	- Reduction of worsening HF symptoms in 18.9% of RM group vs 27.2% in control group, $p = 0.013$ - Reduction of all-cause mortality in RM group (3.4% vs 8.7% in control group, $p = 0.004$) - No difference in HF admissions, $p = 0.38$
MORE CARE [38]	2013	Multicentric, prospective, randomized	865	CRT-D, LVEF ≤ 35% NYHA class III - IV,QRS >120 ms	12.0	- Cardiovascular hospitalizations 27.3% in RM and 26.7% in control group ($p = 0.80$). total mortality at 2 years 11.2% in RM and 9.4% in control group. Cardiovascular mortality at 2 years 8.2% in RM and 7.8% in control group -Decrease in the delay event-detection from 2 days in RM vs 29 days in control group, $p = 0.004$

7. Meta-analysis of published trials

Among 9 studies, five contributed to the meta-analysis of mortality and six to hospitalizations [Appendix 1]. As shown in Fig. 1A there was a reduction in mortality of risk ratio around 16% in favour of RM. (I^2 = 48.7%; [Fig. 1B]; Egger's Intercept = 1.86; tau = 0.53; p = 0.62; Begg and Mazumdar rank correlation tau = 0.4; p = 0.46).

Only five studies reported complete data which allowed us to perform a meta-analysis of mortality. Interestingly, people undergoing RM had a risk ratio of death around 16% lower than those who had no RM. This result confirms the findings of the IN TIME trial as previously reported [36].

The hazard risk in patients not undergoing RM was 15% higher as illustrated in Fig. 2A. (I^2 = 48.3; [Fig. 2B]; Egger's Intercept = 0.44; tau 0.1; p = 0.85; Begg and Mazumdar rank correlation tau = 0.06; p = 0.85.
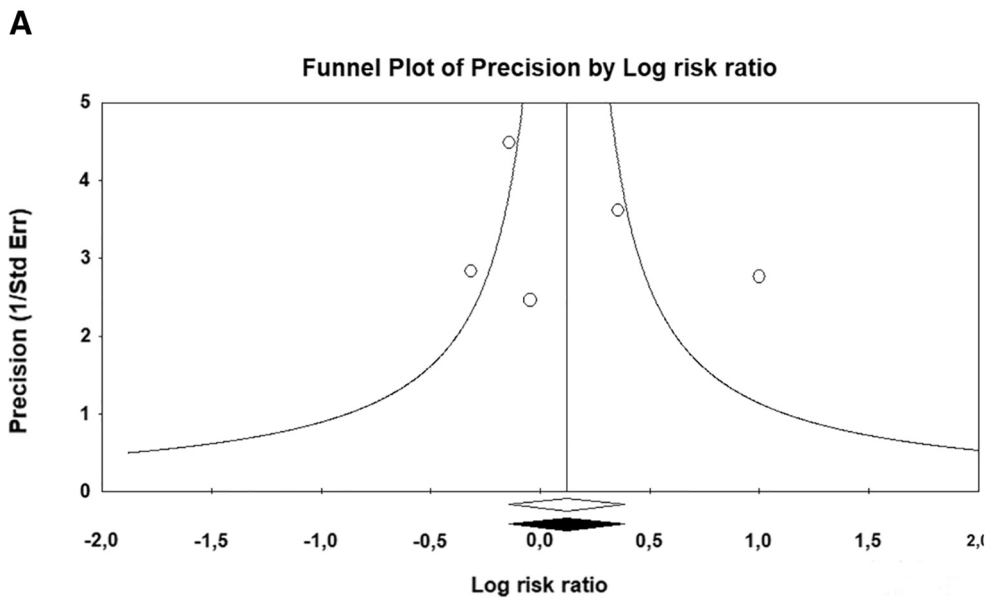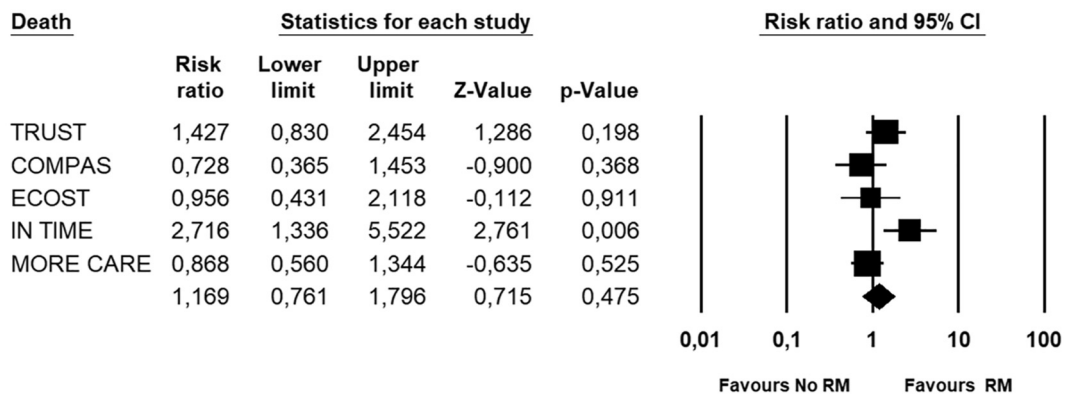
RM could represent an important strategy in order to reduce mortality and hospitalization, especially guided by the reduction of hospitalizations for decompensated HF. As discussed above, predisposing factors to worsening HF such as the onset of atrial and ventricular arrhythmia, an increased number of ventricular ectopic beats, a reduced percentage of biventricular pacing, a reduced daily physical activity of the patient may alert the referring center to take rapid preventing measures.
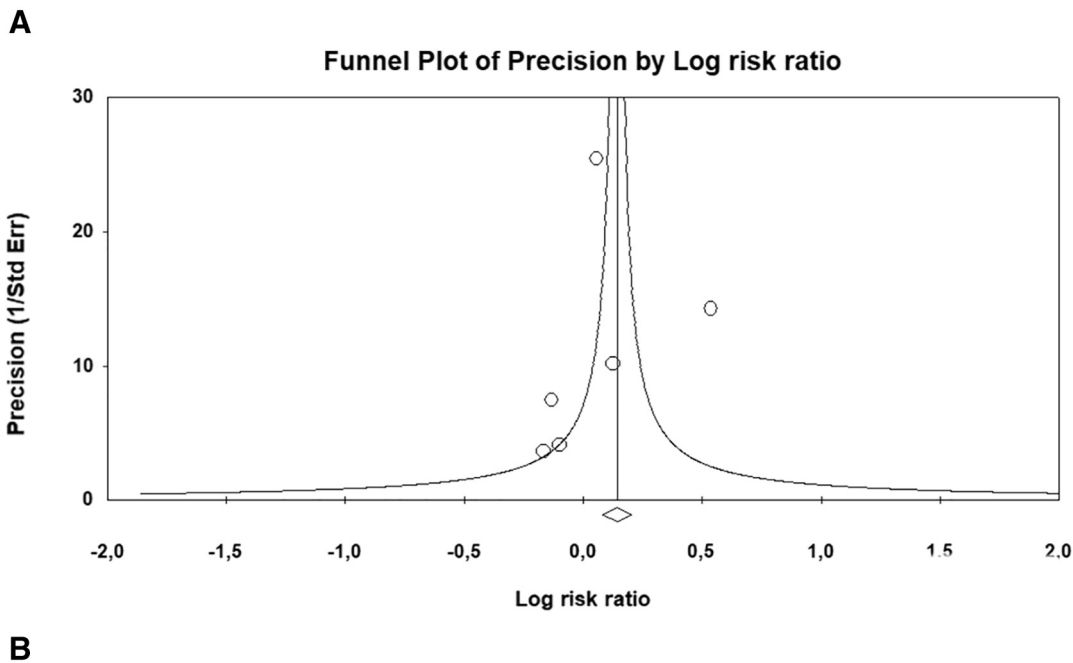
8. Future perspectives

RM is continuously evolving and could become the standard of care in every center, not only in large volume hospitals. The main problem is the lack of uniform reimbursement between countries. Furthermore, RM needs a better organization to overcome alerts received, because it is not an emergency system.

In the future, it could be possible to overcome technological barriers and privacy concerns and to program devices remotely. This opportunity may become important especially for patients living in remote

Death	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
TRUST	1,427	0,830	2,454	1,286	0,198
COMPAS	0,728	0,365	1,453	-0,900	0,368
ECOST	0,956	0,431	2,118	-0,112	0,911
IN TIME	2,716	1,336	5,522	2,761	0,006
MORE CARE	0,868	0,560	1,344	-0,635	0,525
	1,169	0,761	1,796	0,715	0,475

A

B

Fig. 1. A: Forest Plot of the comparison between RM and no RM for mortality. This shows a reduction in mortality of risk ratio around 16% in favour of RM. (I^2 = 48.7%) The low I square shows a low-moderate heterogeneity of the studies included in the paper (see Statistics section). B: Funnel Plot of the comparison between RM and no RM for mortality. Egger's Intercept = 1.86; tau = 0.53; p = 0.62; Begg and Mazumdar rank correlation tau = 0.4; p = 0.46. Both tests were not significant hence we can assume a low bias of the study (see Statistics section).

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
TRUST	1,713	1,492	1,965	7,665	0,000
EVOLVO	0,877	0,674	1,140	-0,979	0,327
COMPAS	0,906	0,565	1,455	-0,408	0,683
EVATEL	1,133	0,934	1,375	1,267	0,205
IN TIME	0,847	0,496	1,446	-0,610	0,542
MORE CARE	1,058	0,979	1,143	1,430	0,153
	1,152	1,084	1,225	4,568	0,000

Statistics for each study

Risk ratio and 95% CI

Favours No-RM   Favours RM

A

B
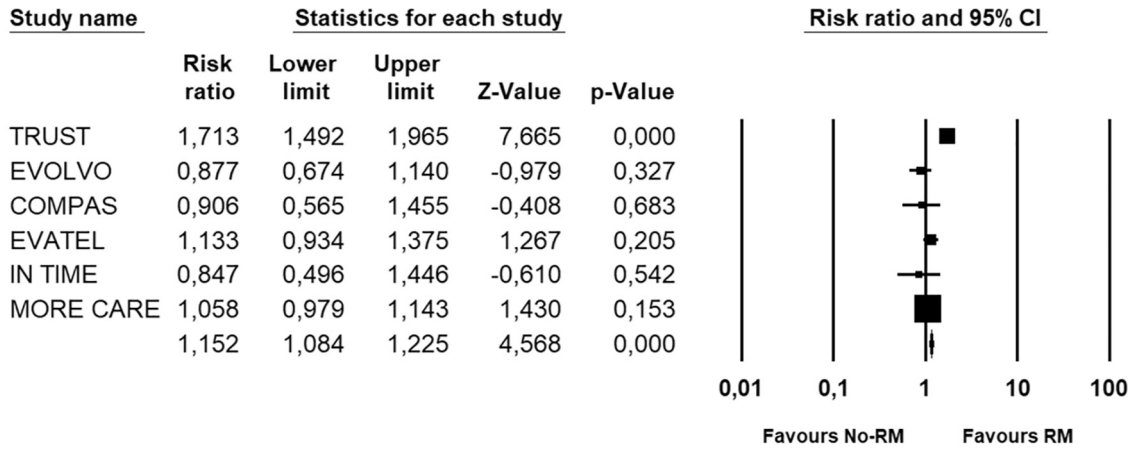
Fig. 2. A: Forest Plot of the comparison between RM and no RM for hospitalizations. The hazard risk of hospitalization in patients not undergoing RM was 15% higher as illustrated. ($I^2 =$ 48.3). The low I square shows a low-moderate heterogeneity of the studies included in the paper (see Statistics section). B: Funnel Plot of the comparison between RM and no RM for hospitalizations. Egger's Intercept = 0.44; tau 0.1; $p = 0.85$; Begg and Mazumdar rank correlation tau =0.06; $p = 0.85$. Both tests were not significant hence we can assume a low bias of the study (see Statistics section).

geographic locations, and for the management of recalls suitable to reprogramming.

Using specific apps in smartphones, patients may have the ability to check the website with information about their own device and communicate with the responsible doctor and nurses.

9. Conclusions

As highlighted recently, the next years will be inevitably characterized by an enormous development of technologies, which will influence patients' management. The benefit coming from RM has been demonstrated not only in terms of clinical effectiveness, but also of costs saving. Moreover, the benefit appears relevant in the reduction of close in-office visits with an easier remote management of CIED patients. HF patients could benefit from remote clinical management using a

multiparametric analysis of transmitted data, which integrate technical information about the device with clinical information about the patient.

As other innovations in telemedicine, RM success requires a standardization of process and a correct integration of the system in a management model, which involves different physicians and health care professionals.

9.1. Statistics

Where possible a meta-analysis was performed. Risk ratio and 95% confidence interval (C.I.) served as primary index statistics for dichotomous outcomes. To overcome the degree of potential heterogeneity of the studies random effects model was applied and I^2 test was performed.

It examines the percentage of interstudy variation, with values ranging from 0% to 100%. An I^2 value <40% indicates no obvious heterogeneity, values between 40% and 70% suggest moderate heterogeneity, and I^2 >70% were considered high heterogeneity.

Furthermore, potential publication bias was evaluated for the primary endpoint by constructing a "funnel plot" which the standard error of the log risk ratio was plotted against the risk ratio. The asymmetry of the plot was estimated both visually and tested by Egger's and Beg and Mazumdar tests. If these tests provide a significant result, it means that the funnel plot is asymmetric. In other words, small studies (i.e., with smaller precision) show larger effect sizes. In contrast, if the tests fail to detect asymmetry ($p = ns$) we can assume a low publication bias.

Comprehensive Meta-Analysis, v.2 (Biostat, Englewood Cliffs, NJ) was used for statistical computations. All p values <0.05 were considered statistically significant and reported as two-sided.

References

[1] A.E. Epstein, J.P. Di Marco, K.A. Ellenbogen, et al., ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities, Circulation 117 (21) (2008) (e350 LP-e408).

[2] S.G. Priori, C. Blomström-Lundqvist, A. Mazzanti, et al., 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC), Eur. Heart J. 36 (41) (2015) 2793–2867.

[3] M. Brignole, A. Auricchio, G. Baron-Esquivias, et al., 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on Cardiac Pacing and Resynchronization Therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association, Europace 15 (8) (2013) 1070–1118.

[4] B.L. Wilkoff, A. Auricchio, J. Brugada, et al., HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations: developed in partnership with the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA); and in collaboration with the American College of Cardiology (ACC), the American Heart Association (AHA), the European Society of Cardiology (ESC), the Heart Failure Association of ESC (HFA), and the Heart Failure Society of America (HFSA). Endorsed by the Heart Rhythm Society, the European Heart Rhythm Association (a registered branch of the ESC), the American College of Cardiology, the American Heart Association, Europace 10 (6) (2008) 707–725.

[5] N. Varma, P. Brugada, Automatic remote monitoring: is there a need? Europace 15 (suppl_1) (2013) i1–i2.

[6] S. Dubner, A. Auricchio, J.S. Steinberg, et al., ISHNE/EHRA expert consensus on remote monitoring of cardiovascular implantable electronic devices (CIEDs), Europace 14 (2) (2012) 278–293.

[7] D. Slotwiner, N. Varma, J.G. Akar, et al., HRS expert consensus statement on remote interrogation and monitoring for cardiovascular implantable electronic devices, Heart Rhythm. 12 (7) (2015) e69–100.

[8] R.P. Ricci, L. Morichelli, L. Quarta, et al., Effect of daily remote monitoring on pacemaker longevity: a retrospective analysis, Heart Rhythm. 12 (2) (2018) 330–337.

[9] N. Varma, A.E. Epstein, A. Irimpen, R. Schweikert, C. Love, TRUST Investigators, Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: the Lumos-T safely reduces routine office device follow-up (TRUST) trial, Circulation 122 (4) (2010) 325–332.

[10] G. Hindricks, C. Elsner, C. Piorkowski, et al., Quarterly vs. yearly clinical follow-up of remotely monitored recipients of prophylactic implantable cardioverter-defibrillators: results of the REFORM trial, Eur. Heart J. 35 (2) (2014) 98–105.

[11] P. Mabo, F. Victor, P. Bazin, et al., A randomized trial of long-term remote monitoring of pacemaker recipients (the COMPAS trial), Eur. Heart J. 33 (9) (2012) 1105–1111.

[12] M. Landolina, G.B. Perego, M. Lunati, et al., Remote monitoring reduces healthcare use and improves quality of care in heart failure patients with implantable defibrillators: the evolution of management strategies of heart failure patients with implantable defibrillators (EVOLVO) study, Circulation 125 (24) (2012) 2985–2992.

[13] L.A. Saxon, D.L. Hayes, F.R. Gilliam, et al., Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: the ALTITUDE survival study, Circulation 122 (23) (2010) 2359–2367.

[14] N. Varma, J.P. Piccini, J. Snell, A. Fischer, N. Dalal, S. Mittal, The relationship between level of adherence to automatic wireless remote monitoring and survival in pacemaker and defibrillator patients, J. Am. Coll. Cardiol. 65 (24) (2015) 2601–2610.

[15] G.H. Crossley, A. Boyle, H. Vitense, Y. Chang, R.H. Mead, The CONNECT (clinical evaluation of remote notification to reduce time to clinical decision) trial: the value of wireless remote monitoring with automatic clinician alerts, J. Am. Coll. Cardiol. 57 (10) (2011) 1181–1189.

[16] N. Varma, J. Michalski, A.E. Epstein, R. Schweikert, Automatic remote monitoring of implantable cardioverter-defibrillator lead and generator performance the lumos-T safely reduces routine office device follow-up (TRUST) trial, Circ. Arrhythm. Electrophysiol. 3 (5) (2010) 428–436.

[17] N. Varma, M.A. Johnson, Prevalence of cancelled shock therapy and relationship to shock delivery in recipients of implantable cardioverter-defibrillators assessed by remote monitoring, Pacing Clin. Electrophysiol. 32 (Suppl. 1) (2009) S42–S46.

[18] L. Guédon-Moreau, D. Lacroix, N. Sadoul, et al., A randomized study of remote follow-up of implantable cardioverter defibrillators: safety and efficacy report of the ECOST trial, Eur. Heart J. 34 (8) (2013) 605–614.

[19] P. Mabo, P. Defaye, N. Sadoul, et al., Remote follow-up of patients implanted with an ICD: the prospective randomized EVATEL study (abstr), Heart Rhythm. 9 (Suppl) (2012) S226–S227.

[20] T. Sanna, H.-C. Diener, R.S. Passman, et al., Cryptogenic stroke and underlying atrial fibrillation, N. Engl. J. Med. 370 (26) (2014) 2478–2486.

[21] R.P. Ricci, L. Morichelli, A. D'Onofrio, et al., Effectiveness of remote monitoring of CIEDs in detection and treatment of clinical and device-related cardiovascular events in daily practice: the home guide registry, Europace 15 (7) (2013) 970–977.

[22] R.P. Ricci, L. Morichelli, M. Santini, Remote control of implanted devices through home monitoring technology improves detection and clinical management of atrial fibrillation, Europace 11 (1) (2009) 54–61.

[23] J.S. Healey, S.J. Connolly, M.R. Gold, et al., Subclinical atrial fibrillation and the risk of stroke, N. Engl. J. Med. 366 (2) (2012) 120–129.

[24] M. Brambatti, S.J. Connolly, M.R. Gold, et al., Temporal relationship between subclinical atrial fibrillation and embolic events, Circulation 129 (21) (2014) 2094–2099.

[25] G.L. Botto, L. Padeletti, M. Santini, et al., Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events, J. Cardiovasc. Electrophysiol. 20 (3) (2009) 241–248.

[26] R.P. Ricci, L. Morichelli, A. Gargaro, M.T. Laudadio, M. Santini, Home monitoring in patients with implantable cardiac devices: is there a potential reduction of stroke risk? Results from a computer model tested through Monte Carlo simulations, J. Cardiovasc. Electrophysiol. 20 (1540–8167) (2009) 1244–1251.

[27] D.T. Martin, M.M. Bersohn, A.L. Waldo, et al., Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices, Eur. Heart J. 36 (26) (2015) 1660–1668.

[28] R.D. Lopes, M. Alings, S.J. Connolly, et al., Rationale and design of the Apixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA) trial, Am. Heart J. 189 (2018) 137–145.

[29] P. Kirchhof, B.F. Blank, M. Calvert, et al., Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the non–vitamin K antagonist oral anticoagulants in patients with atrial high rate episodes (NOAH–AFNET 6) trial, Am. Heart J. 190 (2017) 12–18.

[30] D. Lloyd-Jones, R.J. Adams, T.M. Brown, et al., Executive summary: heart disease and stroke statistics-2010 update: a report from the American Heart Association, Circulation 121 (7) (2010) 948–954.

[31] A. Iorio, F. Rea, G. Barbati, et al., HF progression among outpatients with HF in a community setting, Int. J. Cardiol. 277 (2019) 140–146 (S0167-5273 (18)34223-2).

[32] D. Vollmann, H. Nägele, P. Schauerte, et al., Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure, Eur. Heart J. 28 (15) (2007) 1835–1840.

[33] V.M. Conraads, L. Tavazzi, M. Santini, et al., Sensitivity and positive predictive value of implantable intrathoracic impedance monitoring as a predictor of heart failure hospitalizations: the SENSE-HF trial, Eur. Heart J. 32 (18) (2011) 2266–2273.

[34] N.M. Hawkins, S.A. Virani, M. Sperrin, I.E. Buchan, J.J.V. McMurray, A.D. Krahn, Predicting heart failure decompensation using cardiac implantable electronic devices: a review of practices and challenges, Eur. J. Heart Fail. 18 (8) (2015) 977–986.

[35] D.J. Whellan, K.T. Ousdigian, S.M. Al-Khatib, et al., Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study, J. Am. Coll. Cardiol. 55 (17) (2010) 1803–1810.

[36] G. Hindricks, M. Taborsky, M. Glikson, et al., Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial, Lancet. 384 (9943) (2018) 583–590.

[37] G. Hindricks, N. Varma, S. Kacet, et al., Daily remote monitoring of implantable cardioverter-defibrillators: insights from the pooled patient-level data from three randomized controlled trials (IN-TIME, ECOST, TRUST), Eur. Heart J. 38 (2017) 1749–1755.

[38] B. Giuseppe, D.C. Antoine, Q. Aurelio, et al., Effects of remote monitoring on clinical outcomes and use of healthcare resources in heart failure patients with biventricular defibrillators: results of the MORE-CARE multicentre randomized controlled trial, Eur. J. Heart Fail. 19 (3) (2016) 416–425.

[39] M. Bohm, H. Drexler, H. Oswald, et al., Fluid status telemedicine alerts for heart failure: a randomized controlled trial, Eur. Heart J. 37 (2016) 3154–3163.

[40] J.M. Morgan, S. Kitt, J. Gill, et al., Remote management of heart failure using implantable electronic devices, Eur. Heart J. 38 (30) (2017) 2352–2360.

[41] T. Vogtmann, S. Stiller, A. Marek, S. Kespohl, M. Gomer, V. Kühlkamp, et al., Workload and usefulness of daily, centralized home monitoring for patients treated with CIEDs: results of the MoniC (Model Project Monitor Centre) prospective multicentre study, Europace 15 (2) (2013) 219–226.

[42] J.P. Boehmer, R. Hariharan, F.G. Devecchi, et al., A multisensor algorithm predicts heart failure events in patients with implanted devices: results of the MultiSENSE study, JACC Heart Fail. 5 (3) (2017) 216–225.

[43] L. Padeletti, G.L. Botto, A. Curnis, et al., Selection of potential predictors of worsening heart failure: rational and design of the SELENE HF study, J Cardiovasc. Med. (Hagerstown) 16 (11) (2015).

[44] W.T. Abraham, L.W. Stevenson, R.C. Bourge, J.A. Lindenfeld, J.G. Bauman, P.B. Adamson, Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial, Lancet. 387 (10017) (2018) 453–461.

[45] L. Tavazzi, J.S. Borer, G. Tavazzi, Use and disuse of observational research: the case of remote monitoring in heart failure, Cardiology 137 (1) (2017) 14–19.

[46] R.P. Ricci, A. Vicentini, A. D'Onofrio, et al., Economic analysis of remote monitoring of cardiac implantable electronic devices: results of the health economics evaluation registry for remote follow-up (TARIFF) study, Heart Rhythm. 14 (1) (2018) 50–57.

[47] R.P. Ricci, L. Morichelli, M. Santini, Home monitoring remote control of pacemaker and implantable cardioverter defibrillator patients in clinical practice: impact on medical management and health-care resource utilization, Europace 10 (2008) 164–170.

[48] R.P. Ricci, G. Calcagnini, A. Castro, F. Giada, D. Igidbashan, M. Landolina, D. Melissano, G.B. Perego, T. Toselli, Consensus document on remote monitoring of cardiac implantable electronic devices: technology, indications, organizational models, acceptability, responsibility, and economic issues, G. Ital. Cardiol. (Rome). 12 (6) (2011) 450–467.