Telemonitoring of Outpatients with Heart Failure:

A Search for the Holy Grail?

Running title: van Veldhuisen et al.; Telemonitoring of outpatients with heart failure

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Heart failure (HF) remains a large medical problem, and prevention of decompensation and HF-related hospitalizations is important, not only for the patient, but also from an economic point of view. Close monitoring is crucial, and can be done through a whole spectrum of modalities. This ranges from a (nurse-based) disease management program, to structured telephone support, to remote or telemonitoring with or without the use of an implantable device.\textsuperscript{1-3}

Disease management programs, usually with a specialized nurse, and in the hospital are implemented on a large scale, but the optimal level and intensity of care is still unclear.\textsuperscript{4} Structured telephone support may be useful, and a recent meta-analysis showed a reduction in HF hospitalization, but no effect on mortality.\textsuperscript{2} Remote, home or tele-monitoring using a number of (relatively simple) non-invasive variables such as heart rate, blood pressure, and body weight was also examined in a number of studies, and the same meta-analysis showed that this method reduced both hospitalizations and mortality.\textsuperscript{2} However, 2 recent large studies not included in that analysis did not show such a positive effect.\textsuperscript{5,6} In the American TELE-HF (Telemonitoring to improve outcomes in HF) Study\textsuperscript{5} and in the German TIM-HF (Telemedical Intervention Monitoring in HF) study,\textsuperscript{6} which together randomized 2362 HF patients, no effect on HF hospitalizations or mortality was observed.

In recent years, a number of studies in the field of telemonitoring have been published that measured invasive variables. In the COMPASS-HF (Chronicle Offers Management To Patients with Advanced Signs and Symptoms of HF) study a strategy based on measurement of right-sided intracardiac pressures (with a special transvenous lead: Chronicle, Medtronic) was examined. The primary (composite) endpoint showed a non-significant 21% reduction, but there was a statistically significant, 36% reduction in the time to first hospitalization in the 301 patients studied.\textsuperscript{7} More recently, the results from CHAMPION (CardioMEMS Heart sensor

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Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF patients) have become available. In 550 patients, the value of daily measurement of pulmonary artery pressure measurements was examined. The device used has a passive, wireless, radiofrequency sensor without batteries or leads and results from the device were only available to the physician (through transmission) who could then change (increase) drug treatment. After 6 months, there was a significant 28% reduction in HF related hospitalizations in the treatment group.

Measurement of left-sided (atrial) pressures has only been examined in a small study, which showed potentially interesting findings, but this method may be more complicated, and large-scale data are awaited.

Some diagnostic variables can also be collected when built into an Implantable Cardioverter Defibrillator (ICD) or a Cardiac Resynchronization therapy (CRT) device. The use of ICD and CRT has markedly increased in recent years, and both have received a recommendation in HF patients with a decreased ejection fraction in current guidelines. The diagnostic variables which can be recorded using ICD/CRT devices include measurement of intrathoracic impedance to track changes in thoracic fluid content, heart rate variability, patients’ physical activity level and (atrial and ventricular) arrhythmias. In the PARTNERS (Program to Access and Review Trending Information and Evaluate Correlation to symptoms in patients with HF) study, an increased fluid index (or drop in intrathoracic impedance) was the most sensitive parameter to detect HF hospitalizations. A number of smaller studies measuring intrathoracic impedance (using Optivol, Medtronic) had also shown promising results, but two recent, larger studies failed to confirm these favorable findings. In the SENSE-HF (Sensitivity of InSync Sentry Optivol feature for the prediction of HF) study in 501 patients, the sensitivity of intrathoracic fluid monitoring changed over time, and was lower than earlier reported (up to
42% after 6 months), while the positive predictive value (and specificity) were also low. The DOT-HF (Diagnostic Outcome Trial in HF) was designed to examine whether ambulatory monitoring of intrathoracic fluid monitoring (with Optivol, Medtronic) could improve outcome in patients with HF. However, because of slow enrollment and changes in monitoring technology, the trial was stopped after only 345 of the planned 2400 patients were enrolled. Analysis of these 345 patients showed, that there was an increase of borderline statistical significance of the primary endpoint of all-cause mortality and HF hospitalizations in the (Optivol) access arm that was mainly due to the latter. The number of outpatient visits (“health care utilizations”) was also markedly (almost 3-fold) higher in the access arm.

In the present issue of Circulation, Landolina et al. present results of the EVOLVO (Evolution of management strategies of HF patients with implantable defibrillators) study. The authors enrolled 200 HF patients in six Italian sites, and in whom an ICD (90% CRT-D) had been implanted. The primary endpoint was the rate of emergency healthcare utilizations, defined as visits to the emergency department and urgent (unplanned) in-office visits, for heart failure, arrhythmias or ICD-related events. Half of the patients were randomized to the remote arm, in which all alerts regarding clinical management (intra-thoracic impedance for fluid accumulation monitoring, atrial arrhythmias and ICD-shocks) were turned on for wireless notification through the CareLink (Medtronic). Participating clinics checked a special website once daily for transmitted data. After 16 months follow-up, there was a 35% lower incidence of the primary endpoint in the remote arm than in the control arm (75 versus 117 events, incidence density: 0.59 versus 0.93 events/year, p=0.005). There was also a 21% reduction in total healthcare utilizations (p<0.001). No effect was observed regarding mortality (7 versus 8 deaths), or the number of hospitalizations (of which 76 of the 106 were for worsening of HF). The authors concluded that
remote monitoring reduced emergency department/urgent in-office visits and remarked that it increased efficiency for health care providers.

Although these data from the EVOLVO study\textsuperscript{15} are important and provide new information, some comments must be made. First, the benefit of the approach as described by the authors, was an “increased efficiency for health care providers and improved quality of care for HF patients”. Increased efficiency may be convenient for doctors and nurses, and leads to less anxiety for patients, and possibly lower costs. Less stress may have been present in EVOLVO, and indeed some but not all parameters of quality of life were favourably affected, but the relevance of this finding can be argued, if patients are aware of which of the study arms they participate in. Whether this approach leads to lower costs, we do not know, since they were not reported\textsuperscript{15}. Clearly, fewer urgent visits will reduce costs, but setting up and maintaining a system such as CareLink to analyze and act on transmitted data also carries a price tag, and it would be interesting to see a health-economics analysis of this EVOLVO study. Second, “improved quality of care” would hopefully improve outcome, i.e. reduce (heart failure) hospitalizations and ultimately, mortality, but those effects were not observed in the EVOLVO study. Clearly, the study was not powered for this, but trends were also not observed. Third, in patients in the remote arm, all audible alerts were off (apart from system-integrity alerts), since all alerts regarding clinical management were transmitted through the CareLink Network. In contrast, in patients in the control arm, the alerts were turned on for audible notification (only). Although the EVOLVO study was designed before the results of DOT-HF\textsuperscript{14} became available, it is somewhat remarkable that patients in the control arm received audible alerts, since it had not been proven at the time that such audible alerts would be beneficial. Indeed, given the negative findings of DOT-HF\textsuperscript{14}, this may have caused bias against the control arm. The authors report that 79 (of the
alerts were audible, and that many were apparently not recognized by the patients, or the clinician did not consider them relevant. Fourth and last, in the present study Optivol alerts (intrathoracic impedance changes) were again the most common alert condition (in 274/315 cases [87%] in the remote arm, and in 231/256 cases [90%] in the control arm), which agrees with earlier reports\textsuperscript{13,14}. In the remote arm, after the data were analyzed in more detail using the CareLink information, many patients could however, be reassured and alerts were (most likely) false positives. This brings into attention again sensitivity, but more importantly, specificity issues regarding the use of intrathoracic impedance monitoring\textsuperscript{13,14}. What can be concluded from the EVOLVO study\textsuperscript{15} and what do these data add to the current thinking regarding home or telemonitoring in HF? Although there is a lively and ongoing debate with regard to the value of home monitoring in HF patients\textsuperscript{4,16}, most people would probably agree that many of the measured variables may have some value in detecting early changes leading to a cardiac decompensation, and that these variables could potentially have a place in the management of HF patients. However, not all abnormal values lead to clinical problems and these variables often fluctuate, and particularly the specificity of abnormalities may be low\textsuperscript{14}. Indeed, knowing “too much” may be a problem\textsuperscript{17}, and including the patient in the information loop may not always be wise. In case of audible alerts, this may be hard to ignore, particularly for the patient, who may require treatment or even an urgent hospital visit or overnight stay. The search for an optimal HF disease management program, which will include a home monitoring component in many patients, will continue in the future, and may become a search for the Holy Grail. The EVOLVO study\textsuperscript{16} adds an important piece to this puzzle and shows that with remote monitoring many of these unnecessary health care utilizations can be avoided.
Conflict of Interest Disclosures: Dr. Van Veldhuisen was the Principal Investigator of the DOT-HF study, for which he has received Board Membership fees in the past. Dr. Maass reports having received lecture fees from Medtronic, Biotronik, Boston Scientific and Sorin. The Department of Cardiology, UMC Groningen has received unrestricted research grants from Biotronik and Medtronic.

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