Unverzagt et al., J Clin Trials 2014, 4:6
DOI: 10.4172/2167-0870.1000192

Journal of Clinical Trials
ISSN: 2167-0870

Protocol Open Access

Interventions to Enhance Adherence to Guideline Recommendations in Secondary and Tertiary Prevention of Heart Failure: A Systematic Review

Susanne Unverzagt[1]*, Andreas Klement[2], Gabriele Meyer[3] and Roland Prondzinsky[4]

[1]*Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany*
[2]*Section of General Practice, Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany*
[3]*Institute for Health and Nursing Science, Martin-Luther-University Halle-Wittenberg, Halle, Germany*
[4]*Cardiology/Intensive Care Medicine, Carl von Basedow Klinikum Merseburg, Merseburg, Germany*

Abstract

Background: Heart Failure (HF) is a major clinical and public health problem with strong implications for quality of life and high socioeconomic impact due to costs of treatment. Patients being treated according to the present recommendations show improved survival and lower rehospitalization rates, but poor adherence is considered to be a critical barrier for treatment success. Therefore, we want to investigate interventions aimed at improving adherence of patients to recommendations on HF, e.g. how do physicians approach their patients' problems, provide information and involve individual values and preferences in the process of decision making? To date, many randomized trials have investigated interventions to reduce barriers for adherence, but a systematic review of these interventions is needed.

Methods: This systematic review should evaluate the efficacy and effectiveness of interventions to enhance patient adherence to guideline recommendations in secondary and tertiary prevention of HF. Methodology follows the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. We will include only randomized controlled trials and classify interventions according to their active component as interventions concerning the provider, patient education, and patient reminder, promotion of patients' self-management, organizational change or technical solutions. The primary outcome measure is patient adherence; important patient outcomes such as quality of life, mortality, morbidity, hospital admissions and readmissions, days in hospital, and costs are added as secondary outcomes. A random-effects meta-regression model will be used to simultaneously assess the influence of different strategies on patient adherence. Analyses on heterogeneity will include pre-defined methodological and clinical sources of heterogeneity.

Conclusion: This systematic review should identify major components of successful interventions aimed to foster the therapeutic adherence and/or self-managing abilities of patients. Without appropriate strategies for promoting adherence the transfer of guideline recommendations into daily practice is hindered by many obstacles that reduce the desired health outcome.

Systematic review registration: PROSPERO CRD42014009477.

Keywords: Adherence; Guidelines; Heart failure; Systematic review

Background

Heart Failure (HF) is a major clinical and public health problem with a prevalence of approximately 1-2% of the adult population in developed countries which increases to ≥10% among persons 70 years or older [1]. More than 23 million people suffer worldwide from HF. During the next few years chronic heart failure (CHF) will become the most common cardiovascular disease with a major impact at the level of the individual due to symptom-related incapacity to manage daily life, along with a relatively high socioeconomic impact due to the direct and indirect costs of HF treatment.

The development of treatment concepts during the last three decades can be looked upon as a great success story of cardiovascular medicine. During the so called "cardiovascular continuum", ranging from primary prevention before acute myocardial infarction up to end stages of CHF, which may follow acute myocardial infarction years later, a broad spectrum of evidence based treatment options is available. Clinical guidelines on the management of HF [1-4] recommend drug treatment as well as other interventions, such as self-monitoring and lifestyle modification.

In this context it was shown that patients who are treated according to the current recommendations for CHF show improved survival rates and also lower rehospitalization rates for acute decompensated HF [5-6]. However, clinicians may prescribe evidence-based treatment and recommend lifestyle modifications, but the patients decide whether follow these recommendations [7-8]. Nonadherence is considered to be a critical barrier to treatment success and remains an important challenge to health care professionals. Especially older patients frequently suffer from particular conditions which may limit adherence to drug therapy as rheumatic disorders of hand and fingers hampering removing tablets from blister packages up to cognitive limitations due to different forms and stages of dementia frequently. Non-adherent patients have a higher risk of mortality and an increased rate of hospital re-admission caused by acute decompensated CHF [9-10].

These disease and patient related reasons to focus on CHF are reinforced by reasons related to structural problems in the health care systems in Europe and North America. While health care systems will

***Corresponding author:** Susanne Unverzagt, PhD, Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University Halle-Wittenberg, 06097 Halle (Saale), Germany, Tel: +49-34-5557-4486; Fax: +49-34-5557-3580; E-mail: susanne.unverzagt@medizin.uni-halle.de

Received August 12, 2014; **Accepted** October 31, 2014; **Published** November 03, 2014

Citation: Unverzagt S, Klement A, Meyer G, Prondzinsky R (2014) Interventions to Enhance Adherence to Guideline Recommendations in Secondary and Tertiary Prevention of Heart Failure: A Systematic Review. J Clin Trials 4: 192. doi:10.4172/2167-0870.1000192

be confronted with an increasing number of patients representing the so-called "baby boomer-generation", a significant number of physicians, especially general practitioners, also belonging to the "baby boomer-generation," will retire without adequate succession. These problems of an ageing patient population confronted with a decreasing number of general practitioners will be pronounced in rural areas.

The WHO demanded in 2003 that, "interventions for removing barriers to adherence must become a central component of efforts to improve population health worldwide" [11]. It is increasingly recognized that physicians, nurses, and other health professionals may help their patients to overcome these barriers [12]. Physicians should improve how they approach their patients' problems, how they provide information, and involve individual values and preferences of their patients in clinical decision making. The model of shared decision making can be viewed as the optimal method to realize autonomous decisions of patients and might be the ideal foundation of improved adherence [13].

Contrary to existing systematic reviews [14-15], this review investigates the effectiveness of a broad and complex spectrum of very different interventions to improve adherence to both, medications and lifestyle modifications. Improvements in both fields are needed to improve quality of life, mortality and morbidity in patients with CHF. Some of these interventions are based on personal interactions such as provider or patient education including motivational talks and also cognitive behavioural therapeutic approaches, while others are predominantly characterized by organizational change or technical solutions like individual drug blistering, smartphone reminder applications or extended telemedical home-monitoring solutions. We will summarize the evidence of randomized controlled trials (RCTs) to identify the most effective interventions and we will discuss the conditions and requirements in which these strategies work best. This protocol carefully pre-defines inclusion criteria for participants, intervention and outcomes, search methods, data extraction, data synthesis and the investigation of potential effect modifiers in heterogeneity analyses.

Methods

Objectives

We will conduct a systematic review to evaluate the efficacy, effectiveness, and safety of different strategies that enhance patient adherence in secondary and tertiary prevention of HF. We will include individual-randomized (RCTs) and cluster-randomized controlled trials (c-RCTs) reporting on outcomes of patient adherence, with a follow-up period of at least three months. Trials should be published in English or German.

Participants should be patients with acute and/or chronic HF. The aim of prevention is the reduction of morbidity, mortality, costs, and loss of quality of life. Therefore, we will focus on patients with HF and NYHA ≥ 2 or LVEF <50%. Trials on general CVD or general chronic diseases with separately investigated results for patients with these conditions will also be included.

Interventions will cover all strategies (e.g. primary or secondary outcome) aiming to enhance compliance with evidence-based recommendations on prevention or slowing of progression of HF to preserve quality of life, social participation and general fitness of these patients. These recommendations include pharmacological therapies with diurectics for symptom relief and beta-blockers, ACE- and AT1-inhibitors, aldosteron-antagonists and in certain cases, addition of ivabradine for prognostic improvements (hospitalization and survival rate). They also include non-pharmacological interventions like regular follow-ups, symptom monitoring, flexible diuretic use, weight control, restriction of sodium and fluid intake, stopping smoking, regular aerobic exercise, specialist consultation and regular clinical monitoring [1-4].

Interventions will be classified according to their active component, which might be described by an explicit statement on how the intervention is intended to work, into six main categories following the suggestions on "taxonomy of implementation strategies" [16] with specifications [17-19].

Interventions concerning the provider:

a. Reminder systems

b. Education

c. Audit and feedback

Patient education: individual counselling or group education or training such as

a. Verbal, written or visual instruction for patients

b. Counseling about the patients' underlying disease, the importance of therapy and compliance with therapy, possible side-effects, patient empowerment, couple-focused therapy to increase social support

c. Reinforcement or rewards for both improved adherence and treatment response

d. Lay health mentoring

e. Group meetings

Patient reminder:

a. Reminders, e.g. programmed devices, and tailoring the regimen to daily habits

b. Special 'reminder' pill packaging

c. Appointment and prescription refill reminders

d. Automated telephone counseling

e. Manual telephone follow-up

f. Mailed communications by smartphones, apps

Promotion and empowerment of patients' self-management:

a. Involving patients more in their care through self-monitoring and shared decision making

b. Simplified dosing

c. Dose-dispensing units

d. Strategies for adaptive self-medication in chronic disease states ("pill in the pocket")

Organizational change:

a. Improved pharmaceutical care through simplified dosing and augmented pharmacy services

b. Improved cooperation between different medical disciplines, practices, and other structures of health care providers (e.g. GPs and cardiologists), and/or sectors of care (e.g. hospital services

and community care), and/or other health professionals (e.g. community nurses, nurse practitioners)

c. Changes in organizational structures at practice level (e.g. involvement of nurses in the process of care and/or counseling and/or surveillance)

d. Direct observation of treatments by health workers or family members

e. Family intervention

Technical solutions:

a. Drug blistering

b. Computer-assisted patient monitoring

c. Various ways to increase the convenience of care, e.g. provision at the worksite (such as telemedical home-monitoring systems) and at home

Distinct unimodal strategies can also be combined to multimodal interventions.

Comparators may cover standard care or other interventions. It is necessary to describe in detail what participants in the control group did not receive compared to those in the intervention group.

Outcome

Patient adherence "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with evidence-based recommendations" [20] will be the main outcome of this review. There are three different approaches to determine adherence [21]. The first category compares the quantity of medication taken and compares it with the quantity prescribed over a specific time period. The second type categorizes adherence into categories of poor or good adherence, and the third type summarizes adherence to a variety of recommendations according to an adherence behaviour composite score (e.g. Morisky score [22]). We will accept all these definitions of adherence.

Studies are required to have at least 50% follow-up of participants with one or more measures of medication adherence and three months follow-up. This minimal duration is necessary to describe adherence to long-term regimes as required in treatment of HF and to differentiate between permanent non-compliance of patients to recommendations and so called drug holidays.

Adherence can be measured by direct methods such as blood or urine levels of the drug or its metabolite or indirect methods, such as pill count, pharmacy refill episodes, by medication event monitoring systems, pharmaceutical records, self-reporting through patient diary or clinician impression [17,23]. Indirect measures are limited by the assumption that drug acquisition is a reasonable surrogate for consumption and subjective methods such as patient self-reporting and clinical impression assume truthful reporting.

It is certain that a single outcome may not reflect all important effects the intervention may have. Therefore we investigate mortality, morbidity, quality of life, bed days in hospital, hospital admission and re-admission rates, and healthcare costs, as secondary outcomes. All outcomes will be extracted within the longest available follow-up period.

Literature search

Searches will be conducted in electronic databases (MEDLINE, Embase, CENTRAL, PsycInfo, CINAHL), registers of ongoing and completed trials (http://www.controlled-trials.com, http://www.who.int/ictrp/en/), and reference lists of studies included, and systematic reviews on strategies to identify all relevant, published, and unpublished trials. Due to the relevant improvement in therapies for HF in recent years, a literature search starting in 2000 is considered sufficient for the purpose of this review.

Screening of references and studies

Two reviewers will independently screen titles and abstracts of all potential studies identified by database search and mark potentially eligible studies. We will retrieve the full-text study reports/publication and two review authors will independently screen the full-text and identify studies for inclusion, and record reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, consultation with an additional reviewer. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is examined.

Data extraction

Two authors will independently extract details of study population, interventions, outcomes and effect modifiers by using an assessment form, which was designed especially for the topic of this review and tested in the pilot study. The data extraction form consists of two tables to characterize the study and the suitable comparators. The study table includes the following items:

- Study references and identifier, design (RCT vs. c-RCT), study duration (months), country, number of patients and participating centers, primary site of recruitment (hospital vs. community setting), primary site of intervention (hospital, primary care, specialized care, managed care services), author contact if necessary

Patients: baseline characteristics (age, gender, socio-demographic background, race, smoker, alcohol use), indication (NYHA grade, chronic or acute HF, first diagnosis of HF at within 3 months before randomization), evidence-based recommendations with guidelines, co-morbidities (especially cardiovascular risk factors like diabetes, hypertension, hypercholesterolaemia/ hyperlipidaemia, kidney failure, depression, other).

The table containing the comparators includes an unique identifier and the following information for each of the comparators:

- Intervention and control: description of the active component (does a theoretical mechanism exist), categorization into categories and subcategories, difference between intervention and control group, provider of intervention and/or follow up (hospital and/or ambulatory based specialist, primary care physician, physician assistant, nurse practitioner, health worker or others), communication style integrated in the intervention (patient information only, informed consent, patient participation, shared decision making, other), sample size per group
- Outcomes: adherence and their 95% CI or standard error, primary or secondary outcome, definition of adherence and method of outcome assessment, maximum follow-up, secondary endpoints (mortality, morbidity, quality of life, days in hospital, costs)
- Risk of bias in six domains as described below including number of drop-outs with causes

- Investigated modifying factors and results from subgroup analyses.

In case of missing information on patient adherence in pre-planned subgroup analyses we will contact authors of RCTs.

Risk of bias

Two authors will independently assess the internal validity of eligible studies according to the Cochrane Collaboration risk of bias tool [24] with extensions to c-RCTs [25-27]. These domains describe bias in random sequence generation, allocation concealment, blinded outcome assessment, documentation of incomplete outcome data and selective reporting. Judgment on selective reporting will be restricted to adherence and judged on the basis of reported sample size calculation. Furthermore, baseline comparability between treatment groups and the use of adjustment methods to cope with potential imbalances in both cluster and individual characteristics will be summarized as other sources of bias. Disagreements will be resolved by discussion until consensus is obtained. Risk of bias will be described and judged as high, low, or unclear in six specific domains at both the cluster and patient level.

Data synthesis

Effect measures for the primary endpoint (physician adherence) will be presented as odds ratios with their 95% CI. They can be recalculated from relative risks [24], standardized mean difference with standard deviation [28] or from absolute frequencies [24]. If multiple endpoints describe physician adherence, mean of logarithmic odds ratios will be used to summarize all effect measures. Standard errors from c-RCTs without hierarchic modeling will be corrected with an intra-cluster correlation coefficient suitable for process outcomes in secondary care of 0.06 [29] and the mean number of patients per cluster [24]. We will additionally calculate absolute changes if adequate information is reported.

To synthesize data we will use a random-effects meta-regression model to simultaneously assess the influence of different strategies on the effect measures.

Investigation of heterogeneity

Subgroup and meta-regression-analysis will be performed after the main meta-analysis, and will consider the following possible effect modifiers:

- methodological quality of studies
- in case of eligible data from subgroup analyses: age, gender, socio-economic status, NYHA
- complexity of recommended therapies: evidence-based medications vs. life style modification including weight control, fluid restriction, sodium restriction or aerobic exercise
- Method used to measure and define adherence: direct vs. indirect methods for measurement, definition as quantity of medication taken vs. categorized adherence vs. adherence scores and
- Organizational environment: primary site of intervention (hospital, primary care, specialized care vs. managed care services), provider of intervention and/or follow up (hospital and/or ambulatory based specialist, primary care physician, physician assistant, nurse practitioner, health worker vs. other), communication style integrated in the intervention (patient information only, informed consent, patient participation, shared decision making vs. other).

Discussion

Seeking strategies to improve the adherence of patients to therapeutic recommendations may be of great interest over the broad spectrum of diseases, but improving adherence to drug treatment in HF is of special interest.

While the greatest innovations in cardiovascular medicine have been closely related to technological advances, which have been applied to patient care, it now seems to be time to search for strategies for long lasting, successful patient participation in the therapeutic process [30]. Future research has to look for impediments to guideline implementation and adherence and for strategies to overcome these obstacles.

One of the major strengths of this approach is reflected by the intention to support the implementation of best presently available external evidence into daily practice or clinic, to ensure that especially patients treated for HF will receive the optimal guideline based treatment in a participatory and sustainable way. In contrast to common approaches this review will not only look for new or optimized technical or pharmaceutical treatment solutions, it will moreover look at how to apply this knowledge and try to provide answers on how to achieve long lasting patient collaboration. For this reason this review will also investigate person and structure based interventions being applied to motivate patients for better adherence. This, on the other hand, also signifies the main limitation of this review because many of the techniques and tools investigated, such as for example willingness for patient participation or shared decision making by nurses or physicians may cause qualitative differences in patients' cooperation, but will hardly be standardized for a quantifiable analysis. This point at least leads to the principal criticism, that there are major limitations in measuring adherence directly and independently from patients. All questionnaire and technical approaches remain at least approximations to real patient adherence to drug therapy and lifestyle modifications.

Finally, interventions for implementation are complex generally involving multiple interacting components. In all primary studies, we are interested in the efficacy of the active component of these interventions which should be standardized and categorized into our taxonomy of implementation strategies. But reducing a complex system to its component parts amounts to irretrievable loss of what makes it a system [31]. Therefore we have to cautiously differentiate this theoretical study mechanism from "non-core" features which adapt local needs and circumstances and will be investigated in heterogeneity analyses.

Conclusion

Looking at drug therapy in HF as a model for successful development of evidence based drug treatment strategies during the last decades; it is disappointing, that these effective modalities cannot be fully transferred into the care of patients in daily clinical practice.

Patient adherence is therefore the logical and necessary link between medical counselling in accordance to guideline recommendations and the clinical result of this treatment. Without appropriate strategies for promoting adherence the transfer of guideline recommendations into daily practice is hindered by many obstacles that reduce the desired health outcome. Hence, future research should focus on examining these barriers and develop concepts for successful joint management of chronic diseases.

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