Title: Polypharmacy in Heart Failure, a growing challenge

Lead Author:

Claire A Rushton – Lecturer in Nursing, School of Nursing and Midwifery, Keele University, Staffordshire

Additional authors:

Umesh T. Kadam - Senior Lecturer in General Practice/Epidemiology, Health Services Research Unit, North Staffordshire Medical Institute, Stoke-on-Trent, Staffordshire

Name and address of the author responsible for correspondence:

Ms C. A. Rushton

School of Nursing and Midwifery

Clinical Education Centre

University Hospital of North Staffordshire NHS Trust

Newcastle Road

Stoke-on-Trent

Staffordshire

ST4 6QG

Email: c.a.rushton@nur.keele.ac.uk

Telephone: 01782 556619

Word count: 3001 (tables and references not included in the count)

Abstract

Current guidelines in Heart failure recommend 'add on' prescribing of evidence based medicines aimed at improving symptoms and prognosis. Heart failure patients therefore commonly receive multiple drug therapies and this 'polypharmacy' is set to increase with the recognition of new potential drug targets. Drug regimes in heart failure are further complicated by increasing age and high levels of comorbidity inherent in this patient group. Nurses are central to the patient's care pathway and the commencement and titration of medicines are a key component of the patient's management plan. The development of nursing specialism in heart failure alongside independent prescribing have further extended nurse's responsibilities. Polypharmacy is an important consideration for nursing and this paper will provide an overview of the development of drug therapies in heart failure as well as the scope of polypharmacy for this group. The key implications of polypharmacy in heart failure will be explored which include side effects, drug interactions, prescription errors, optimal clinical prescribing and patient adherence.

Key Words: heart failure, polypharmacy, nursing, side effects, prescribing, adherence.

Background

The prevalence of heart failure in the Western world is approximately 2% and this figure is set to rise in an ageing society. In older populations the percentage of people with heart failure rises abruptly to 7% in the 75-84 year age group and 15% in the 85 year and over age group (Davies, Hobbs et al. 2001). Despite the development of a plethora of pharmacological and non-pharmacological therapies for heart failure over the past three decades, mortality rates remain high. Over a third of heart failure patients die within a year of diagnosis (Cowie et al, 2000), a figure similar to outcomes for many common cancers. Management of heart failure is becoming ever more complex with the increasing average age of the heart failure patient. Older age in heart failure is associated with a higher number of diseases per patient and comorbidity is now the norm in heart failure (Braunstein et al, 2003), with the proportion of patients experiencing more than five comorbidities increasing over recent years to 58% (Wong et al, 2011). This comorbidity predisposes heart failure patients to polypharmacy due to the potential for an increased number of medications for each disease indication and also the widespread variation in the application of current heart failure guidelines to the comorbid patient (Sturm et al, 2006). Before we take a closer look at the nature and implications of polypharmacy in heart failure it is first necessary to clarify the meaning of 'polypharmacy'.

Definitions of polypharmacy

The meaning of 'polypharmacy' lacks consensus in the literature but two definitions are commonly used. The first and most frequent definition relates to the number of medications that an individual takes with various minimum drug counts used (Linjakumpu et al, 2002, Cannon et al, 2006). The other common use of 'polypharmacy' refers to the use of potentially inappropriate medications or medications that are not clinically indicated (Hajjar et al, 2005). There are difficulties with both of these definitions when evaluating pharmacotherapy. A linear relationship between the number of drugs that are prescribed for a patient and the number of drug related problems has been demonstrated (Viktil et al, 2006). The implication of this when evaluating risks and benefits of treatment regimes is that a definitive cut-off point for the number of drugs to define polypharmacy is inappropriate. Secondly it has been argued that using the two meanings, often interchangeably within the

literature, have resulted in 'polypharmacy' taking on a negative 'value' (Bushardt et al, 2008). Yet patients, particularly those with complex chronic conditions and comorbidities such as heart failure, may require multiple drugs to improve their conditions. Indeed evidence based guidelines support the use of multiple therapies (NICE 2010). Neither definition embraces one of the ongoing challenges in heart failure therapy which is the 'underuse' of certain evidenced based medications. This discussion will explore polypharmacy in its literal sense meaning 'multiple drug therapies' which includes the number and range of drug therapies for heart failure patients and implicitly accommodates discussion around the drugs that are and are not indicated in heart failure.

The development of pharmacotherapy in heart failure

Heart failure is a complex multisystem syndrome, caused by diverse aetiology, which implies that the heart's ability to maintain physiological function is impaired. Heart failure is classified in current guidance as heart failure with left ventricular systolic dysfunction (LVSD) and heart failure with preserved ejection fraction (HFPEF) (NICE 2010). Much of the development of heart failure pharmacotherapy has been based on evidence relating to patients with LVSD. There remains little conclusive evidence on the outcomes of common heart failure drugs on patients with HFPEF (Leibundgut et al, 2007). The following overview of pharmacological developments is therefore restricted to LVSD. However, given the need to manage the complex aetiology of HFPEF e.g. treatment of hypertension or dyslipidaemia, the implications of polypharmacy in HFPEF still apply.

Pharmacological developments in heart failure have been driven to an extent by the evolving definition and understanding of the heart failure syndrome and associated pathophysiologic processes. Traditionally the understanding of heart failure as predominantly a haemodynamic syndrome led to the investigation and discovery of the benefits of vasodilators (e.g. nitrates and hydralazine) to supplement digoxin and diuretics. This combination was found to improve ventricular function and reduce mortality (Cohn et al, 1986). Angiotensin Converting Enzyme Inhibitors (ACEI) as potential vasodilators were then tested and found to be superior to other vasodilators demonstrating benefits over and above their vasodilator abilities (Flather et al, 2000). This led to interest in the function of ACE inhibition within the Renin-Angiotensin-

Aldosterone (RAA) pathway and the developing interest in and understanding of neurohormonal processes in heart failure. Research into a number of drugs aimed at antagonism of RAA pathway ensued. Recognition of Angiotensin II as important in ventricular remodelling soon led to the development of Angiotensin Receptor Blockers (ARB) (McMurray et al, 2003). Aldosterone was also noted to impact on heart failure progression particularly in relation to myocardial and vascular fibrosis and led to the development of Aldosterone Antagonists (AA) to be added to ACEI (Pitt et al, 1999). Other neurohormonal pathways then became the focus of attention such as the sympathetic nervous system which resulted in the recognition of the positive benefits of adding beta blockade in reducing heart failure progression and mortality (Packer et al, 1996).

Each drug developed targets a different pathophysiological mechanism associated with the heart failure syndrome. This together with the ethical constraints in using placebo-controlled trials or withdrawing beneficial medications from trial participants, has led to the evidence that supports pharmacotherapy in heart failure being developed from data largely generated in 'add on' trials (Flesch, Erdmann 2006). The positive outcomes identified from adding new drugs to patients' current regimes has led to the cumulative list of evidence based therapies that heart failure patients can now expect as their disease progresses (see figure 1). A patient in end stage heart failure receiving nationally guided therapy can expect to receive 6 or more medications for their heart failure alone.

Future developments

New insights into the heart failure syndrome generated by basic science have stimulated interest into heart failure at an intracellular and molecular level. Myocytic processes have been targeted for investigation including cellular hypertrophy, fibrosis, inflammation, calcium sensitivity and metabolic processes amongst others (Kaye, Krum 2007). This together with the developing understanding of the influence of genetics and epigenetics in heart failure (Katz 2008) creates an array of potential pharmacological targets. Whilst preliminary research in some of these areas has been unpromising the potential for production of a variety of new candidates for addition to the heart failure drug collection remains.

The scope of polypharmacy in heart failure

As well as managing heart failure, clinicians need to address causative factors and comorbidities. The aetiology of heart failure is diverse and may be related to cardiac pathologies such as atherosclerosis, valvular heart disease or cardiomyopathy or non cardiac pathologies such as pulmonary hypertension or thyroid disease. The range of comorbidities commonly found in the heart failure population are equally diverse including hypertension, arthritis, kidney disease, diabetes and chronic obstructive pulmonary disease and comorbid 'states' including anaemia, obesity and depression (Braunstein et al, 2003, Wong et al, 2011, Havranek et al, 2002) , all of which may require additional pharmacological management.

The average number of medications identified by a cross sectional survey of patients with self reported heart failure (n=534) was 6.4 (Wong et al, 2011). This number is reflected in a larger study of heart failure patients on hospital discharge (n=30774). The average number of drugs was 7.5 which included 11.1 daily doses with the top 10% of patients taking 11 medications with at least 18 doses daily (Masoudi et al, 2005). Of these drugs 60% were cardiovascular and 40% were non cardiovascular medicines. The most common non- cardiovascular drug classes included those for lung disease, hypothyroidism, diabetes, gastrointestinal and psychiatric conditions. Both studies demonstrated an increase in the number of drugs prescribed over previous years particularly non cardiovascular drugs. This potentially reflects the increased comorbidity in heart failure (Wong et al, 2011) but also the change in drug profile for heart failure patients with an increase in the prescription of drugs demonstrated to improve survival e.g. ACEI and beta blockers and a reduction in the prescription of drugs with less clear or no benefit on survival e.g. digoxin (Lee, Mamdani et al. 2004).

Additional to prescribed medication, patients have access to over the counter medications and other drugs at home including left over or previously discontinued prescription medications. Investigation into the nature of polypharmacy in older adults has found that most take one or more non prescription medications with 50% taking between 2 and 4 over the counter medications (Stoehr et al, 1997). The complexity of managing pharmacotherapy for this patient group is intensified by the fact that the medications that patients bring to and report as taking at clinic have

been found to differ from what they actually take regularly at home for approximately 50% of patients (Yang et al, 2001).

Implications

Side effects and drug interactions

The number of medicines that a patient is prescribed has been associated with an increased risk of drug related problems (Viktil et al, 2006), drug interactions (Ledwidge et al, 2004) and poorer physical and overall health status (Kadam 2011). One study found that 17% of heart failure patients report adverse effects from their drug regimes (De Smedt et al, 2009). As well as the increased risk of side effects and drug interactions from multiple drug therapy in heart failure, the condition itself results in altered drug metabolism and elimination secondary to altered liver and renal perfusion (Faulx, Francis 2008). These effects are exacerbated by age and yet it is well recognised that the development of pharmacology in heart failure has been driven by clinical trials whose inclusion criteria may not reflect the average older heart failure patient with coexisting disease (Heiat et al, 2002). Transferring this evidence into practice can therefore be difficult and whilst medications are generally beneficial they still have the potential to do harm. The combination of drugs used in heart failure carries risks of renal deterioration, hyperkalaemia and hypotension (Flesch, Erdmann 2006) and these can be exacerbated in the elderly (Leibundgut et al, 2007). The three RAA antagonists (ACEi, ARB and AI) used in heart failure can each cause reduced renal function and increased potassium levels due to their potassium sparing properties. Using these drugs in combination further increases the risk of side effects (Juurlink et al, 2004, Cohn, Tognoni 2001). Diuretics can also deteriorate renal function particularly in the elderly and should be used at the minimum effective dose (Leibundgut et al, 2007). Whilst heart failure licensed beta blockers have been found to be safe in the elderly (Flather et al, 2005), the potential for symptomatic hypotension is high. Clinicians need to be aware of the side effects and use the 'start low, go slow' techniques recommended in current guidance (NICE 2010) with regular monitoring for signs of clinical deterioration following drug commencement and dose titration.

Other cardiovascular and non cardiovascular drugs can cause adverse reactions in heart failure or exacerbate the condition. These drugs should be avoided or used with caution (see table 1 for common examples).

Influence of polypharmacy on prescription errors

Drug errors including incorrect dose and frequency, omissions and inappropriate prescriptions are a potential hazard for patients prescribed multiple drug regimes. Heart failure patients are at risk of potentially inappropriate medication and dangerous drug interactions due to the number of medications that they are prescribed at the same time (Cannon, Choi et al. 2006) and also because of the frequency of hospital admissions in heart failure. The healthcare interface between primary and specialist led care is a common point where medication changes are made and relies on good communication between clinicians and patients to prevent drug omissions and prescription errors (Coleman et al, 2005).

Influence of polypharmacy on clinician prescribing

Heart failure pharmacotherapy is frequently characterised in the literature by the 'underuse' or inappropriate application of evidence based therapy. A common explanation for this is the reluctance of clinicians to prescribe common heart failure drugs (such as ACEI and beta blockade) to people with comorbidities (such as Chronic Obstructive Pulmonary Disease or renal dysfunction) for fear of adverse effects. In a large European study (n=11062) only 56% of heart failure patients from primary care were prescribed rational drug regimes and therapy was strongly influenced by age and comorbidities. The remaining 44% of patients were not on guided drug regimes despite taking co-morbidity into account (Sturm et al, 2003). It may be that guideline adherence is higher than is commonly reflected in quantitative analyses of prescription data when patient reported contraindications are taken into account (Oertle, Bal 2010). However it is becoming clearer that with careful prescribing people with comorbidities can safely tolerate most heart failure medicines (Rich 2005) and this is reflected in the current guidance (NICE 2010). One factor that might contribute to under dosing of heart failure drugs is the slow titration required for example ACEI should be incrementally increased at 1-2 week intervals and it may be that discharge from hospital before optimum dose is reached can lead to patients receiving prolonged suboptimal dosing (Ryder, Travers et al. 2003b). Whilst still not

optimal (Komajda et al, 2005) guideline adherence has been found to improve when care is directed by heart failure specialists resulting in reduced inappropriate, omitted or incorrectly dosed medications (Ledwidge et al, 2004) and one way to improve adherence might be the quick up-titration of medicines by specialist nurses before discharge (Ryder et al, 2003). The improved application of guidelines by heart failure specialists has also been demonstrated for beta blockade (Mariani et al, 2008). However it has to be noted that this improved adherence to guidelines comes at the inevitable expense of increased numbers of medicines and doses and increased risk of drug interactions and adverse effects.

Influence of polypharmacy on patient adherence

Approximately 90% of heart failure patients have been assessed as not being fully compliant with medicine regimes. Non adherence to medication can lead to exacerbation of heart failure and is an important factor in preventable hospital admissions and increased healthcare costs (Hauptman 2008). In terms of polypharmacy it is not the number of medications taken by the average heart failure patient that has been found to impact on adherence (Shalansky, Levy 2002) but the complexity of drug regimes that require repeated daily doses and frequent dose titration (Paes et al, 1997). Additionally there is growing evidence that it is patients' perception of medication barriers or lack of self efficacy that leads to non adherence rather than the number or frequency of medications (Wu et al, 2008). Patients taking multiple drug therapies for different conditions have reported that drug regimes can be restricting and demanding and whilst they may acknowledge the necessity of some drugs they have an aversion to taking them (Townsend et al, 2003). Patients may doubt the efficacy of a drug treatment or feel that symptom improvement reflects a reduced need for medication. This implies that psychosocial factors that include patient understanding impact greatly on whether polypharmacy is important in non-adherence and supports the move towards guidance focusing on concordance rather than compliance (NICE 2009). Non adherence is a complex problem associated with multiple factors that are both intrinsic to the patient (attitudes, aptitude, perception, understanding, medical problems, etc) and extrinsic to the patient (treatment regimes, healthcare systems, socio-economic status etc) (World Health Organization 2003). Practitioners need to engage patients in treatment

decisions and take account of the range of influences that might impact on the optimum drug regime for individual patients.

Implications of polypharmacy for nursing

Polypharmacy continues to be a significant issue in heart failure. Drug therapies are a necessary and important part of patient management in order to improve prognosis and reduce mortality but there is currently limited information to guide optimal drug regimes for older patients with comorbidity. Nurses play a central role in the assessment, diagnosis and clinical management of heart failure patients and in recent years have extended their responsibilities to include independent prescribing. Nurses are therefore in a prime position to oversee the management of complex drug regimes including the commencement and titration of drugs. Nurse's have a responsibility to ensure that patients' drug regimes are safe, appropriate and effective and are well placed to keep close supervision on patients' response to therapy. Nurses should ensure regular review of patients' treatment regimes (see table 2) in order to discontinue medications that are not clinically indicated and optimise evidenced based heart failure treatments whilst taking the context of the patient's individual circumstances into account.

Patients need clear communication regarding the evidence that supports medications so that they can make informed decisions. These treatment decisions may include a 'trade off' between quality and quantity of life and patient centric decisions are more likely to improve adherence with treatment regimes. Educational interventions need to promote self efficacy so that patients are informed of the possible side effects of medications and are able to recognise changes in their condition that require clinician review. Communication also needs to be clear between clinicians within and outside of clinical settings so that treatment objectives and regimes remain consistent across healthcare interfaces.

Key points:

- Older age and comorbidity in heart failure predisposes patients to polypharmacy

- Polypharmacy is a growing challenge with new developments in heart failure pharmacotherapy
- Polypharmacy is associated with increased risk of drug interactions, adverse reactions and prescription errors
- Clinician adherence to evidenced based guidelines is suboptimal
- Drug adherence in heart failure is influenced by multiple factors including self efficacy and complex drug regimes
- Nurses need to ensure that patient's drug regimes are safe, appropriate and effective.
- Communication of drug regimes needs to be clear between patients and clinicians across healthcare interfaces.

Figure 1: Development of evidence based heart failure pharmacotherapy guideline

Table 1: Potential drug contraindications in heart failure

Drug	Examples	Mechanism of adverse effect	Time to onset	Recommendation
Class 1 and 111 Antiarrhythmics (excluding Amiodarone and Dofetilide)	Disopyramide Lidocaine Flecainide Sotalol	Reduced cardiac contractility Proarrhythmic effects	Hours to months	Avoid use Consider Amiodarone or dofetilide for patients with symptomatic or non-device managed arrhythmias
Calcium channel blockers	Verapamil Diltiazem Nifedipine Nicardipine	Reduced cardiac contractility Neurohormonal activation	2 to 3 months	Avoid use
B2 Agonists (Bronchodilators)	Terbutaline Salbutamol	Increased heart rate Hypokalemia Arrhythmias	Unknown	Avoid systemic administration and use via inhaled route at lowest effective dose
Carbamazepine	N/A	Reduced cardiac	Unknown	Avoid if possible

		contractions and heart rate Altered electrophysiology		
Tricyclic Antidepressants	Amitriptyline	Reduced cardiac contractility Proarrhythmic effects	Weeks to years	Avoid if possible, use other agents for depression and neuropathy
Amphetamines	Racemic amphetamine Methamphetamine	Tachycardia Arrhythmias	Unknown	Avoid use
Metformin	N/A	Increased anaerobic glucose metabolism and elevated lactate	Anytime – sensitive to renal function changes	Avoid in HF patients with NYHA class III or IV or those with frequent decompensations. Monitor all other HF patients taking Metformin
Corticosteroids	Hydrocortisone Cortisone	Sodium and fluid retention Hypertension	Days to weeks	Use lowest effective dose Monitor for new or increased HF symptoms
Nonsteroidal Anti-Inflammatory Drugs	Diclofenac Ibuprofen Indomethacin High dose aspirin	Reduced renal blood flow Sodium and fluid retention Blunted response to diuretic therapy Increased systemic vascular resistance	Days up to 1 month	Avoid in symptomatic LVSD if possible Low dose Aspirin should be used for primary or secondary prevention of cardiovascular disease where indicated
(Amabile, Spencer 2004)				

Table 2: Medication review checklist

Is there a clear indication for the drug?

Is the medication known to be effective for the condition?

Is the dosage correct?

Are there any clinically significant drug interactions?

Are there any clinically significant drug-disease interactions?

Is the duration of therapy appropriate?

Is the drug being used to treat the adverse effect of another medication?

Is the drug causing a significant adverse effect?

Is the drug the least expensive of equally effective alternatives?

(Zarowitz 2006)

Amabile C, Spencer A (2004) Keeping Your Patient With Heart Failure Safe: A Review of Potentially Dangerous Medications. *Archives Internal Medicine* 164(7):709-720.

Braunstein J, Anderson G, Gerstenblith G et al (2003) Noncardiac comorbidity increases preventable hospitalizations and mortality among medicare beneficiaries with chronic heart failure. *Journal of the American College of Cardiology* 42(7):1226-1233.

Bushardt R, Massey E, Simpson T, Ariail J, Simpson K (2008) Polypharmacy: Misleading, but manageable. *Clinical Interventions in Ageing* 3(2):383-389.

Cannon K, Choi M, Zuniga M (2006) Potentially Inappropriate Medication Use in Elderly Patients Receiving Home Health Care: A Retrospective Data Analysis. *The American Journal of Geriatric Pharmacotherapy* 4(2):134-143.

Cohn J, Archibald D, Ziesche S et al (1986) Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure. *New England Journal Medicine* 314(24):1547-1552.

Cohn J, Tognoni G (2001) A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure. *New England Journal Medicine* 345(23):1667-1675.

Coleman E, Smith J, Raha D, Min S (2005) Post hospital Medication Discrepancies: Prevalence and Contributing Factors. *Archives Internal Medicine* 165(16):1842-1847.

Cowie M, Wood D, Coats A (2000) Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 83:505-510.

Davies M, Hobbs F, Davis R et al (2001) Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *The Lancet* 358(August):439-444.

De Smedt R, Denig P, Haaijer-Ruskamp F, Jaarsma T (2009) Perceived Medication Adverse Effects and Coping Strategies Reported by Chronic Heart Failure Patients. *International Journal of Clinical Practice* 63:233-242.

Faulx M, Francis G (2008) Adverse Drug Reactions in Patients with Cardiovascular Disease. *Current Problems in Cardiology* 33(12):703-768.

Flather M, Yusuf S, Køber L et al (2000) Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *The Lancet* 355(9215):1575-1581.

Flather M, Shibata M, Coats A et al (2005) Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *European Heart Journal* 26(3):215-225.

Flesch M, Erdmann E (2006) The Problem of Polypharmacy in Heart Failure. *Current Cardiology Reports* 8:217-225.

Hajjar E, Hanlon J, Sloane R et al (2005) Unnecessary Drug Use in Frail Older People at Hospital Discharge. *Journal of the American Geriatrics Society* 53(9):1518-1523.

Havranek E, Masoudi F, Westfall K, Wolfe P, Ordin D, Krumholz H (2002) Spectrum of heart failure in older patients: results from the National Heart Failure Project. *American Heart Journal* 143(3):412-417.

Heiat A, Gross C, Krumholz H (2002) Representation of the elderly, women, and minorities in heart failure trials. *Archives of Internal Medicine* 162:1682-1688.

Juurlink D, Mamdani M, Lee D et al (2004) Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study. *New England Journal Medicine* 351(6):543-551.

Kadam UT (2011) Potential health impacts of multiple drug prescribing for older people: a case-control study. *British Journal of General Practice* 61:128-130.

Katz A (2008) The "Modern" view of heart failure, How did we get here? *Circulation, Heart Failure* 1:63-71.

Kaye D, Krum H (2007) Drug discovery for heart failure: a new era or the end of the pipeline? *Nature Reviews* 6(February):127-139.

Hauptman P (2008) Medication Adherence in heart Failure. *Heart Failure Review* 13:99-106.

Ledwidge M, Travers B, Ryder M, Ryan E, McDonald K (2004) Specialist care of heart failure improves appropriate pharmacotherapy at the expense of greater polypharmacy and drug-interactions. *European Journal Heart Failure* 6(2):235-243.

Lee D, Mamdani M, Austin P et al (2004) Trends in Heart Failure Outcomes and Pharmacotherapy: 1992 to 2000. *American Journal Medicine* 116(May):581-589.

Leibundgut G, Pfisterer M, Brunner-La Rocca H (2007) Drug treatment of chronic heart failure in the elderly, *Drugs & Aging* 24(12):991-1006.

Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivelä S, Isoaho R (2002) Use of medications and polypharmacy are increasing among the elderly. *Journal of Clinical Epidemiology* 55:809-817.

Mariani M, Vella G, Bianchi C, Verde S, De Maria R, Pirelli S (2008) Implementation of beta-blockade in elderly heart failure patients: Role of the nurse specialist. *European Journal of Cardiovascular Nursing* 7(3):196-203.

Masoudi F, Baillie C, Wang Y et al (2005) The complexity and cost of drug regimens of older patients hospitalized with heart failure in the United States, 1998–2001. *Archives of Internal Medicine* 165(October):2069-2076.

McMurray J, Östergren J, Swedberg K et al (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *The Lancet* 362(9386):767-771.

NICE (2009) Medicines Adherence: Involving patients in decisions about prescribed medicines and supporting adherence. London, NICE.

NICE (2010) *Chronic heart failure: National clinical guideline for diagnosis and management in primary and secondary care*. London, Royal College of Physicians

Oertle M, Bal R (2010) Understanding non-adherence in chronic heart failure: a mixed-method case study. *Quality and Safety in Health Care* 19(6):1-5.

Packer M, Bristow M, Cohn J et al (1996) The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. *New England Journal Medicine* 334 (21):1349-1355.

Paes A, Bakker A, Soe-Agnie C (1997) Impact of dosage frequency on patient compliance. *Diabetes Care* 20:1512-1517.

Pitt B, Zannad F, Remme W et al (1999) The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. *New England Journal Medicine* 341(10):709-717.

Rich M (2005) Heart failure in the oldest patients: the impact of comorbid conditions. *American Journal Geriatric Cardiology* 14(3):134-141.

Ryder M, Travers B, Timmons L, Ledwidge M, McDonald K (2003) Specialist nurse supervised in-hospital titration to target dose ACE inhibitor – is it safe and feasible in a community heart failure population? *European Journal of Cardiovascular Nursing* 2(3):183-188.

Shalansky S, Levy A (2002) Effect of number of medications on cardiovascular therapy adherence. *Annals Pharmacotherapy* 36(10):1532-1539.

Stoehr G, Ganguli M, Seaberg E, Echement D, Belle S (1997) Over-the-counter medication use in an older rural community: the MoVIES Project. *American Geriatric Society* 45(2):158-165.

Sturm H, Haaijer-Ruskamp F, Veeger N, Balje-Volkers C, Swedberg K, van Gilst W (2006) The relevance of comorbidities for heart failure treatment in primary care: A European survey. *European Journal of Heart Failure* 8(1):31-7.

Townsend A, Hunt K, Wyke S (2003) Managing multiple morbidity in mid-life: a qualitative study of attitudes to drug use. *British Medical Journal* 327:837-840.

Viktil K, Blix H, Moger T, Reikvam A (2006) Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. *British Journal of Clinical Pharmacology* 63(2):187-195.

Wong C, Chaudhry S, Desai M, Krumholz H (2011) Trends in comorbidity, disability, and polypharmacy in heart failure. *American Journal Medicine* 124(2):136-143.

World Health Organization (2003) Adherence to Long-term Therapies: Evidence for Action. Geneva, Switzerland: World Health Organization

Wu J, Moser D, Chung M, Lennie T (2008) Predictors of medication adherence using a multidimensional adherence model in patients with heart failure. *Journal Cardiac Failure* 14(7):603-614.

Yang J, Tomlinson G, Naglie G (2001) Medication Lists for Elderly Patients Clinic-Derived Versus In-Home Inspection and Interview. *Journal of General Internal Medicine* 16(2):112-115.

Zarowitz B (2006) Medication Overuse and Misuse. *Geriatric Nursing* 8;27(4):204-206.