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RESEARCH ARTICLE

The Effectiveness of Chronic Care Management for Heart Failure: Meta-Regression Analyses to Explain the Heterogeneity in Outcomes

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Objective. To support decision making on how to best redesign chronic care by studying the heterogeneity in effectiveness across chronic care management evaluations for heart failure.

Data Sources. Reviews and primary studies that evaluated chronic care management interventions.

Study Design. A systematic review including meta-regression analyses to investigate three potential sources of heterogeneity in effectiveness: study quality, length of follow-up, and number of chronic care model components.

Principal Findings. Our meta-analysis showed that chronic care management reduces mortality by a mean of 18 percent (95 percent CI: 0.72–0.94) and hospitalization by a mean of 18 percent (95 percent CI: 0.76–0.93) and improves quality of life by 7.14 points (95 percent CI: –9.55 to –4.72) on the Minnesota Living with Heart Failure questionnaire. We could not explain the considerable differences in hospitalization and quality of life across the studies.

Conclusion. Chronic care management significantly reduces mortality. Positive effects on hospitalization and quality of life were shown, however, with substantial heterogeneity in effectiveness. This heterogeneity is not explained by study quality, length of follow-up, or the number of chronic care model components. More attention to the development and implementation of chronic care management is needed to support informed decision making on how to best redesign chronic care.

Key Words. Heart failure, chronic care management, quality improvement, statistical heterogeneity, systematic review

Heart failure poses significant challenges to health care systems. Health care demands as well as health care costs are likely to rise (Lee et al. 2004; Liao, Allen, and Whellan 2008), since the prevalence of heart failure is expected to increase substantially due to aging and increased survival (Cowie et al. 2002; Levy et al. 2002; Najafi, Jamrozik, and Dobson 2009). Moreover, there is a considerable gap between appropriate care for chronic conditions and the care actually received. Finally, there is an increasing need for more patient-centered care (McGlynn 2003; Fonarow 2006; Bosch et al. 2009).

To address these challenges (IOM 2001; Bodenheimer and Fernandez 2005), various approaches have been proposed to improve the care for patients with heart failure. Perhaps best known are the concept of disease management and the chronic care model (CCM), while case-management, integrated care, and care coordination are also often mentioned in relation to chronic care management (Gress et al. 2009). The CCM is widely adopted as an evidence-based tool to improve chronic care (Wagner et al. 2001; Coleman et al. 2009; Busse et al. 2010).

Notwithstanding the awareness among policy makers, health care professionals, and patients of the importance of chronic care management, coming to strong conclusions regarding the effectiveness of chronic care management interventions has been limited. Substantial heterogeneity between study outcomes—the variation in effectiveness between studies is higher than is to be expected by chance alone—limits insight into the effectiveness of chronic care management (Mattke, Seid, and Ma 2007; Clark, Savard, and Thompson 2009; Coleman et al. 2009). This statistical heterogeneity is not only caused by clinical diversity (e.g., differences in interventions, like type and number of included CCM components, and outcomes studied) but

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also by methodological diversity (e.g., differences in length of follow-up and study design).

Insight into heterogeneity in effectiveness is needed to support the understanding of and decision making on chronic care management strategies. Some reviews tried to address the heterogeneity in outcomes by subgroup analysis (Gonseth et al. 2004; Kim and Soeken 2005; Roccaforte et al. 2005; Taylor et al. 2005). However, meta-regression analyses are needed to determine whether the differences between subgroups are stronger than is to be expected by chance alone. Although meta-regression analysis is a more promising tool to identify the characteristics of programs that predict better outcomes (Clark, Savard, and Thompson 2009), this has only been performed once restricted to randomized clinical trials (Gohler et al. 2006).

This paper presents an overview of reviews and studies with the aim to provide insight into the currently available evidence of chronic care management interventions, taking the clinical and methodological variation into account. In addition, meta-regression analyses were performed to gain insight in three potential causes of heterogeneity. It was hypothesized that differences in outcomes between the studies could be explained by differences in the following factors: (1) methodological quality of the studies; (2) length of follow-up; and (3) number of CCM components addressed by the interventions. This paper aims to support the understanding of and decision making on chronic care management strategies for heart failure by reporting on the effect and their factors explaining the heterogeneity in effectiveness between chronic care management interventions.

METHODS

Literature Search

Electronic database searches for English language systematic reviews and meta-analyses published between 1995 and 2009 were conducted in Medline and CINAHL, using the following Medical Subject Headings (MeSH): *patient care team, patient care planning, primary nursing care, case management, critical pathways, primary health care, continuity of patient care, guidelines, practice guideline, disease management, comprehensive health care, and ambulatory care*. These were combined with the MeSH term *heart failure*. In addition, *disease state management, disease management, integrated care, coordinated care, and shared care* in combination with *heart failure* were searched as text words in title and/or abstract words.

Study Inclusion and Data Extraction

Systematic reviews and primary papers were included if they focused on (1) heart failure as the main condition of interest; (2) adult patients as the main receivers of the interventions; and (3) interventions addressing at least two CCM components (Wagner et al. 2001). Studies published before 1995 were excluded; around that year chronic care management strategies became an important issue (Norris et al. 2003). Case reports and expert opinions were also excluded. Two reviewers (H. D. and L. S.) independently extracted data, using separate data entry forms for systematic reviews and primary papers. Disagreements were resolved by consensus with the third author (L. L.).

Assessing the Sources of Heterogeneity

Substantial heterogeneity in effectiveness across chronic care management interventions is likely, that is, differences in study outcomes are probably greater than is to be expected by chance alone (Clark, Savard, and Thompson 2009; Coleman et al. 2009). We identified three factors that may explain the heterogeneity in effectiveness: study quality, length of follow-up, and the number of CCM components.

First, study quality is expected to explain part of the heterogeneity in outcomes, but this has not yet been tested by means of meta-regression analyses (Gonseth et al. 2004; Kim and Soeken 2005; Roccaforte et al. 2005; Taylor et al. 2005). We used the validated Health Technology Assessment—Disease Management (HTA-DM) instrument to classify the primary studies as demonstrating either low (<50 points), moderate (50–69 points), or high quality (70–100 points) (Steuten et al. 2004). The HTA-DM instrument reliably measures the methodological quality of health technology assessments of disease management (Steuten et al. 2004). We used this instrument to determine to what extent study quality explains the heterogeneity in results between studies.

Second, length of follow-up was assessed as chronic care management interventions require behavioral, organizational, and cultural changes, which tend to take considerable time to take effect (Grol et al. 2007). Length of follow-up equals the reported number of months of the follow-up period.

Third, the number of CCM components was taken into account as more comprehensive programs were expected to be more effective (Wagner et al. 2005). The number of CCM components addressed by the chronic care

management interventions was identified following the coding scheme of Zwar et al. (2006): self-management support (SMS) (i.e., supporting patients to manage their condition, for instance, by routinely assessing progress and education); delivery system design (DSD) (i.e., the organization of providing care such as planned visits and other roles/teams); decision support (DS) (i.e., integration of evidence-based clinical guidelines into practice, for instance, by reminder system and feedback system); and clinical information systems (CIS) (i.e., information systems to capture and use critical information like reminders and feedback on performance).

Data Analyses

Data collected from reviews were descriptively analyzed, and data gathered from primary studies were descriptively analyzed and meta-analyzed. The outcomes measured most frequently, that is, hospitalization rate, mortality, and quality of life, were meta-analyzed. *Review Manager (RevMan 5.0.2)* was used to compute the pooled overall effects and the pooled effects for the subgroups of the three factors, that is, quality of study (poor, moderate, or good), length of follow-up (less than 1 year or longer), and number of components (two, three, or four). Pooled risk ratios for dichotomous outcomes were analyzed with the Mantel–Haenszel method using the random effect model (Lipsey and Wilson 2001). Pooled mean differences for continuous outcomes were analyzed with the random model of Dersimonian and Laird (Lipsey and Wilson 2001).

Meta-regression analysis was performed to determine to what extent the heterogeneity is explained by the quality of the studies, the length of follow-up, and the number of CCM components, if at least 10 studies could be included in the analyses (The Cochrane Collaboration 2009). In contrast with the subgroup analyses, all factors were taken into account as continuous variables. The effect sizes of primary studies were weighted using the inverse variance weight formulas (Lipsey and Wilson 2001) and imported together with the covariates into the *SAS* statistical package (version 9.2) (van Houwelingen, Arends, and Stijnen 2002). The extent to which the three factors explained the variance between studies was examined by fitting of univariable meta-regression models (Thompson and Higgins 2002). The relative decrease of the between-study variance in the univariable model compared to an intercept only model was interpreted as the percentage of heterogeneity explained.

RESULTS

Results of the Search

Fifteen systematic reviews and 46 primary studies (reported in 47 papers) were included (Figure 1). A description of the included reviews is available online as are all the references of these papers (Supporting Information, Appendix S1). The number of primary papers included in the reviews varied from 6 to 54. The included set of primary papers consists of 32 randomized controlled trials (RCTs), 4 nonrandomized controlled clinical trials, 9 before-after studies, and 1 chart review.

Findings from the Systematic Reviews

The definitions of chronic care management as well as the nature of the included interventions varied. Some interventions were purely physician driven, other were nurse led, some were clinic based, other involved home care, and so on (Appendix S1). A common aspect of the included interventions was a strong focus on reducing hospital admissions, and hence on (post)discharge planning and self-management. The reported outcome measures varied. Almost all reviews reported hospitalization, whereas other outcomes, like patient satisfaction and quality of life, were measured by less than half of the reviews.

Overall, the reviews showed positive effects, although with substantial heterogeneity between study outcomes. Most meta-analyses revealed a significant reduction on all-cause hospitalization (McAlister et al. 2001; Gonseth et al. 2004; Gwadry-Sridhar et al. 2004; Phillips et al. 2004; Roccaforte et al. 2005; Taylor et al. 2005; Gohler et al. 2006) with a relative risk reduction ranging from 12 to 25 percent. Results on mortality were less convincing; only two reviews reported a significant positive effect (Roccaforte et al. 2005; Gohler et al. 2006). Results on quality of life were inconclusive, as it was less frequently used as an outcome measure and only once meta-analyzed (Appendix S1).

Several meta-analyses included subgroup analyses to determine whether specific variables, like age or length of follow-up, were associated with the effectiveness of chronic care management interventions. To find out whether the differences between subgroups were stronger than was to be expected by chance alone, a meta-regression analysis should be performed. However, we found only one study that included a meta-regression analysis (Gohler et al. 2006). Since Gohler et al. limited this meta-regression analysis

Figure 1: Study In/Exclusion Flowchart

to RCTs, insight into the effect of the three selected factors, that is, study quality, length of follow-up, and number of components, is limited.

Findings from the Primary Studies

Of the 46 included primary studies, 44 percent scored “good” on methodological quality (Ekman et al. 1998; Stewart, Pearson, and Horowitz 1998; Gattis et al. 1999; Stewart, Marley, and Horowitz 1999; Blue et al. 2001; Capomolla et al. 2002; Doughty et al. 2002; Harrison et al. 2002; Krumholz et al. 2002; Riegel et al. 2002; Stewart and Horowitz 2002; Ansari et al. 2003; Bouvy et al. 2003; Stromberg et al. 2003; Atienza et al. 2004; DeBusk et al. 2004; Austin et al. 2005; Ducharme et al. 2005; Dunagan et al. 2005; GESICA 2005), 41 percent scored “moderate” (Rich et al. 1995; Weinberger, Oddone, and Henderson 1996; Fonarow et al. 1997; West et al. 1997; Cline et al. 1998; Shah et al. 1998; Heidenreich, Ruggerio, and Massie 1999; Oddone et al. 1999; Bull, Hansen, and Gross 2000; Hughes et al. 2000; Costantini et al. 2001; Holst et al. 2001; Pugh et al. 2001; Whellan et al. 2001; Kasper et al. 2002; McDonald et al. 2002; Benatar et al. 2003; Laramée et al. 2003; Vavouranakis et al. 2003 Naylor et al. 2004), and 15 percent scored “poor” (Roglieri et al. 1997; Branch 1999; Rainville 1999; Rauh et al. 1999; Akosah et al. 2002; Azevedo et al. 2002; Tsuyuki et al. 2004). Length of follow-up varied between 3 and 50 months; two studies reported more than 1 year (Stewart and Horowitz 2002; GESICA 2005). The numbers of studies addressing four, three, or two CCM components were 18, 17, and 11 studies, respectively. The component of chronic care management included most frequently was SMS ($n = 43$), followed by DSD ($n = 38$), CIS ($n = 37$), and DS ($n = 27$) (Table 1).

Notwithstanding the differences in the operationalization of the CCM components between studies, some general trends could be identified. SMS often consisted of patient education and telephone follow-up, DSD was often realized by the introduction of a specialized nurse and/or multidisciplinary team, and CIS mainly consisted of telephone follow-up and DS of protocols for chronic care management. Most studies were performed in primary and secondary care settings with about half of the studies starting after hospitalization. The study aims varied between improving medication prescription (e.g., appropriate beta-blocker prescription), medication adherence (e.g., beta-blocker use), and self-management (e.g., by providing education, self-management monitoring tools, exercise or diet advice), usually with a strong focus on reducing hospitalization.

Table 1: Overview of Primary Studies

<i>Author, Year of Publication</i>	<i>Population*</i>	<i>Intervention</i>	<i>Components</i>	<i>Follow-Up (Months)</i>	<i>Quality (Study Design)</i>
Akosah et al. (2002)	N: 38/63; Age: 68/76*; Male: 71/43*; NYHA: NR; Country: USA	Short-term, multidisciplinary, aggressive-intervention in HF clinic following hospital discharge primarily focused on patient education and medication titration	DSD, SMS	12	40 (other)
Ansari et al. (2003)	N: 54/51; Age: 69/70; Male: 94/98; NYHA: NR; Country: USA	Nurse practitioners initiate and titrate beta-blockers supervised by two cardiologists at a single academically affiliated Veterans Affairs medical center	DSD, DS	12	80 (RCT)
Atienza et al. (2004)	N: 164/174; Age: 69/67; Male: Total: 60; NYHA: 2.5/2.5; Country: Spain	Comprehensive hospital discharge planning, a visit by the primary care physician after discharge to monitor and reinforce the educational knowledge, telemonitoring, and close follow-up at a HF clinic	DSD, SMS, CIS	12	80 (RCT)
Austin et al. (2005)	N: 100/100; Age: 71.9/71.8; Male: 67/64; NYHA: 2.4/2.5; Country: UK	Cardiac rehabilitation program including patient education, exercise training and lifestyle modifications, and eight-weekly clinic attendance with cardiologist and nurse	DSD, SMS, DS	5.5	70 (RCT)
Azevedo et al. (2002)	N: 157/182; Age: 69/65; Male: 52.2; NYHA: NR; Country: Portugal	Outpatient management at HF clinic by a multidisciplinary team after hospital discharge based on current RCTs and tailored to individual's patient characteristics	DSD, DS	12	40 (CCT)

continued

Table 1. Continued

Author, Year of Publication	Population*	Intervention	Components	Follow-Up (Months)	Quality (Study Design)
Benatar et al. (2003)	N: 108/108; Age: 62/63; Male: 36/38; NYHA: Total: 3.1; Country: USA	Nurse telemanagement model provided during a period of 3 months after hospital discharge, incorporating an advanced practice nurse supervised by a cardiologist and home monitoring devices to measure and transfer physiological signs	DSD, SMS, CIS	12	65 (RCT)
Blue et al. (2001)	N: 84/81; Age: 76/74; Male: 64/51; NYHA: 3.2/3.18; Country: Scotland	Nurse specialist making a number of planned home visits of decreasing frequency, supplemented by telephone contact as needed, to educate, monitor, teach self-monitoring and management, liaise with other health care and social workers, and provide psychological support	DSD, SMS, DS, CIS	12	75 (RCT)
Bouvy et al. (2003)	N: 74/78; Age: 69/70; Male: 72/60; NYHA: 2.54/2.31; Country: the Netherlands	Monthly consultations provided by trained pharmacist, including an initial interview regarding patients' drug use and subsequent follow-up for 6 months with computerized medication history, to improve diuretic compliance	DSD, SMS, DS, CIS	6	75 (RCT)
Branch (1999)	N: 23/23; Age: Total: 66; Male: Total: 52; NYHA: NR; Country: USA	CHF clinic that aims to maximize outpatient management by employing a multidisciplinary team of care providers and intensive patient and family education, communication, and involvement	DSD, SMS, DS	3	20 (BA)

continued

Table 1. Continued

Author, Year of Publication	Population*	Intervention	Components	Follow-Up (Months)	Quality (Study Design)
Bull, Hansen, and Gross (2000)	N: 40/71; Age: Total: 74; Male: not stated; NYHA: NR; Country: USA	A professional–patient partnership model of discharge planning, including provider education, patient needs assessment, and information for patient and carers given by the nurses and social workers at the hospital	SMS, CIS	2	50 (CCT)
Capomolla et al. (2002)	N: 112/122; Age: 56/56; Male: 84/84; NYHA: I–II (%): 66/65; Country: Italy	Day hospital follow-up care within a HF unit, which implemented an individualized HF management program by a multidisciplinary team, including education	DSD, SMS, DS, CIS	12	70 (RCT)
Cline et al. (1998)	N: 80/110; Age: Total: 76; Male: Total: 53; NYHA: 2.6/2.6; Country: Sweden	Education on HF and self-management, with follow-up at an easy access nurse-directed outpatient clinic for 1 year after discharge. The nurses received a lecture and could consults the cardiologist	DSD, SMS, DS	12	60 (RCT)
Costantini et al. (2001)	N: 283/173; Age: 72/69; Male: 43/41; NYHA: NR; Country: USA	A cardiologist and nurse care manager at an academic medical center reviewed patient's data and made guideline-based recommendations regarding ACE inhibitor; ECG and implementation of daily weights used for the care manager sheet. The nurse provided patient education, assessed discharge needs, and evaluated patient's ability to comply with prescribed plan	DSD, SMS, DS, CIS	NR	50 (CCT)

continued

Table 1. *Continued*

<i>Author, Year of Publication</i>	<i>Population*</i>	<i>Intervention</i>	<i>Components</i>	<i>Follow-Up (Months)</i>	<i>Quality (Study Design)</i>
DeBusk et al. (2004)	N: 228/234; Age: Total: 72; Male: 48/54; NYHA: NR; Country: USA	Nurse case management provided education, structured telephone surveillance, and treatment for heart failure given by five HMO's hospitals. Coordination of patients' care with primary care physicians according to the study protocol	DSD, SMS, DS, CIS	12	80 (RCT)
Doughty et al. (2002)	N: 100/97; Age: 73/74; Male: 64/57; NYHA: 3.8/3.8; Country: New Zealand	Integrated primary/secondary care involving a clinical review at a hospital-based HF clinic early after discharge, education sessions, a personal diary to record medication and body weight, information booklets, and regular (12 months) clinical follow-up alternating between GP and HF clinic	DSD, SMS, DS, CIS	12	80 (RCT)
Ducharme et al. (2005)	N: 115/115; Age: 68/70; Male: 73/71; NYHA: 3.3/3.2; Country: Canada	A structured multidisciplinary outpatient clinic environment with complete access to cardiologists and allied health professionals, patient education, and telephone follow-up	DSD, SMS, CIS	6	80 (RCT)
Dunagan et al. (2005)	N: 76/75; Age: 71/69; Male: 41/47; NYHA: 2.9/2.9; Country: USA	Scheduled telephone calls by specially trained nurses working at the hospital promoting self-management and guideline-based therapy as prescribed by primary physicians, additional to an educational booklet that is part of usual primary care	SMS, DS, CIS	12	80 (RCT)

continued

Table 1. Continued

Author, Year of Publication	Population*	Intervention	Components	Follow-Up (Months)	Quality (Study Design)
Ekman et al. (1998)	N: 79/79; Age: Total: 80; Male: 58/63; NYHA: 3.2/3.2; Country: Sweden	A nurse-monitored, outpatient care program aiming at symptom management, including education, cooperation of nurses and center doctors, telephone follow-up stated in practical guidelines	DSD, SMS, DS, CIS	6	70 (RCT)
Fonarow et al. (1997)	N: 214/214; Age: Total: 52; Male: Total: 81; NYHA: NR; Country: USA	Comprehensive HF management program, including guideline-based medication management, nurse provided individual and group education and cardiologist follow-up care and telephone follow-up after discharge	SMS, DS, CIS	6	50 (BA)
Gattis et al. (1999)	N: 90/91; Age: 72/63*; Male: 69/67; NYHA: NR; Country: USA	Clinical pharmacist evaluation, which included medication evaluation, therapeutic recommendations to the attending physician, patient education, and follow-up monitoring	DSD, SMS, DS, CIS	6	70 (RCT)
GESICA (2005)	N: 760/758; Age: 65/65; Male: 73/69; NYHA: NR; Country: Argentina	Frequent telephone follow-up from a single surveillance center provided by nurses trained in HF to monitor and reinforce self-management performed by using a predetermined questionnaire	DSD, SMS, DS, CIS	16	85 (RCT)
Harrison et al. (2002)	N: 92/100; Age: 76/76; Male: 53/56; NYHA: 2.9/2.8; Country: Canada	The transitional care used a comprehensive evidence-based protocol for counseling and education for HF self-management plus additional and planned linkages to support individuals in taking charge of aspects of their care given by hospital and community nurses	DSD, SMS, DS, CIS	2.8	70 (RCT)

continued

Table 1. Continued

Author, Year of Publication	Population*	Intervention	Components	Follow-Up (Months)	Quality (Study Design)
Heidenreich, Ruggiero, and Massie (1999)	N: 68/86; Age: 74/75; Male: 58/58; NYHA: NR; Country: USA	Multidisciplinary program of patient education, daily self-monitoring, and physician notification of abnormal weight gain, vital signs, and symptoms given by small practices (largely primary care) of a multispecialty group	SMS, CIS	12	65 (CCT)
Holst et al. (2001)	N: 36/36; Age: Total: 54; Male: Total: 81; NYHA: NR; Country:	Comprehensive management program of cardiology assessment, intensive education, and referral to a tailored exercise program	DSD, SMS	6	50 (BA)
Hughes et al. (2000)	Australia N: 981/985; Age: 70/70; Male: 97/96; NYHA: NR; Country: USA	Home-based primary care, including a primary care manager, 24-hour contact for patients, and home-based primary care team participation in discharge planning	DSD, CIS	12	60 (RCT)
Kasper et al. (2002)	N: 102/98; Age: 60/64; Male: 65/56; NYHA: 2.2/2.5; Country: USA	Multidisciplinary team including nurse coordinator (monitored by telephone calls), CHF nurse (adjusting medication in CHF clinic), CHF cardiologist (decision support for nurses), and primary physician (received updates and managed all not CHF-related problems); intervention given during 6 months	DSD, SMS, DS, CIS	6	65 (RCT)

continued

Table 1. Continued

Author, Year of Publication	Population†	Intervention	Components	Follow-Up (Months)	Quality (Study Design)
Krumholz et al. (2002)	N: 44/44; Age: 76/72; Male: 48/66; NYHA: NR; Country: USA	Face-to-face education session followed by a telemonitoring phase by the nurse for a total intervention period of 1 year. This telephone contacts reinforced care domains but did not modify current regimens or recommendations; the patient learned to understand when and how to seek and access the care	DSD, SMS	12	70 (RCT)
Laramée et al. (2003)	N: 141/146; Age: 71/71; Male: 48/50; NYHA: 2.3/2.2; Country: USA	Four major components: early discharge planning, patient and family CHF education, 12 weeks of telephone follow-up, and promotion of optimal CHF medications given by a CHF case manager of the hospital	DSD, SMS, DS, CIS	3	60 (RCT)
McDonald et al. (2002)	N: 51/47; Age: 71/71; Male: 63/68; NYHA: 3/3; Country: Ireland	Specialist nurse-led education and specialist dietitian consults during admission, also given to patient's carer. In addition, patients were discharged with a letter to the referring physician about the study and that management of HF-related issues should be referred to the clinic or the nurse. Telephone follow-up to ascertain clinical status and discuss problems	DSD, SMS, CIS	3	55 (RCT)

continued

Table 1. *Continued*

<i>Author, Year of Publication</i>	<i>Population*</i>	<i>Intervention</i>	<i>Components</i>	<i>Follow-Up (Months)</i>	<i>Quality (Study Design)</i>
Naylor et al. (2004)	N: 118/121; Age: 76/76; Male: 40/ 44; NYHA: NR; Country: USA	A 3-month comprehensive transitional care intervention directed by advanced practice nurse (APN), including discharge planning and home follow-up. APN received a training program guided by a multidisciplinary team of HF experts, implemented an evidence-based protocol, focused on collaboration between caregivers	DSD, SMS, DS, CIS	12	60 (RCT)
Oddone et al. (1999) and Weinberger, Oddone, and Henderson (1996)	N: 249/255; Age: 63/63; Male: Total: 99 (not disease specific reported), NYHA: 2.5/2.6; Country: USA	A team consisting of a nurse and a primary care physician taking care of discharge planning, arrangement of visits with primary care clinic after discharge, telephone follow-up, review of treatment plans during primary clinic visits consisting of an inpatient and outpatient component	DSD, SMS, CIS	6	55 (RCT)
Pugh et al. (2001)	N: 27/31; Age: 71/77; Male: 44/42; NYHA: 2.6/2.6; Country: USA	Patient education, monitoring and providing care by a nurse case manager of the clinic across the care continuum	SMS, CIS	6	60 (RCT)
Rainville (1999)	N: 17/17; Age: 73/67; Male: 47/53; NYHA: 2.9/3.2; Country: USA	A pharmacist and clinical nurse specialist identified patient issues that posed potential risk for rehospitalization, determined corrective action, and gave patient education	DSD, SMS, CIS	12	45 (RCT)

continued

Table 1. Continued

Author, Year of Publication	Population†	Intervention	Components	Follow-Up (Months)	Quality (Study Design)
Rauh et al. (1999)	N: 347/407; Age: 74/76; Male: 76/74; NYHA: NR; Country: USA	A multidisciplinary team approach included an intensive education program, aggressive pharmacologic treatment for patients with advanced CHF, and telephone follow-up following the developed treatment protocols	DSD, SMS, DS, CIS	3	45 (BA)
Rich et al. (1995)	N: 142/140; Age: 80/78; Male: 32/41; NYHA: 2.4/2.4; Country: USA	A nurse-led multidisciplinary intervention consisting of comprehensive education (patient and family), prescribed diet, social-service consultation and planning for an early discharge, a review of medications, and after discharge intensive follow-up	DSD, SMS, CIS	1.5	60 (RCT)
Riegel et al. (2002)	N: 130/228; Age: 73/75; Male: 54/46; NYHA: NR; Country: USA	Standardized telephonic case-management intervention after hospital discharge using decision-support software based on guidelines, and automatically produced reports sent to the physicians	DSD, SMS, DS, CIS	6	75 (RCT)
Roglietti et al. (1997)	N: 149/149; Age: NR; Male: Missing; NYHA: NR; Country: USA	A comprehensive disease management program for CHF, based on national guidelines, including patient education, telemonitoring of patients, and physician education	SMS, DS, CIS	12	25 (BA)
Shah et al. (1998)	N: 27/27; Age: Total: 62; Male: 100/100; NYHA: Total: 2.6; Country: USA	Education, self-measurement instruments and 24-hour telephone access to a nurse to report changes in combination with telephone contact to monitor. Nurses report the physician monthly	DSD, SMS, CIS	8.5	55 (BA)

continued

Table 1. Continued

Author, Year of Publication	Population [†]	Intervention	Components	Follow-Up (Months)	Quality (Study Design)
Stewart, Pearson, and Horowitz (1998)	N: 49/48; Age: 76/74; Male: 45/52; NYHA: 2.5/2.4; Country: Australia	Multidisciplinary home-based intervention of a single home visit (by a nurse and pharmacist) to optimize medication management, identify early deterioration, and intensify medical follow-up and caregiver vigilance as appropriate. Additional education and incremental monitoring by their physician if needed	DSD, SMS, CIS	6	70 (RCT)
Stewart, Marley, and Horowitz (1999)	N: 100/100; Age: 75/76; Male: 65/59; NYHA: 2.7/2.6; Country: Australia	Multidisciplinary home-based intervention comprised a single home visit (by a cardiac nurse) to optimize medication management, identify early clinical deterioration, and enhance self-monitoring	DSD, SMS, DS, CIS	6	75 (RCT)
Stewart and Horowitz (2002)	N: 149/148; Age: 75/75; Male: 56/56; NYHA: 2.6/2.7; Country: Australia	Multidisciplinary home-based intervention by a cardiac nurse and pharmacist to optimize medication management, identify early clinical deterioration, and enhance self-monitoring. Nurses provided a critical link to the appropriate health care if problems arose	DSD, SMS, CIS	50.4	70 (RCT)
Stromberg et al. (2003)	N: 52/54; Age: 77/78; Male: 63/59; NYHA: 3.0/2.9; Country: Australia	Follow-up at a nurse-led heart failure clinic; given individualized education and psychosocial support, and protocol led medication changes	DSD, SMS	12	90 (RCT)

continued

Table 1. Continued

Author, Year of Publication	Population [†]	Intervention	Components	Follow-Up (Months)	Quality (Study Design)
Tsuyuki et al. (2004)	N: 140/136; Age: 72/71; Male: 58/58; NYHA: 2.3/2.2; Country: Canada	Two stage intervention: (1) a pharmacist nurse assessed each patient and made recommendations to the physician to adjust ACEs; (2) patient education about self-management, adherence aids, newsletters, telephone hotline, and follow-up at 2 weeks, then monthly for 6 months after discharge	SMS, CIS	6	45 (RCT)
Vavouranakis et al. (2003)	N: 28/33; Age: Total: 65; Male: Total: 88; NYHA: Total: 3.4; Country: USA	A home-based intervention including education and follow-up by nurses supervised by a cardiologist	DSD, SMS, CIS	12	65 (BA)
West et al. (1997)	N: 45/50; Age: Total: 66; Male: Total: 71; NYHA: Total: 2.3; Country: USA	A physician-supervised, nurse-mediated, home-based system to promote optimal dose of drugs by consensus guidelines; promote of low sodium intake and surveillance of symptoms and worsening	DSD, SMS, DS, CIS	6	55 (BA)
Whellan et al. (2001)	N: 117/117; Age: Total: 62; Male: Total: 62; NYHA: Total: 2.7; Country: USA	CHF disease management program at a tertiary care center, including patient education and regular (telephone) follow-up	DSD, SMS, DS, CIS	12	60 (BA)

*p-value < .05.
[†]N(I/C); mean age (I/C); % male (I/C); NYHA class (I/C) and country.
BA, before-after study; CCT, nonrandomized controlled clinical trial; CIS, clinical information system; DSD, delivery system design; DS, decision support; RCT, randomized controlled trial; SMS, self-management support.

Hospitalization

The measures of all-cause and HF hospital admission varied between the studies (e.g., at least one hospitalization, length of stay, and cumulative hospital days). The relative risk of at least one hospitalization for any cause was measured most frequently ($n = 27$) (Rich et al. 1995; Fonarow et al. 1997; Cline et al. 1998; Ekman et al. 1998; Shah et al. 1998; Stewart, Pearson, and Horowitz 1998; Oddone et al. 1999; Stewart, Marley, and Horowitz 1999; Hughes et al. 2000; Blue et al. 2001; Pugh et al. 2001; Capomolla et al. 2002; Doughty et al. 2002; Harrison et al. 2002; Krumholz et al. 2002; Riegel et al. 2002; Stewart and Horowitz 2002; Laramée et al. 2003; Stromberg et al. 2003; Atienza et al. 2004; DeBusk et al. 2004; Naylor et al. 2004; Tsuyuki et al. 2004; Austin et al. 2005; Ducharme et al. 2005; Dunagan et al. 2005; GESICA 2005). The result of five studies were not included in the meta-analysis because of missing data (Shah et al. 1998; Krumholz et al. 2002; Stromberg et al. 2003) or because preliminary results were reported (we only included the last results of the same primary study) (Stewart, Pearson, and Horowitz 1998; Stewart, Marley, and Horowitz 1999). In total, 22 studies were included in our meta-analysis on all-cause hospitalization (i.e., the number of patients with at least one all-cause hospitalization during the study period).

The pooled relative risk for all-cause hospitalization with chronic care management compared with the control intervention (mostly usual care) is 0.82 (95 percent CI: 0.72–0.94; I^2 : 84 percent). Subgroup analyses showed that studies of good methodological quality, with a follow-up period of at least 1 year, and studies reporting on interventions including three CCM components demonstrated a significant reduction in the number of patients with at least one all-cause hospitalization. The associations suggested by the subgroup analyses, like the positive association between the study quality and hospitalization, were tested by the meta-regression analysis. Meta-regressions showed no significance of the three factors ($p > .50$), which implies that these could not significantly explain the heterogeneity between the studies.

Mortality

Twenty-nine studies reporting on all-cause mortality were included in our meta-analysis (Rich et al. 1995; Cline et al. 1998; Ekman et al. 1998; Gattis et al. 1999; Oddone et al. 1999; Rainville 1999; Blue et al. 2001; Pugh et al. 2001; Akosah et al. 2002; Azevedo et al. 2002; Capomolla et al. 2002; Doughty et al. 2002; Kasper et al. 2002; Krumholz et al. 2002; McDonald

et al. 2002; Stewart and Horowitz 2002; Ansari et al. 2003; Bouvy et al. 2003; Laramée et al. 2003; Atienza et al. 2004; DeBusk et al. 2004; Naylor et al. 2004; Austin et al. 2005; Ducharme et al. 2005; Dunagan et al. 2005; GESICA 2005). Overall, the pooled effect showed a significantly reduced relative risk of mortality (RR: 0.82; 95 percent CI: 0.76–0.93; $I^2 = 0$ percent). This implies that the chance to die during the follow-up period is reduced by 18 percent for patients receiving chronic care management.

Subgroup analyses showed that pooled effects for studies of a moderate quality, with a follow-up period of less than 1 year, or on three CCM components were not associated with a significant reduction of mortality (Table 2). Meta-regression analysis was used to determine whether the variables were associated with the effect, as no heterogeneity had to be explained ($I^2 = 0$ percent). The meta-regression analysis showed that none of the variables were associated with the effect of chronic care management on mortality ($p > .05$).

Quality of Life

A variety of instruments was used to assess quality of life; the Minnesota Living with Heart Failure (MLHF) questionnaire was used most frequently ($n = 14$) (Stewart, Marley, and Horowitz 1999; Holst et al. 2001; Doughty et al. 2002; Harrison et al. 2002; Kasper et al. 2002; Benatar et al. 2003; Bouvy et al. 2003; Vavouranakis et al. 2003; Atienza et al. 2004; Naylor et al. 2004; Austin et al. 2005; Ducharme et al. 2005; Dunagan et al. 2005; GESICA 2005). The scores of the MLHF questionnaire range from 0 (best quality of life score) to 105 (worst quality of life score). For the meta-analysis, results of seven studies could be used (Holst et al. 2001; Harrison et al. 2002; Benatar et al. 2003; Bouvy et al. 2003; Vavouranakis et al. 2003; Naylor et al. 2004; Austin et al. 2005), the remaining studies were excluded because of missing or skewed data (Stewart, Marley, and Horowitz 1999; Doughty et al. 2002; Kasper et al. 2002; Atienza et al. 2004; Ducharme et al. 2005; Dunagan et al. 2005; GESICA 2005).

The meta-analysis demonstrated a significant improvement in quality of life of 7.14 points on the MLHF questionnaire (95 percent CI: –9.55 to –4.72). Subgroup analyses showed that the pooled effect of studies of a good quality, with a follow-up of less than 1 year, or on two or three components are significantly positive (Table 2). The heterogeneity between the studies in the subgroups is substantial (I^2 : 50–90 percent) or considerable ($I^2 > 75$ percent). Meta-regression analysis could not be performed, as fewer than 10 studies were available.

Table 2: Results Meta-Analysis and Meta-Regression

	No. of Studies	No. of Participants	Relative Risk (95% CI; I^2) [†]	Explained Heterogeneity (p -Value)
Hospitalization	22	6,586	0.82 (0.72–0.94; 84%)*	
Quality				
Poor	1	276	1.12 (0.84–1.50; NA)	1.7% (.616)
Moderate	8	1,868	0.78 (0.53–1.14; 92%)*	
Good	13	4,442	0.86 (0.78–0.96; 61%)*	
Length of follow-up				
<1 year	10	2,590	0.81 (0.58–1.12; 91%)*	3.1% (.566)
≥ 1 year	12	3,996	0.85 (0.77–0.95; 60%)*	
Number of components				
2	3	361	1.02 (0.82–1.25; 0%)*	1% (.789)
3	8	2,186	0.69 (0.49–0.97; 94%)*	
4	11	4,039	0.91 (0.83–1.01; 54%)*	
Mortality	27	6,832	0.82 (0.76–0.93; 0%)*	
Quality				
Poor	3	474	0.69 (0.50–0.95; 10%)*	No
Moderate	8	1,797	1.00 (0.78–1.28; 21%)*	heterogeneity
Good	15	4,327	0.79 (0.67–0.93; 30%)*	(.915)
Length of follow-up				
<1 year	11	2,268	0.94 (0.74–1.18; 0%)*	No
≥ 1 year	16	4,564	0.79 (0.68–0.91; 29%)*	heterogeneity
				(.781)
Number of components				
2	5	692	0.67 (0.50–0.91; 8%)*	No
3	10	2,050	0.88 (0.69–1.13; 19%)*	heterogeneity
4	12	4,090	0.85 (0.73–0.98; 17%)*	(.191)
			<i>Mean Difference (95% CI; I^2)[‡]</i>	
Quality of life	7	992	–7.14 (–9.55–4.72; 78%)*	
Quality				
Poor	0	NA	NA	NA
Moderate	4	588	–6.65 (–14.19–0.88; 78%)*	
Good	3	404	–10.93 (–16.96 to –5.71; 50%)*	
Length of follow-up				
<1 year	5	692	–10.64 (–15.77 to –5.51; 78%)*	NA
≥ 1 year	2	300	–1.71 (–10.68–7.25; 63%)*	
Number of components				
2	1	72	–21.00 (–33.23 to –8.77; NA)*	NA
3	3	456	–9.19 (–14.67 to –3.70; 56%)*	
4	3	464	–4.32 (–14.46 to 5.82; 85%)*	

Boldface type indicates overall analysis.

* p -value < .05.

[†]Relative risk for CCM within the various subgroups.

[‡]Mean difference for CCM within the various subgroups; CI, confidence interval; I^2 , statistical heterogeneity.

DISCUSSION

This systematic review showed that predominantly positive effects of chronic care management on clinical outcomes and health care consumption were reported by earlier reviews. Since size and significance of the effects vary due to considerable methodological and clinical heterogeneity between the reviews and their included studies, we performed a meta-regression analysis. The analysis showed a significant reduction of 18 percent in mortality, irrespective of the differences between the studies. Furthermore, all-cause hospitalization and quality of life improved significantly, yet, with substantial heterogeneity between the studies, which could not be explained by the quality of the studies, the length of follow-up, or the number of CCM components.

In addition to previously published reviews and studies, this review gives a comprehensive overview of previously published reviews and studies as well as a meta-regression analysis to explain the heterogeneity in outcomes. Although several reviews showed substantial differences in effect of chronic care management in subgroup meta-analyses for the quality of the studies, the direction of these differences was inconsistent between these reviews (Gonseth et al. 2004; Kim and Soeken 2005; Roccaforte et al. 2005; Taylor et al. 2005). None of these reviews had tested these associations suggested by the subgroup analysis with meta-regression analysis. Length of follow-up was studied in one meta-regression study only. In line with our results, Gohler et al. (2006) concluded that the effect on hospitalization remained when follow-up exceeded 3 months. In addition, these authors reported substantial effects on mortality due to diversity in length of follow-up, but significance of this explained heterogeneity was not reported ($I^2 = 34$).

Our study aimed to find out whether the number of CCM components is positively associated with the effect of chronic care management, as comprehensive programs are expected to be more effective (Wagner et al. 2005). We found no association between the number of components and the effect of chronic care management. However, other aspects of chronic care management interventions such as the integration of the components could also influence its effectiveness. Only one earlier review tried to explain heterogeneity by characteristics of chronic care management using meta-regression analysis. Gohler et al. (2006) found that the number of disciplines participating in the chronic care management interventions explained 60 and 68 percent of the differences in effect size for mortality and hospitalization, respectively. These results are in line with several subgroup analyses previously published

(McAlister et al. 2001; Duffy, Hoskins, and Chen 2004; Sochalski et al. 2009) and imply that chronic care management is more effective if more disciplines participate. Subgroup analysis identified several other characteristics that might influence the effectiveness of chronic care management interventions: in-person communication (Sochalski et al. 2009), follow-up at the outpatient clinic (Whellan et al. 2005), complex programs that include hospital discharge planning and no delay in postdischarge clinic follow-up (Phillips et al. 2005), patient education (McAlister et al. 2001; Windham, Bennett, and Gottlieb 2003; Yu, Thompson, and Lee 2006), and ongoing patient monitoring (Ansari et al. 2003; Yu, Thompson, and Lee 2006). However, the influence of these characteristics must be interpreted with caution, as the reported associations were not tested by meta-regression analyses.

Several limitations should be noted. First, even though an extensive search, based on the WHO's broad definition of chronic care management, was performed, we restricted the selection of our primary studies to published reviews. As a consequence, publication bias might have influenced the results, since more negative results and/or recently published studies were not included. However, this limitation will probably be limited, as the reviews included were peer reviewed and most of them included a publication bias analysis. Next, it is disputable whether the HTA-DM instrument—the only tested instrument for assessing the quality of complex interventions—properly measures the items that bias the effect of the interventions for heart failure, as it primarily focuses on the quality of reporting. Third, we limited our analysis to three a priori selected variables, that is, the quality of the studies, the length of follow-up, and the number of CCM components. However, additional causes of heterogeneity are suggested and should be further studied. For instance, it was suggested that more recent studies showed a lower or no effectiveness of chronic care management interventions compared with earlier studies (Clark and Thompson 2010). Although additional analyses of our dataset showed that year of study performance did not explain heterogeneity (data not shown), more recent studies should be included in future reviews since we only included studies from before 2006. Besides year of study performance, other causes of heterogeneity should be studied such as contextual factors (e.g., professional's behavior and unit of randomization) as well as characteristics of the intervention (e.g., combination of CCM components and intervention intensity). For example, almost all studies randomized on patient level except four studies, with contamination as well as limited insight in the contextual influences as a consequence. Furthermore, results of our subgroup analysis should be interpreted with caution, since these results

are more than once based on fewer than 10 studies. Meta-regression analysis gave the opportunity to restrict this limitation for the length of follow-up and the study quality by including these variables as continuous variables. Finally, analyses of heterogeneity are limited by the quality and comprehensiveness of data reported in the primary studies. In particular, the care received by the control group, as well as results, such as *p*-values and standard deviations, was frequently not fully reported and therefore excluded from our meta-analysis.

As insight into the effect of chronic care management for heart failure is limited, more efforts should be made to assess the effectiveness. In particular, the follow-up period of chronic care management should be extended to enable the assessment of the effects after several years. Complex improvements, which need behavioral, organizational, and cultural changes, need time to take effect. Only Stewart and colleagues had a follow-up period of more than 2 years, but the intervention in this study consisted of just one home visit (Stewart and Horowitz 2002). Furthermore, the influence of co-morbidity, which is highly prevalent in the heart failure population (Bayliss, Ellis, and Steiner 2007; Marengoni et al. 2009), needs to be addressed, which the earlier primary studies failed to do. Moreover, effectiveness is most frequently assessed using clinical outcomes, like mortality and hospitalization, whereas more patient-centered outcomes are less frequently monitored. Meanwhile, a great variety of instruments that are sometimes difficult to compare is used to measure outcomes, like patient satisfaction and medication adherence, which complicates comparing or pooling of data.

Consequently, insight into the influence of other factors of chronic care management than those three studied in our review (study quality, length of follow-up, and number of CCM components) is needed. Although these three variables for the subgroup analyses and meta-regression were selected on the basis of available evidence (McAlister et al. 2001; Windham, Bennett, and Gottlieb 2003; Yu, Thompson, and Lee 2006), heterogeneity between studies regarding the effect on quality of life and hospitalization might be caused by variables other than those measured, such as the extent to which the components are implemented and the contextual setting (Berwick 2008; Clark and Thompson 2010), which highlights the need for multilevel analysis. Even though context and manner of implementation are expected to influence the effectiveness of chronic care management, as implementing such complex interventions is essentially a process of social change (Berwick 2008; Lemmens et al. 2008; Clark and Thompson 2010), studies revealed little about these influences. For instance, professional behavior is likely to influence the effectiveness of chronic care

management interventions (Clark and Thompson 2010). More attention should be paid to proper development and implementation of chronic care management programs to use its full potential to create a comprehensive care for chronically ill.

CONCLUSION

Our meta-regression analysis showed that mortality is reduced by chronic care management, irrespective of the differences between the studies included. Furthermore, the meta-regression analysis revealed that all-cause hospitalization and the quality of life could significantly be improved by chronic care management. The study quality, the length of follow-up, and the number of CCM components do not determine the effectiveness of chronic care management. Considering the unexplained heterogeneity in effectiveness across chronic care management interventions, more attention to the development and implementation of chronic care management is needed to support informed decision making about how to best redesign chronic care.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.

Appendix S1: Overview of Systematic Reviews Included.

Appendix S2: Detailed Description of Primary Studies Included.

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