Diagnosing arrhythmias in general practice: the BEAT study
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Chapter 7

General discussion
INTRODUCTION

The studies described in this thesis evaluate the introduction of a new tool to diagnose cardiac rhythm disturbances in general practice. Until now, generally available diagnostic tools lacked sufficient predictive power to enable GPs to perform an adequate diagnostic evaluation of patients presenting with palpitations and/or lightheadedness in daily practice. At the time this study was started, two types of mobile recorders were available: 24-48 hour continuous recorders (Holter), and intermittent or event recorders, that could be used for a longer time frame. The recorder that seemed most adequate for diagnosing intermittent symptomatic episodes was the continuous event recorder (CER). Before implementing this new diagnostic tool into general practice, we studied the diagnostic performance of a CER for evaluating patients presenting with the aforementioned symptoms in general practice. In this chapter the main findings of the studies are discussed in the light of methodological issues and recommendations for future research and health care are presented.

MAIN FINDINGS

In patients presenting with palpitations and/or lightheadedness, we compared usual care with the CER as an additional diagnostic tool in patients in whom cardiac disease was excluded, based on a standard 12-lead electrocardiogram (ECG) or by physical exam. In both strategies, usual care group versus CER group, the final diagnosis as established by the participating GPs was chosen as the primary outcome of this study. At 6 months, this outcome was compared between the two strategies. Secondary endpoints were differences in the number of explained episodes and type of the arrhythmia, as well as time needed to diagnose an episode. An inventory of the capability of GPs to assess the presence of cardiac arrhythmias, and which clinical signs and symptoms were used in predicting the presence of arrhythmias was done in order to optimize selection of patients for future application of the CER. Finally, the influence of the CER on quality of life (QoL) and induction of anxiety in patients were evaluated.

GPs were able to explain 62% of the episodes of patients without the use of a CER, compared to 82% in the intervention group with the CER. Also, the type of final diagnosis differed between both groups. After 6 months of follow up, more relevant cardiac diagnoses were established in the patients of the intervention group compared to usual care group (22% versus 7%). In the intervention group more often atrial fibrillation (AF) and supraventricular tachycardia (SVT) was diagnosed, in the usual care group more psychological problems were established by the GPs. We considered these differences to be of clinical relevance.
In the intervention group, at two weeks, 79% of all relevant arrhythmias were diagnosed and 73% of all less relevant arrhythmias. At 3 weeks, 96% of all relevant and 85% of the less relevant arrhythmias were recorded. Therefore, with a 2-3 weeks registration time, the burden of carrying the device and diagnostic yield are best balanced.\textsuperscript{5}

At baseline, all patients in both groups reported greater anxiety and lower quality of life (QoL) than a healthy population. At 6 weeks there were no differences found in anxiety and QoL between the CER group and the usual care group. At 6 months the usual care group showed an improvement in QoL and less anxiety compared to the CER group although both groups had improved. The type of final diagnoses influenced both anxiety and quality of life but could not fully explain these differences.\textsuperscript{6}

GPs had no specific clinical parameters on which they can base their diagnosis. &lt;GPs have referred 40 out of 127 patients to a specialist, of whom 28 patients (70%) did not have relevant cardiac problems. Accurate prediction of the presence of an arrhythmia in patients presenting with palpitations is difficult without the use of additional diagnostic instruments like a CER.\textsuperscript{7}

The conclusion from an extensive literature search was that Holter monitors have a lower diagnostic yield than event recorders. Automatically triggered recorders detect more arrhythmias than patient triggered devices. The choice of the device not only depends on the characteristics of the symptoms and the patient, but also on the aim of the diagnostic process.\textsuperscript{8}

**GENERAL POINTS OF DISCUSSION**

**Study design**

A hierarchical approach to the assessment of new diagnostic technology has been advocated and used in the field for many years by various researchers.\textsuperscript{9} This approach entails assessment of technical development, diagnostic performance, diagnostic and possible prognostic effects, effectiveness, patient and societal outcomes and cost effectiveness of the new technology.

Technical development of the CER was performed and appropriately tested by Card Guard, the manufacturer of the CG-6106 loop recorder. This recorder continuously registers and updates a two lead ECG. When a patient chooses to activate the recorder it stores information 30 seconds before and 2 minutes after the moment of activation. A maximum of three registrations can be stored in the memory, hereafter an acoustic signal indicate that the memory is fully stored. Only after sending the ECGs by telephone could the memory be overwritten.
The next step would be assessment of test characteristics. New diagnostic tests are usually evaluated in a diagnostic accuracy study design. In such a study the index test is compared with a reference standard. Although this type of design may be recommended, it was not feasible in the BEAT trial. An ECG registration during actual complaints is often regarded as the most optimal or acceptable reference standard. ECG registration during complaints, activated by the patient is precisely what an event-recorder is providing. Therefore the CER, although introduced as the index test, also served as the reference standard.

The design of a (open label) randomised clinical trial was chosen. Usual care was compared with a diagnostic strategy that included the introduction of a CER as an additional diagnostic tool in general practice. In both strategies, the final diagnosis as established by the participating GPs, with or without the availability of the CER, and not the diagnosis as provided by the CER per se, was chosen as the primary outcome measure of this study. Advantages of such a design are that not only ‘test-characteristics’ are assessed, but also the impact of using the new diagnostic tool on health and health care.

Alternative designs and their limitations

An alternative design to the RCT, would have been to provide all patients in the usual care group afterwards with a CER as well (a variation on a cross-over design). But this design would have been corrupted by time, as GPs would know that patients in the usual-care group would be evaluated with a CER 6 months after the first consultation for their complaints. GPs might adept their diagnostic strategy, knowing that after a while patients in the usual-care group would be evaluated anyhow.

Another alternative would have been to use the new diagnostic strategy in all patients but only directly provide the test results to the treating physician and patient for those randomly assigned to the intervention strategy and provide the results of the CER after finishing of the study in the usual care group. We judged this strategy not ethical, nor feasible, due to a possibly important and clinically relevant delay in the usual care group. Moreover, providing results after for example six months (at the last registration moment of the study) would have changed usual care, as GPs would have been informed of results of usual-care patients during the trial, thereby discovering a possible effect of the CER-strategy.

Limitations of the RCT-design

Blinding patients and treating physicians for the type of intervention was not possible. Also, we judged blinding of GPs not desirable, as we were not interested in the diagnostic information per se, but in the consequences associated with the whole strategy. GPs therefore had to be informed of the results of the CER-monitoring.
Current clinical practice was used as the control strategy for the study. We recognize that current clinical practice is, in many instances, more unstructured and documentation of relevant information may be lacking. Performance in the context of a study might help structure and streamline clinical practice, initiate collection of relevant information, and enhance communication between physicians mutually and between physicians and their patients. Therefore usual care during our trial period might have been more intense than common practice because for all patients the GPs had to register an extensive medical history and physical examination. The net effect in the context of the trial would be a decrease in the difference between usual care and the intervention group.

We used a stratified randomization procedure, whereby we stratified for GP, to make sure that every GP has an equal amount of patients in the intervention group as well as in the control group.

Generalizibility of the results
The study was performed in a heterogeneous group of both urban and suburban GP practices from different parts of the Netherlands (Amsterdam, Almere, Breda, Etten Leur). Sixty nine GPs participated. Because of this diversity of GP practices and patients, the BEAT study provides a fair reflection of the average Dutch GP practice and their patients. All recordings made with the CER were assessed by a staff member of the department of cardiology of the Academic Medical Center of Amsterdam. The yield of the CER recordings may therefore be lower in standard clinical practice, where the recording is not supervised. Another small study suggested, however, that the diagnostic yield of the device was also high in a non-supervised setting.14

We asked GPs to include every consecutive patient with palpitations and/or light-headedness as a new complaint. In the Netherlands 8/1000 patients consult the GP yearly with complaints of palpitation. Palpitations are most prevalent in patients above the age of 45, with a peak incidence in the very old.15 Our study population had a rather young mean age (51 years) and a majority of female patients (74%). This mean age corresponded with the mean age of the populations from 28 reviewed studies in the systemic literature search. Across all studies, the mean age of the populations was between 45-55 years and the majority of patients was female.8

So it appears that a different group of patients is included in trials including our trial. Therefore, we decided to conduct a retrospective chart review on recruitment among 27 of the 69 participating GPs. From the chart review, it appeared that about half of the eligible patients were not included. In one third of these cases, GPs forgot to include the patient in the trial (33%). In less than a quarter of the cases (21%) the GP was convinced of the diagnosis after history taking and physical examination and did not want the patient to be included in our study anymore The group of patients included consisted of patients
in whom the GP was uncertain about the diagnosis. This may have led to a relatively younger group of patients, in whom an arrhythmia was not an obvious diagnosis. This selection process probably led to the inclusion of patients who would otherwise have been referred to a cardiologist for diagnostic workup and who would benefit from the introduction of a CER as an additional diagnostic tool in general practice in the future. Anyhow, this selective inclusion did not affect the contrast between both parallel groups of patients.

**IMPLICATIONS FOR MEDICAL PRACTICE**

**The significance of diagnosing palpitations**

In the BEAT study, the CER was used in 127 patients and paroxysmal atrial fibrillation (PAF) was demonstrated in 12 patients. In the usual care group (n = 117), PAF was diagnosed in two patients (9% versus 2% respectively). Diagnosing PAF is clinically as important as diagnosing permanent AF, because both forms of AF share an equal burden of morbidity and mortality and increase the risk of death, congestive heart failure and embolic phenomena, including stroke. The mortality rate of patients with AF is about twice the mortality rate of patients with a normal sinus rhythm. AF is associated with a near 5 fold increase in the rate of ischemic stroke and one in every 6 strokes occurs in a patient with AF. Besides, it is known that stroke associated with AF is more severe than ischemic stroke due to other causes. This increased stroke severity is independent of advanced age and other stroke risk factors, and is related to greater volumes of more severely hypoperfused tissue, leading to larger infarct size and greater risk of severe hemorrhagic transformation.

Therefore primary concern in patients with AF is the prevention of stroke and diagnosing AF should be followed by secondary preventive treatment to lower stroke risk. Patients with AF and an additional risk-factor for stroke qualify for oral anticoagulant treatment. Vitamin K antagonists reduce the risk of stroke with more than 60%, aspirin with about 20%. New oral anticoagulants such as the thrombin inhibitor dabigatran or the FXa antagonists apixaban and rivaroxaban have been shown to be very promising for the prevention of stroke, and may replace vitamin K antagonists in the long run.

In older (>65yr) asymptomatic patients with AF, there seems little need to pursue sinus rhythm [AFFIRM]. For these patients a (lenient) rate control suffices. However, in younger patients as well as in older patients who remain symptomatic despite rate control a rhythm control strategy is advocated. This may require cardioversion, antiarrhythmic drug therapy, or ablation therapy. Apart of that, adequate therapy of concomitant cardiac diseases is required.
Quality of life in AF-patients may be considerably impaired, mainly because of their inability to perform normal daily physical activities due to risk of, or exacerbation of symptom.\textsuperscript{28} One-third of AF-patients experience anxiety or depression, significantly correlated with diminished QoL.\textsuperscript{29-31}

**Differences in diagnoses between the two study groups**

Compared to the usual care group, more relevant arrhythmias were diagnosed in the CER group, and less psychiatric diagnoses were made. In 35\% of patients in the usual care group, the GP thought of anxiety, panic disorder and stress related problems, compared to only 15\% in the intervention group. Due to randomization, we expected an equal number of patients with psychiatric problems in the intervention and control group. An explanation for the differences in diagnoses between control and intervention group patients (less psychiatric diagnoses, more cardiac diagnoses in the intervention group) could be misclassification by the participating GPs. This phenomenon has also been observed in a study by Lessmeier et all, where in a retrospective survey of 107 consecutive patients re-entry paroxysmal supra-ventricular tachycardia (PSVT) was not recognized by initial medical evaluation in 59 (55\%) of 107 patients referred for electro physiologically guided therapy. Prior to eventual identification of PSVT, physicians (non psychiatrist) attributed symptoms to panic, anxiety, or stress in 32 (54\%) of those 59 patients. Females were more likely than males to have symptoms ascribed to psychiatric origin (65\% vs 32\%).\textsuperscript{32}

Mumford identified physical symptoms without a likely organic disease as main reason in 15\% of consultations in primary care.\textsuperscript{33} It is known from literature that the majority of palpitations are medically benign. Weber and Kapoor found that only 43\% of patients with complaints of palpitations had a cardiac origin.\textsuperscript{34} In our study, we observed that patients at baseline had an elevated anxiety level and lower QoL compared to healthy populations. It is to be expected that patients with complaints of palpitations visiting a physician will be apprehensive for having a heart disease.\textsuperscript{6} Patients with ongoing complaints of palpitations, will have the tendency to seek help repeatedly as long as a diagnosis is not established. These patients might undergo a variety of, often unnecessary, diagnostic procedures with very limited diagnostic and therapeutic value.\textsuperscript{1} The introduction of CER in general practice could diminish this risk of excess diagnostic procedures and unnecessary referrals.

In patients with complaints of palpitations the awareness of heartbeat may trigger anxiety attacks. These sensations (which may result from a normal extrasystole, physical exertion, emotions, or an ingested substance like caffeine) are experienced by the patient as threatening. This triggers arousal, which in turn increases heartbeat and sets up a cycle.\textsuperscript{35,36} This phenomenon could explain the elevated anxiety level and lower QoL
in our study group. This group of patients is often referred to as patients with medically unexplained physical symptoms (MUPS) and in those patients GPs in the usual care group might have considered a psychiatric diagnosis more often than GPs from the intervention group, especially when a probable diagnosis was established with the use of the CER. Another explanation could be the co-existence of two disorders at the time of presentation of the complaints; patients can suffer from cardiac as well as psychiatric problems and the GP might only recognize one of those. Recognition of a rhythm disturbance is facilitated by the CER in the intervention group, and not in the control group of patients.\(^3\) The total number of relevant and less relevant diagnosis in the intervention group is much higher. We assume that part of the patients labeled with psychiatric symptoms in the usual care group would probably have been diagnosed by CER with an arrhythmia either relevant or less relevant. Using the CER as an additional diagnostic tool to exclude or include cardiac causes of palpitations will be helpful for both patient and doctor. From the patient’s point of view a explanation for their symptoms by the general practitioner without referral to specialist secondary care is considered an important advantage. In our study most arrhythmias turned out to be benign without the need of further workup by a cardiologist. Thus, with the use of a CER many patients could stay under the care of the GP, thereby reducing referrals to secondary care and maybe preventing psychiatric labeling of the symptoms. When during episodes of palpitations, minor or no rhythm disturbances were registered, rhythm strips of the CER provided the GP with means for adequately reassuring patients. It is an objective and lucid way of reassuring patients that there is not a cardiac cause for their complaints.

**IMPLICATIONS FOR FUTURE RESEARCH**

**Costs**

Our study did not include costs involved when adding the device as a diagnostic tool in everyday general practice. The last few years some areas in the Netherlands started implementing the CER in daily care. The average costs for using a CER during two weeks is about 190 euro’s per patient (price level 2011). One method to reduce the cost will be to better select patients who would benefit most of a diagnostic work-up with a CER. Some other studies did look for these correlations between patient- and symptom characteristics and the risk of having serious arrhythmias, but no study succeeded in identifying characteristics with enough predictive power.\(^3\) The intervention group of the Beat study existed of only 127 patients, also resulting in a low statistical power and a small number of possible predictors for having a relevant
arrhythmia. To increase power, a much larger study has to be performed. Until these predictors for the presence of relevant arrhythmias are known, the results of our study suggest a best practice is to hand out a CER to all patients with palpitations in whom the results of the initial evaluation are negative (which occurs more frequently in paroxysmal, short-lasting palpitations) in order to distinguish between relevant and less relevant palpitations rather than selecting patients based on certain signs or symptoms. Further research is needed to determine what the costs of the CER are for patient, doctor and society, and whether the use of this additional diagnostic tool in general practice is cost effective.

**Duration**

In our study the time-frame to record was based on timeframes used in other studies. In the literature there is no consensus about the optimal duration of recording with a CER. In our study the diagnostic yield rapidly diminished after two weeks. In two weeks 79% of all relevant arrhythmias were diagnosed. For longer periods of monitoring it is important to weight the decreasing yield of the CER against the burden to carry a device, or charge the healthcare system with lengthy registrations. Since our studied group was small, cost-effectiveness for the optimal time-frame should be studied in a larger cohort study.

**Applicability of the CER**

Since we started the BEAT study, new recorders have been developed. These new digital recorders are capable of automatic activation based on heart rate and irregularity combined with patient triggered activation and simultaneous multichannel recording (from 1 to 12 channels). These possibilities will expand the traditional uses of ambulatory ECG for arrhythmia detection. These advances, in addition to the availability of inexpensive large storage capacities, and long-term continuous high-quality ambulatory ECG monitoring, have opened new potential uses for the CER in special populations. For example as a screening tool for patients with a-symptomatic AF. A-symptomatic AF or silent AF seems common and may have the same prognostic implications as symptomatic AF. Little is known about demographic features and prognostic information in patients with a-symptomatic AF. It is usually diagnosed incidentally during routine physical examinations, pre-operative assessments or population surveys. Some studies in elderly patients reported an incidence of a-symptomatic AF of between 10% and 40%. The CER with the automatic activation function can be used for a diverse population, for instance patients with hypertension and a certain age that are at risk of having AF. It might be of mayor interest to perform a community wide study to document silent AF and this way reduce the risk on stroke by appropriate pharmacological interventions.
IMPLICATIONS FOR GENERAL PRACTICE.

The BEAT study showed that the CER is a safe and effective additional diagnostic tool to evaluate complaints of palpitations or light-headedness in general practice. It provides high-quality diagnostic information in a short period of time. For the GP, the high degree of specificity achieved by requiring the patient to activate the device at time of symptoms is important. This may result in early detection of arrhythmias, and adequate filtering and priority grading of referrals for patients requiring further investigation while reducing the load of unnecessary referrals for primary diagnosis. Furthermore, the absence of abnormalities registered during paroxysms of palpitations may provide reassurance to patient as well as to GP. To identify patients at a high risk for relevant arrhythmias, thereby facilitating selective use of CER, more research is needed.
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