Current clinical evidence for remote patient management

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Remote patient management is an act of telemedicine that can be practiced in the form of ‘remote follow-up’ or as ‘remote monitoring’. Pacemaker (PM) and implantable cardioverter defibrillator (ICD) patients are ideally suited to remote management.1 On the one hand, at a remote follow-up, it is easy to inquire about symptoms in order to adjust, for example, medical treatment. It is also easy to remotely check the data contained in their device (related to arrhythmias and technical parameters) either because the system can update and make available the data daily, or because the data have been transmitted on a scheduled basis on the day of the remote visit. On the other hand, these devices are ideally suited for remote monitoring, either for strictly event-monitoring through alerts, which may lead to patient contact depending on their clinical relevance,2 or for scheduled monitoring on a regular basis (web site data display without an alert). The initial interest for remote management of PM/ICD recipients was to resolve the problem of distance from the hospital for some patients which made in-person evaluation difficult and expensive travel, especially when increased frequency of visits to the hospital.3 Then, the convenience was recognized for clinics themselves—remote management saved physician and nurse time in an era of growing numbers of PM/ICD patients, while maintaining the patient satisfaction.4 Most importantly, physicians realized that remote management had very important potential benefits to improve the quality of care.5,6 This is because remote monitoring enabled early diagnosis3,7 of technical or arrhythmic issues. The very promising results of these early studies, some of them being small retrospective analyses or registries, led to the conduction of large randomized trials in order to provide a high level of evidence for the multiple advantages of remote patient management. Here, we report the results of these large clinical trials (Table 1). To analyse their results, it is necessary to understand the respective methodologies employed8–10 and, critically, the operating mode of the remote monitoring system used. Indeed, each of the five ICD manufacturers has its own monitoring system with its own particular features.

The first large randomized trial of remote monitoring was TRUST, which utilized Biotronik Home Monitoring® technology.11 TRUST randomized almost 1500 patients to remote management, with a single scheduled in-person visit per year and three remote follow-ups vs. conventional care with four scheduled face-to-face evaluations. Remote patient management promoted greater adherence to long-term follow-up, and did not increase the incidence of major adverse events such as death, incidence of stroke, and events requiring cardiac surgical interventions (e.g. device explantations or lead revision). When inclusive of all patient encounters (i.e. scheduled and unscheduled), health-care utilization was reduced by ~50% (Figure 1 left). The second important endpoint of TRUST was early detection during continuous remote monitoring. Despite extension

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of face-to-face encounters, evaluation of symptomatic was advanced to 2 days compared with over 1 month in conventional care. Median time from onset to physician evaluation of combined first atrial fibrillation (AF), ventricular tachycardia, and ventricular fibrillation (VF) events in Home Monitoring was 1 day, dramatically less than the value in conventional care of 35.5 days (Figure 1, middle). Importantly, this early detection ability was maintained for silent problems (Figure 1, right).

The benefits of remote monitoring were evaluated in PM recipients in the COMPAS trial, also using Biotronik Home Monitoring®. This prospective randomized study including 538 patients with a conventional DDD PM indication showed that remote monitoring was as safe as conventional scheduled follow-ups during 18-months of follow-up in term of major adverse events, enabled the early detection of a variety of adverse events, and significantly decreased (36% reduction; Figure 2) the number of ambulatory follow-up visits. Interestingly, the results suggested that remote monitoring could have an impact to decrease atrial arrhythmia and stroke-related hospitalizations. However, the trial was not powered to address these endpoints, nor for heart failure-related hospitalizations and these must be further studied.

The CONNECT study in ICD patients employed a different remote monitoring technology (Medtronic Carelink® Network) with the objective of determining whether automatic alerts reduces the time from a clinical event to a clinical decision in response to some arrhythmias, cardiovascular disease progression, and devices issues compared with patients receiving standard in-office care. Clinical events’ were defined as those generating an alert by the Carelink system. These included clinical events detected by the device [atrial tachycardia (AT)/AF daily burden ≥ 12 h per day, ventricular rate during AT/AF ≥ 120 b.p.m. for ≥ 6 h AT/AF per day, 2 shocks delivered, all therapies exhausted in a zone] and lead/device integrity events [lead impedance out of range, VF detection/therapy off, low battery voltage elective replacement index (ERI), and excessive charge time end of service]. Besides the automatic alerts to clinician from the ICDs of the remote arm, the last four events generated audible alerts for the patients of both remote and in-office arm. The time to clinical decision was defined as the time from device detection of the event to a decision being made in response to the event, as reported by the clinician or as evidenced by data obtained at interrogation. This large multicentre, prospective, randomized study included 1997 patients without permanent AF receiving an ICD or a cardiac resynchronization therapy-defibrillator (CRT-D). The entire device data were viewed by the physician every 3 months for 15 months, either remotely or in clinic according to the randomization group and two more in-clinic visits were performed at months 1 and 15. The results indicated that the median time from clinical event to clinical decision per patient was very significantly reduced from 22 days for the in-office care to 4.6 days for the remote monitoring. These results confirmed that earlier detection is one of the undeniable strengths of ICDs remote management.

The CONNECT study provokes some questions, firstly methodological, and then concerning the relevance of the endpoint. As the study was not blinded, the results for the primary end point are subject to caution because the evaluation criteria are not hard. For example, the investigator might have taken its decisions more quickly in the remote group to advantage this group. Then, 57% of the events did not trigger an automatic clinical alert because the alert was programmed off or the alert was not reset after being previously triggered. Moreover, because of technical issues, only 55% of the triggered alerts were successfully transmitted to the clinician. Such a huge loss of reporting power may be attributed to the lack of full maturity of this particular technology at the time of the study. The assessment of the time to decision should have taken into account events which failed to alert the clinician, as this represents application of this particular technology in real world practice.

The results from TRUST, COMPAS, and CONNECT illustrate the early detection ability of remote monitoring technologies. However, from our point of view, the reaction time is a relevant parameter only for some events. For instance, the onset of ERI or an excessive charge time may not require urgent intervention since a 3-month delay from the alert to change the device before end of life is generally authorized. In contrast, it is crucial to quickly reprogram the device to ensure the safety of the patient, e.g., if the VF zone has been programmed off in error (1.8% events in the CONNECT study). It also seems essential to quickly see a patient who received

<table>
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<th>Study name</th>
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<th>Methods</th>
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<td>Home Monitoring</td>
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<td>1450</td>
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<td>RCT</td>
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<td>Major adverse events</td>
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<tr>
<td>Guedon-Moreau</td>
<td>2012</td>
<td>ECOST</td>
<td>Home Monitoring</td>
<td>ICD</td>
<td>RCT</td>
<td>473</td>
<td>27 months</td>
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ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy-defibrillator; RCT, randomized clinical trial.
two shocks (chosen threshold to trigger an alert in CONNECT),
either in case of appropriate shocks to modify his antiarrhythmic
treatment or ATP programming, or, in case of inappropriate
shocks, to prevent recurrence. Also, it may be better to react to
the first shock. But in case of shock, the alert system has a merely
relative interest since in almost all cases it is a highly symptomatic
event that encourages the patient to contact his physician.
However, notification of antitachycardia pacing, which is asymptom-
atic, is very useful as evidenced by the ECOST study (see below).14
These alerts may sometimes presage electrical storms with multiple
shocks or heart failure, or, if inappropriate, the occurrence of in-
appropriate shocks. Atrial fibrillation alerts (83% events in the
CONNECT study) deserve a dedicated study to learn how they
should be managed since their urgency greatly depends on the
profile of the patient (e.g. CHADS score) in whom the event
occurs. Finally, the number and extent of outside-the-norm mea-
sures which command response is worth investigating, in the
context of multiple parameters provided by remote monitoring.
Depending on these thresholds, it might be excessive to react ur-
gently to a single out-of-range lead impedance alert. Repetitively ab-
normal values carry greater significance and requirement for
evaluation. But the reaction should be sufficiently early to avoid in-
appropriate shocks. The importance of engineering technology to
meet clinical demands is illustrated by this scenario. For instance,
a deficiency with the Carelink® system is that the ICD must be
interrogated with the programmer to allow the notification of a
second alert for the same parameter. This demands an otherwise
needless in-person encounter simply to maintain the system’s
early detection capability, for each notification feature.

The main objective of the ECOST study15 was to demonstrate the
safety of remote monitoring using Biotronik Home Monitoring® and
results strengthened and extended findings in TRUST. The primary
endpoint included a broad spectrum of serious adverse events, in-
cluding death from any cause, cardiovascular, and procedure- or
device-related major adverse effects, which were evaluated during
a long-term follow-up. An adverse event was considered as major
if it: (i) was fatal or life-threatening; (ii) prompted or prolonged a hos-
pitalization; (iii) caused major or permanent disability or injury; or (iv)
required an intervention to prevent permanent disability or injury.
Post-implantation, 433 patients were randomized either to the
remote follow-up group or to the control group. After a first
3-month follow-up, the patients of the two groups were seen by
the cardiac electrophysiologist in the ambulatory department once
a year and every 6 month respectively (i.e. less frequently than in
TRUST). The results indicated, as shown on Figure 3 that remote
monitoring was non-inferior to ambulatory follow-ups during a
24-month mean follow-up (i.e. a longer interval than in TRUST).
Similar observations were made in the per-protocol and the
intention-to-treat analyses. Results of ECOST secondary analyses
have high clinical value. Remote monitoring was associated with a
76% reduction of capacitor charges, exerting a favourable impact
on battery longevity. Moreover, Home Monitoring® reduced the
number of actually delivered shocks (−71%) (Figure 4) and was asso-
ciated with a 52% reduction in the number of patients with inappro-
priate shocks (with a 72% reduction in the risk of inappropriate
shock-related hospitalizations). Avoiding inappropriate shocks is one
of the most challenging aspects of ICD management. Although the
merits of correct programming of ICD detection parameters are
crucial to the occurrence of inappropriate therapies, the ECOST
study brought the novel observation that Home Monitoring® also
provides a tool to decrease the inappropriate therapy incidence.

The EVOLVO study focused on evaluating urgent in-office visits
for 200 patients with heart failure.16 It did not compare remote mon-
itoring vs. ambulatory follow-up, but rather on two strategies for
patient management. The devices were checked every 4 months, ex-
clusively at the hospital for patients in the control group and every 2
months remotely for patients in the remote group. During ambula-
tory visits patients were questioned about their symptoms and treat-
ment of heart failure could be adjusted. In addition, alert systems,
mainly for lead/device integrity, the AT/AF burden and intrathoracic

Figure 1 The TRUST trial. Home Monitoring (HM) reduced cardiac-resource utilization [scheduled and unscheduled clinic and hospital visits
(including responses to HM event notifications)] by 45% in 1 year (left) yet enabled early detection of arrhythmias (middle) and silent events
(right). Compiled with permission from Varma et al.11
 impedence (OptiVol) were in place for all patients, either as audible alerts in the control group, or as remote alerts with the Carelink® remote monitoring system. In the event of audible alert, an urgent visit had to be scheduled unless it was an OptiVol-related alert and the problem could be resolved by phone contact with the patient. In the event of remote alert, an urgent visit had to be scheduled only if needed after checking the ICD data on the Carelink® web site. The conclusion of the study is that remote monitoring reduced by 35% emergency department/urgent in-office visits. This reduction was not really a surprise as the study protocol imposed more urgent visits in the control group. Besides, one can question the need to urgently address the cause of most of the alerts that occurred during the study (21 AT/AF alerts and 4 lead/device integrity alerts, which include low battery voltage ERI). The EVOLVO study shows that remote monitoring increased the efficiency for health-care providers and improved quality of care by reducing the rate of ambulatory visits in heart failure patients. However, cardiologists still need to learn to more effectively manage patients with heart failure remotely.

Remote monitoring generates enormous data sets of real-world patients. Although not traditionally associated with the high level of evidence as defined in international guidelines, registry data of this form provide an opportunity for outcomes analyses otherwise unavailable. In the USA, the ALTITUDE study group coordinates research into relevant clinical questions using the Boston LATITUDE® patient management system database. Survival is determined from the Social Security Death Index, and device electrograms are adjudicated by an expert panel, with good inter-observer agreement. The ALTITUDE survival study of ICD and CRT device recipients implanted, for primary or secondary prevention of sudden cardiac death included 69 556 remotely networked patients compared with 116 222 patients followed up in device clinics only. The striking finding was that 1- and 5-year survival rate were higher for the patients receiving remote follow-up compared with patients receiving in-clinic follow-up with a 50% relative reduction in the risk of death [ICD hazard ratio (HR), 0.56; CRT-D HR, 0.45; P < 0.0001]. Despite the lack of randomization and the lack of clinical data, the conclusion stating that remote monitoring is able to favourably influence the survival is likely reliable given the study size. However, the terms of the study do not allow identifying the causes of this influence. The ALTITUDE group has also provided insights into several other issues, e.g. effects of programming on shocks incidence and success.18,19
ECOST study: Delivered shocks

Table: 1

<table>
<thead>
<tr>
<th>Total number of delivered shocks</th>
<th>Active</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>p&lt;0.05</td>
<td>657</td>
<td>193</td>
</tr>
<tr>
<td>Mean per patient-month: 0.04±0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients: 47</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Range [Nb shocks]: [0-33]</td>
<td>[0-116]</td>
<td></td>
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</table>

Figure 4 Remote Monitoring induced reduction in the risk of delivered shocks in the ECOST study.

Summary

Studies in remote patient management, initially with the modest aims of alleviating challenges with patient travel distance to hospital, more recently have highlighted much greater advantages. Large prospective trials, beginning with TRUST and following with ECOST, have consistently demonstrated safety and ability for early detection of device or patient problems. This latter, a feature of remote monitoring function (as opposed to remote follow-up), permits early clinical intervention when needed. This ability may have benefits for monitoring integrity and function of implanted hardware, morbidity from atrial fibrillation and heart failure and reducing the incidence of inappropriate shocks and charged shocks whether delivered or not. Moreover, it has a positive impact on the survival of patients. The medico economic analyses of some of these large randomized trials to further support use of remote monitoring are awaited.

In conclusion, large prospective randomized trials to date indicate that remote monitoring is clinically much more effective and efficient than conventional follow-up. Collectively, these results provide greater clinical evidence to guide future consensus and guideline development on CIED monitoring to spur adoption of a new standard.


References

20. Wilkoff BL, Aurichio A, Brugada J, Cowie M, Ellenbogen KA, Gillis AM 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