Quality of life in patients with cardiac disease

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VOOR ROOS EN MIJN OUDERS

CONTENTS

CHAPTER 1

Aims and outlines of this thesis

Aims and outlines

Measurement of quality of life (QOL) as an indicator of health outcome has become increasingly important for cardiac patients, where the goal of treatment is not only to improve prognosis, but also to relieve symptoms and improve function. Research has demonstrated that variables other than disease symptoms and pain are more important to patients for their quality of life. In particular, areas such as patients' physical performance and psychological and social functioning have been recognized as important determinants. Also burden of symptoms and perceptions of well-being must be considered. In the case of angina pectoris, nitrates can effectively control symptoms of angina pectoris and have been demonstrated to reduce mortality in patients with acute myocardial infarction. In addition, based on the results of the GISSI-3 and the ISIS-4 studies, it is clear that nitrates can be safely used for long-term treatment. However, little is known about their net effects on current health-related QOL indices. The objective of **chapter 2** is to discuss the beneficial and harmful effects of nitrates. For that purpose, the results of two studies on nitrate therapy in the Netherlands are discussed.

In chapter 2 we conclude that once-daily dosage regimens of isosorbide mononitrate (ISMN) are more effective anti anginal treatments than daily administration of multiple small doses of the compound. This might be because nitrate tolerance is less likely to develop. Nitrates are nitric oxide (NO) donors. Patients with coronary artery disease may or may not have endothelial dysfunction of coronary arteries and, thus, dysfunctional endogenous NO. Patients with dysfunctional endogenous NO production may better benefit from effective nitrate treatment than do others. However, this has not been tested. Patients with diabetes mellitus, hypertension, smoking, and cholesterolemia, are particularly at risk of early endothelial dysfunction. **Chapter 3** tries to test the hypothesis that such patients might better benefit from effective NO donor therapy than do patients without such concomitant conditions. For this purpose we perform a multiple linear regression analysis of the comparative study of 1,350 patients with stable angina pectoris, treated for 6 months with either 50 mg ISMN administered orally at 8

hours AM or with standard multiple daily oral doses of the compound. The objective of the study is to assess whether the presence of concomitant conditions, particularly those associated with early endothelial dysfunction, are independent determinants of the better benefit from effective nitrate therapy.

As stated earlier, chronic nitrate therapy administered once-daily may be more convenient to patients and may better protect them from nitrate tolerance than multiple daily dose nitrate therapy. This was supported by the Dutch study of patients with stable angina pectoris as described in chapter 2 and 3: once daily therapy improved not only New York Heart Association (NYHA) anginal class and patient compliance but also QOL. The primary objective of the study described in **chapter 4** is to assess whether the above Dutch study was reproducible, and could be generalized across nations / populations. The secondary objective is to assess the effects of treatment modality on patients' satisfaction with their disease state, and on their NYHA heart failure class. In order to reduce between subject variability of symptoms, and, thus, enhance the sensitivity of testing, a self-controlled study design is chosen with all of the patients starting on multiple dose nitrate therapy, and, after 3 months switching to once-daily nitrate therapy for three more months. Patients are recruited from hospitals in Germany, Portugal , and the Czech Republic.

In the retrospective study described in chapter 3 we found that anginal patients with concomitant diabetes or hypercholesterolemia derived more benefit from changing over to a once daily regimen than did patients without. In contrast, anginal patients with concomitant hypertension or smokers derived less benefit. However, retrospective studies are at risk of confounding and recall bias, and have to be confirmed by prospective data. The IQOLAN (International Quality Of Life ANgina study), an international survey with a focus on QOL in nitrate-treated patients with angina pectoris gave us the opportunity to assess this issue prospectively in **chapter 5**. Thus, we assumed that anginal patients with comorbidities may better benefit from a once-daily dosage regimen than patients

without. For that purpose we compare improvements of QOL after 3 month multiple dose and after 3 month once daily treatment in patients with and without comorbidities.

From the previous chapters we learned that chronic nitrate treatment is safe and efficacious for the symptomatic treatment of stable angina pectoris. Once daily dosages regimens provided better therapeutic efficacy than did multiple daily dosages. Possible explanations included less risk of nitrate tolerance with nitrate low periods for several hours per day, better patient compliance with once daily dosages, and better protection from the circadian peak frequencies of angina pectoris during daytime. Nitrates release NO from the nitrate molecule. NO has a vasoprotective potential, because it has vasodilatory, anticoagulant, and antioxidative properties, antagonizes leukocyte-adhesion, and smooth-muscle-proliferation. These effects are assumed to be clinically relevant, substantiated by the fact that a variety of cardiovascular conditions such as hypertension, diabetes, hypercholesterolemia, and cigarette smoking are associated with an impairment of endothelium-dependent NO activity. This could mean, that anginal patients with such comorbidities might better benefit from nitrate therapy than their counterparts without. The survey in **chapter 6** was designed as a multinational study, evaluating the effect of a switch from multiple daily to a once-daily nitrate treatment on the QOL and anginal symptoms of patients with stable angina pectoris. The first objective is to compare predefined quality of life indices and NYHA anginal class before versus after replacement of multiple daily with once-daily nitrate therapy, and to assess whether the results of the previous chapters are reproducible in a larger study and across more countries. The second objective is to investigate the influence of cardiovascular risk factors and comorbidities on the observed changes in QOL and NYHA anginal class. This is the final chapter concerning nitrate therapy.

Chapter 7 focuses on quality of life with heart failure. Patients able to cope with all of the unpleasant aspects of their medical condition, generally, have better levels

of well-being than those unable to cope. What are determinants of “ability to cope”? It has been suggested that adequate objective information of patients on their physicomedical condition is an important factor. Also, social identification of patients with their counterparts has been suggested as a possible contributory factor. This may be particularly true for patients from moderate or low social class, as not infrequently observed in patients with heart failure. We hypothesized that in patients with heart failure “inability to cope” would be associated not only with low QOL, but also with lack of adequate medical information and lack of social identification with the patients’ counterparts. We also assumed that the latter factors may be direct contributors to low QOL. In order to assess these hypotheses we study 60 patients with stable chronic heart failure in this chapter. All of the patients are assessed by a test battery consisting of validated questionnaires.

Therapeutic interventions have been demonstrated to beneficially influence quality of life of patients with cardiovascular conditions. E.g. in the previous chapters we showed that once-daily dosage schedules of nitrates significantly improved QOL in patients with stable angina pectoris. In the past few years also psychological interventions have been successfully employed. Particularly, providing adequate medical information and avoiding patients to identify themselves with fellow-sufferers who are doing worse, and, instead, identifying themselves with those who are doing better, were significant contributors to both better ability to cope with the unpleasant aspects of the underlying condition and better self-perceived quality of life as described in chapter 7. However, we don’t know whether we can improve QOL by increasing patients’ ability to cope. In addition, gender and psychic tension have been recognized as important determinants of QOL in cardiac patients. . The objective of **chapter 8** is to assess two questions (1) whether we can improve QOL by increasing the patients’ ability to cope with the unpleasant aspects of a possible underlying heart condition, (2) whether gender and level of psychic tension interact or act independently. For that purpose we study 38 patients who are on the waiting list for coronary angiography. All of the patients are to be assessed by test batteries consisting of validated questionnaires.

Chapter 9 concerns an early discharge protocol after primary angioplasty for acute myocardial infarction and focuses on feasibility and QOL. At our hospital we described an easy and practical score for early risk stratification in patients with ST-segment elevation treated with primary angioplasty. This score reliably identifies a large group of patients at very low risk, who may safely be discharged early after primary angioplasty. The score is based on coronary anatomy and flow parameters and can be applied immediately after the angioplasty. As a consequence, we developed a study that evaluates a short-stay protocol after myocardial infarction and primary angioplasty in a selected low-risk patient population. This protocol includes intensive out-patient follow up and cardiac rehabilitation for secondary prevention therapies. The objective of this chapter is to investigate the feasibility of the short-stay protocol after myocardial infarction and primary angioplasty in a selected low-risk population and to evaluate QOL.

CHAPTER 2

Quality of life in angina therapy:

Focus on the beneficial effects of nitrates

Introduction

Measurement of quality of life (QOL) as an indicator of health outcome has become increasingly important for patients with coronary artery disease (CAD), where the goal of treatment is not only to improve prognosis, but also to relieve symptoms and improve function [1,2] . Recent research has demonstrated that variables other than disease symptoms and pain are more important to patients for their quality of life. In particular, areas such as patients' physical performance and psychological and social functioning have been recognized as important determinants. Also burden of symptoms and perceptions of well-being must be considered. Nitrates can effectively control symptoms of angina pectoris and have been demonstrated to reduce mortality in patients with acute myocardial infarction [3,4] . Based on the results of the GISSI-3 [5] and the ISIS-4 [6] studies, it is clear that nitrates can be safely used for long-term treatment. However, little is known about their net effects on current health-related QOL indices. Nitrates can be effectively applied for controlling symptoms of angina pectoris not only in patients with significant coronary artery disease but also in patients with other forms of ischemia, such as variant angina [7] and microvascular dysfunction [8]. They have also been demonstrated to increase angina-free walking [9] and to decrease exercise-induced ischemia [10]. A major problem with chronic treatment is nitrate tolerance which is probably caused by GTP-depletion in the vascular smooth muscle cells [11] , rather than some sort of receptor-mediated mechanism. Although it soon develops during continued therapy (limiting the usefulness of continued therapy), it can be prevented by asymmetric dosage regimens (e.g., b.i.d. therapy at 7 a.m. and noon or once-daily controlled release). Although these regimens do not provide 24 hour antianginal and anti-ischemic effects, they do give a sustained increase in exercise tolerance during the first part of the day with its circadian peak frequencies of anginal attacks [12,13], and, thus, have become a widely accepted approach [14,15,16]. So far, little is known about the net effects of these regimens on current health related quality of life indices. This question is particularly relevant because these compounds produce significant adverse effects such as headache, hypotension, and reflex tachycardia [17].

In 1985, isosorbide mononitrate (ISMN) in a once daily 30% immediate-release plus 70% sustained - release (IR-SR) formulation was introduced [18]. It offered a number of theoretical advantages over conventional isosorbide mononitrate or dinitrate when immediately administered on arising [19].

Isosorbide mononitrate provided better bioavailability than isosorbide dinitrate because it had no first-pass metabolism therefore it might be more effective in preventing drug tolerance than multiple-dose regimens given throughout the day. In addition, once-daily instead of multiple-dose therapy might be more convenient for individual patients and might therefore provide better patient compliance.

The immediate-release component of the preparation might better protect patients from their circadian peak frequencies of angina pectoris early in the morning.

Beneficial effects of nitrates

The pharmacological effects of the organic nitrates depend on the underlying pathophysiological mechanisms leading to ischemic heart disease (table 1). Although early in the development of coronary atherosclerosis the effects of endothelium-dependent vasodilators such as acetylcholine and ATP are usually impaired, the endothelium-independent vasodilator effects of nitrates remain intact[20,21,22]. Even in saphenous vein bypass grafts this is so [23].

TABLE 1.

Beneficial effects of nitrates
1. Vasodilatation of coronary arteries
2. Reduction of preload and afterload on the heart
3. Redistribution of flow to vulnerable subendocardial areas
4. Beneficial effect in hypertensive crisis
5. Beneficial effect in adult respiratory distress syndrome
6. Reduction of remodeling
7. Blockade of platelet aggregation
8. Blockade of leukocyte adhesion to the vascular endothelium
9. Protection of endothelial cells from oxidative stress
10. Antagonism of LDL oxidation

However, with advanced coronary atherosclerosis the development of atheromatous plaques results in narrowing of lumen and restricted blood flow. The peripheral effects of nitrates may become more important. Nitrates produce a vasodilatation of the venous vasculature. Dilatation of venous capacitance vessels diminishes venous return to the heart, reducing diastolic volume and pressure. This decreases diastolic wall tension, one of the contributors to the oxygen demand of the heart. Thus, by decreasing preload on the heart, the oxygen needs of the heart diminish. Other effects of nitroglycerin administration also contribute to its beneficial effect in angina. Nitrates cause relaxation of resistance vessels, which decreases afterload placed on the heart. Reducing afterload decreases oxygen demands of the heart, just as reducing preload does. The nitrate effect on resistance arteries generally requires higher concentrations than those needed for venodilatation. Another feature of organic nitrate action in angina pectoris is redistribution of blood flow to the subendocardial areas of the heart, which are especially vulnerable to ischemia. By decreasing preload, nitrates reduce ventricular filling pressure and increase the time available for endocardial perfusion. In management of angina pectoris caused by coronary artery spasm, the organic nitrates, in addition to effects described above, are useful because of dilatation of constricted coronary vessels. We should add that these beneficial effects of nitrates are not necessarily restricted to angina pectoris, but may occur in any form or expression of heart disease (e.g. different forms of heart failure) [24]. Hypertensive crisis and adult respiratory distress syndrome are noncardiac conditions frequently accompanied by heart failure, pulmonary oedema, or angina pectoris and infarction. Nitroglycerin has been unequivocally shown to influence these conditions beneficially and to perform better than nifedipine for that purpose [25,26,27].

Newly recognized beneficial effects of nitrates

The pharmacological action of nitrovasodilators appears to be quite similar to that of endothelium derived relaxing factor (EDRF). EDRF is formed in and released from endothelial cells of blood vessels and the heart, and has been shown to be

nitric oxide (NO) [28]. Vasodilator substances such as acetylcholine, histamine, bradykinin, and adenosine triphosphate act on endothelial cells at their respective receptors to release NO, which subsequently diffuses into the vascular and cardiac smooth muscle cells. It activates cGMP- dependent protein kinase through the second messenger cGMP. This enzyme promotes relaxation of the contractile elements of the cell in several ways, including limiting Ca2+ entry through channels and a direct decrease in the sensitivity of contractile proteins to Ca2+. The modification of intracellular calcium levels seems to be the mode of action of the vasoconstrictor compounds norepinephrine, angiotensin II, and serotonin, although a different second messenger (i.e.,IP3) is involved. Recent research has also indicated that these vasoconstrictors stimulate growth factors (i.e., cytokines, vascular endothelial growth factor, insulin, etc.), causing proliferation of fibroblasts, proliferative angiogenesis, vascular muscle cell hypertrophy, apoptosis (programmed cell death) of hypertrophied cells, and atherogenesis. Such effects are currently considered a major mechanism of left ventricular hypertrophy in hypertension and/or remodelling in ischemic heart disease. Unlike these vasoconstrictors, the vasodilator NO inhibits the proliferation of vascular smooth muscle cells [29,30] which may contribute to the regression of hypertrophy in such conditions similarly to the regression induced by ACE-inhibitors. However, prospective studies in man are still lacking. Other possibly beneficial effects of NO and its donors have been recognized. NO-donors are not only vasodilators, but also block platelet aggregation, probably by preventing the stimulation of thrombocytic soluble guanylate cyclase [31]. Nitrates, in combination with prostacyclin or its analogues, have, therefore, been proposed as a useful antithrombotic therapy [32,33].

A number of potentially beneficial effects of nitrates have been attributed to their capability to scavenge superoxide. First, they inhibit monocyte and macrophage adhesion to vascular endothelial cells, presumably by antagonizing the oxidation of the lipid cell membrane which triggers the expression of adhesion molecules by endothelial cells in vitro and in vivo [34,35] . Second, they protect the endothelium from oxidative stress, a term frequently used to refer to oxidative damage of DNA

and other tissues of the cell leading to cell dysfunction, and ultimately apoptosis [36,37,38] . Third, they inhibit the 15-lipoxygenase-mediated oxidation of LDL, which is considered an important factor early in the pathogenesis of atherosclerosis [34,39] .

Harmful effects of nitrates

Despite the growing literature attesting to the beneficial effects of NO-donors, other reports have suggested that NO has harmful properties as well. First, it may cause severe hypotension and blood flow abnormalities. Second, a rebound hypertension as well as rebound pulmonary hypertension after withdrawal has been reported [40]. Third, it contributes to a catecholamine hyporesponsiveness of the vasculature [41]. Fourth, it stimulates negative inotropic cytokines such as TNF, giving rise to myocardial depression [42] . Reversible myocardial depression following reperfusion of ischemic myocardium was documented in patients following myocardial infarction, cardiopulmonary bypass, thrombolytic therapy and coronary angioplasty [43,44]. The condition was associated with increased levels of NO products, and is currently referred to as the stunned myocardium, the mechanism of which was presumed to be cytokine-stimulated and NO-mediated [45]. Recent research indicates that rather than NO itself the reaction product of NO with superoxide, peroxynitrite, is responsible for the delayed reversibility of cardiac muscle mitochondrial dysfunction, an effect which is prevented by the free radical scavenger urate if present in the blood at physiological levels [36,46]. So, patients with a stunned myocardium may actually benefit from withdrawal of uricosuric compounds, and NO donors may be continued. Fifth, high concentrations of NO have been shown to disrupt metabolism, damage DNA, and cause cell death, suggesting that this free radical might cause direct tissue injury [47]. Nitroglycerine intravenously administered in high dosages may give rise to the formation of toxic nitrites which in turn can oxidize the iron of hemoglobin converting it to methemoglobin. Also, they may give rise to neural toxicity as well as carcinogenity[48].

Clearly, NO does more than just cause vasodilatation, and the precise role in humans has not been fully established. Even so, the balance of arguments is

currently in its favour. Also with usual dosages (e.g., 5-isosorbide mono- or dinitrate in a dosage of 15-120 mg daily [14]) serious side effects and toxicity are rarely encountered in everyday cardiology practice.

Long term efficacy, side effects and quality of life of isosorbide mononitrate IR-SR formulation

Efficacy

It is obvious that nitrates can be used safely for long-term treatment. However, little is known about long term efficacy, side effects and quality of life during continued treatment. Two large, open label studies recently completed addressed these issues [49,50]. A total of 1350 patients with stable angina pectoris were treated for three months with conventional ISMN/ISDN 10-20 mg twice or three times daily, and subsequently, for the same period with once-daily 50 mg IR-SR formulation [49]. A total of 1212 patients could be evaluated after six months. Not only did patients experience a 22.2% (p=0.03) reduction of anginal attack frequency during the second period, but also drug compliance improved by 23.8% (p=0.02). The investigators subsequently tested the hypothesis that 100 mg IR-SR formulation may perform even better than 50 mg; they used the same study design for assessment. In 505 patients with stable angina pectoris, 100 mg IR-SR for three months produced a further 13.9% (p=0.001) and 2% (p=0.01) further improvement of patient compliance. The better compliance may explain part of the improved efficacy, but not all of it. Table 2 shows a comparison of multiple dose and 100 mg IR-SR formulation as calculated by the product of odds ratios of ‘multiple dose/50 mg IR-SR’ and ’50 mg IR-SR/100 mg IR-SR’. Although this is an extrapolation, it may be acceptably valid since the procedure is straightforward and the data are from similar institutions and investigators [19]. The largely unchanged quantity of sublingual nitroglycerin required in the studies was consistent with the situation in which an improved angina classification is associated with increased physical activities.

Side effects

Drug tolerance did not develop after 50-100 mg IR-SR formulation, patients' self-assessed rating scores continued to improve rather than to deteriorate on higher dosages [49,50]. Drug tolerance did not develop in three more open label trials from other groups (n=30-45 patients per study) [51,52,53] after 6 to 13 months of treatment, whereas improvement of anginal attack frequencies, and level of ST-depression during angina were similar to those in the above two studies. Except for headache, other side effects of 50-100 mg isosorbide mononitrate IR-SR formulation were rare and negligible. Headache, nonetheless, occurred as frequently as with multiple ISMN/ISDN dosages in between 41 and 67% of the patients [49,50]. Particularly during the first weeks of treatment, headache is commonly reported. For example, in a six-week double-blind, parallel-group study, both IR-SR formulation 50-100 mg once daily and conventional isosorbide mononitrate 80-120 mg daily necessitated drug withdrawal in up to 17% of the patients [54].

TABLE 2. Odds ratios* of symptoms and Quality-of-life indices of patients with stable angina pectoris treated with 50 mg and 100 mg isosorbide mononitrate IR-SR formulation once daily vs. standard multiple dose ISMN/ISDN.

	Odds ratios Multiple dose/ 50 mg IR-SR	p value	Odds ratios Multiple dose/ 100 mg IR-SR	p value
Mobility index	0.83	<0.001	0.69	<0.001
Side effect index	0.99	0.85	0.96	<0.001
Anginal pain index	0.64	<0.001	0.56	<0.001
Anginal pain index 8-10 hr am	0.65	0.006		
Psychological well-being index	0.87	0.036	0.75	<0.001
Patient compliance	0.50	<0.001	0.48	<0.001
Sublingual nitroglycerin consumption	0.94	0.68		

**odds ratios = mean scores during multiple-dose conventional isosorbide mononitrate/mean scores during IR-SR formulation treatment*

In a double-blind study by our group, [55] it was demonstrated that this effect can be avoided to a great extent by starting with isosorbide mononitrate dosages as low as 25-30 mg daily. Such dosages of IR-SR formulation have become available recently.

Quality of life

Important quality of life indices were also addressed in two studies [49,50]. A once-daily dose of 50 mg IR-SR for three months gave significantly better scores than multiple-dose conventional ISMN/ISDN: mobility index improved 5.5% ($p=0.04$), and psychological well-being index improved 5.6% ($p=0.04$). In addition, 100 mg IR-SR once daily for three months gave better scores than 50 mg IR-SR: 20.3% ($p<0.001$) and 5.8% ($p<0.001$) further improvement of mobility and psychological well-being indices. Table 2 shows the extrapolated odds ratios of multiple dose/100 mg IR-SR calculated by the products of odds ratios 'multiple dose/50 mg IR-SR' and '50 mg IR-SR/100 mg IR-SR' from the two separate studies [49,50]. Although based on extrapolation, these estimates suggest that in particular high-dose IR-SR formulation may provide a considerable further improvement of mobility and psychological well being.

Discussion

Unfortunately, none of the long term studies on IR-SR isosorbide mononitrate formulation were blinded, and so the risk of placebo effects partly explaining the results can not fully be ruled out. A current problem with designing long-term nitrate studies is that it is ethically increasingly difficult to replace nitrate therapy with placebo in symptomatic patients even though improved survival with long-term nitrate therapy has not been unequivocally proven. At the least, the results of the large QOL studies [5,6] do not support the presence of major placebo effects in the data, since important changes occurred in the mobility and psychological well-being indices rather than in the anginal pain and side effect indices, which are generally particularly susceptible to placebo effects in QOL assessments [2].

The primary approach of patients with angina pectoris must involve the adequate treatment of their coronary condition, e.g. by coronary bypass surgery or percutaneous coronary angioplasty, rather than treatment with nitrates. If patients remain symptomatic despite adequate treatment, or if they have to wait for such interventions or do not qualify for them for any other reason, nitrates as well as other antianginal drugs should be considered. Parker and Parker [56] recently reviewed prescribing patterns regarding current nitrate therapy and recommended that (1) slow-release nitrates, rather than beta-blockers or calcium channel blockers, be given as an initial preventive therapy for stable angina pectoris, particularly in patients who respond well to sublingual nitroglycerin; and (2) beta-blockers or calcium channel blockers be given as initial therapy in patients with coexistent hypertension and/or a history of MI. We suggest that nitrates be routinely added in the latter category, given their apparent improvement of various QOL indices. A particularly interesting aspect of treatment with nitrates, although predominantly of a theoretical nature so far, is their potential to offer more than just symptomatic treatment [17]. Nitrates, being NO donors, have been thought to reduce remodelling [29], blockade platelet aggregation [30], and adhesion receptors of vascular endothelial cells [35], and probably most importantly to protect the endothelium from oxidative stress by scavenging superoxide [38]. Angiotensine II is an important producer of oxygen free radicals and it is this property that is largely held responsible for the deleterious effects of the compound on the myocardium as well as vascular endothelium [57]. A supposed antagonistic effect between NO and angiotensin II on oxygen free radicals is a plausible hypothesis [58] to explain the widely published beneficial effect of ACE inhibitors on the efficacy of nitrate treatment [59]. The risk of hypotension with nitrates is small because the compound has little influence on systemic blood pressure and the same applies with the IR-SR formulation. The risk of methaemoglobin due to overdosing [14] should be better prevented by a once-daily IR-SR formulation with predictable pharmacokinetic pattern than by multiple dosages of conventional nitrates.

We conclude that IR-SR isosorbide mononitrate has a rapid onset of action, is clinically efficient, and provides better quality of life than the conventional ISMN/ISDN. Tolerance with continued use of the formulation has not yet been reported. Long-term efficacy data both of isosorbide mononitrate IR-SR and conventional ISMN/ISDN are limited so far. A large study in patients with angina pectoris (International Quality Of Life assessment of patients with Angina pectoris on Nitrate therapy – IQOLAN) addressing long term effects, is discussed in the next chapters.

References

1. Mayou R., B. Bryant. Quality of life in cardiovascular disease. Br Heart J 69 (1993) 460-466.
2. Thompson D., K. Meadows, R. Lewin. Measuring quality of life in patients with coronary heart disease. Eur Heart J 19 (1998) 693-695.
3. Morris J., J. Cowan. Nitrates in myocardial infarction: A current perspective. Can J Cardiol 11(1995) 5B-10B.
4. Jugdutt B. Nitrates in myocardial infarction: A review. Cardiovasc Drugs Ther 8(1994) 635-646.
5. Anonymous. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano po lo Studio della Soppravivenza nell' infarto Miocardico. Lancet 343 (1994) 1115-1122.
6. Anonymous. ISIS-4: a randomised factorial trial assessing only oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Fourth International Study of Infarct Survival. Lancet 345 (1995) 669-685.
7. Kugiyama K., H. Yasue, K. Okumara. Nitric oxide activity is deficient in spasm arteries of patients with coronary spastic angina. Circulation 94 (1996) 266-272.
8. Diver D., P. Ferreira, B. Sharaf, et al: Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing. Am J Cardiol 74 (1994) 531-537.
9. Nijberg G., P. Carleus, E. Lindstrom. The effect of isosorbide-5-mononitrate Durules on exercise tolerance in patients with exertional angina pectoris. A placebo controlled study. Eur Heart J 7 (1986) 835-842.
10. Parker J., G. Wisenberg. Antianginal effects of sustained release isosorbide-5-mononitrate. Circulation 80 (1989) s2:267.
11. Watanabe H., M. Kakihana, S. Ohtsuka, T. et al: Platelet cyclic GMP, a potentially useful Indicator to evaluate the effects of nitroglycerin and nitrate tolerance. Circulation 88 (1993) 29-36.

12. Scheidel B., G. Lenhard, H. Blume. Chronopharmacology of isosorbide-5-mononitrate(immediate release, retard formulation). Eur J Clin Pharmacol 36 (1989) 177-178.
13. Lemmer D., B. Scheidel, H. Blume, et al: Clinical Chronopharmacology of oral sustained-release iso-5-mononitrate. Eur J Clin Pharmacol 40 (1991) 71-75.
14. Thadani U., R. Lipicky. Short and long-acting oral nitrates for stable angina pectoris. Cardiovasc Drugs Ther 8 (1994) 611-623.
15. Nordlander R. Can nitrate tolerance be avoided with once-daily administration of isosorbide-5-mononitrate 60 mg in Durules? Eur Heart J 10 (1989) s:73.
16. Klemsdal U., R. Giesdal. Intermittent or continuous transdermal nitroglycerin: still an issue, or I s the case closed? Cardiovasc Drugs Ther 10 (1996) 5-11.
17. Niemeyer M., T. Cleophas. Nitrates may provide benefits other than just symptomatic treatments. Cardiologie 4 (1997) 205-208.
18. Igendaay A., G. Klein, K. Rehm. Vergleichende Pharmacokinetik retardierter Mononitratpräparate. Münch Med Wochenschr 129 (1987) 34-36.
19. Cleophas T., M. Niemeyer, Zwinderman A. et al: A new immediate/sustained-release formulation of isosorbide mononitrate. Cardiologie 6 (1999) 358-363.
20. Conti C. Why use nitrate in 1990? Eur Heart J 12 (1991) SA 2-4.
21. Anggard E. Endogenous nitrates-implications for treatment and prevention. Eur Heart J 12 (1991) SA 5-8.
22. Parker J et al. Nitrates and angina pectoris. Am Journal of Cardiology 72 (1993) 3c-8c.
23. Berglund H., H. Luo, T. Nishioka et al: Preserved vasodilatory response to nitroglycerin in saphenous vein bypass grafts. Circulation 94 (1996) 2871-2876.

24. Remme W. Pathophysiology and therapy of heart failure, New insights and developments. Part ll. Neth J Med 43 (1993) 125-146.
25. Bussmann W., P. Kenedi, H. von Mengelen et al: Comparison of nitroglycerin with nifedipine in patients with Hypertensive crisis. Kardiologie 82 (1993) 33-37.
26. Rossiant R., Falke K., F. Lopez F et al: Nitric oxide for adult respiratory distress syndrome. N Engl J Med 328 (1993) 299-305.
27. Kaplan N. Treatment of hypertension. In: Kaplan NM, ed. Clinical hypertension. Baltimore: Wilkens&Wilkens (1994)145-170.
28. Ignarro L., R. Byrns, K. Wood. Pharmacological and biochemical properties of endothelium-derived relaxing factor (EDRF): Evidence that EDRF is closely related to nitric (NO) radical. Circulation 74 (1986) II-287.
29. Garg V., A. Hassid. Nitric oxide-generating vasodilators and cyclic guanosine monophosphate inhibit mitogenesis of rat vascular smooth muscle cells. J Clin Invest 83 (1989) 1774-1777.
30. Johnson D., Dell Italia L. Cardiac hypertrophy and failure in hypertension. Current Opin Nephrol Hypertens 5 (1996) 186-191.
31. Graaf de J., J. Bange, S. Moncada et al: Nitric oxide functions as an inhibitor of platelet adhesion under flow conditions. Circulation 85 (1992) 2284-2290.
32. Radomski M., S. Moncada. Biological role of nitric oxide in platelet function. In: Moncada S., E. Higgs, J. Berrazueta, eds. Clinical relevance of nitric oxide in the cardiovascular system. Madrid: EDICOMPLET (1991) 45-56.
33. Sinzinger H., F. Rauscha, J. O'Grady et al: Prostaglandin I2 and the nitric oxide donor molsidomine have synergistic effects on thromboresistance in man. Br J Clin Pharmacol 33 (1992) 289-292.
34. Catapano A. Antioxidant effect of flavonoid and nitric oxide. Angiology 48 (1997) 39-44.
35. Kubes P, M. Suzuki, D. Granger. Nitric oxide: an endogenous modulator of leukocyte adherence. Proc Natl Acad Sci USA 88 (1991) 4651-4655.

36. Rongen G., P. Smits, Th. Thien. Endothelium and the role of nitric oxide. Neth J Med 44 (1994) 26-35.
37. Sarafin T., D. Bredsen DE. Is apoptosis mediated by reactive oxygen species? Free Radic Res 20 (1994) 1-6.
38. Stamler J. Redox Signaling: nitrosylation and related target interactions of nitric oxide. Cell 78 (1994) 931-936.
39. Steinberg D., S. Partasarathy, T. Carew et al: Beyond cholesterol, modifications of low-density lipoprotein that increase its atherogenicity. N Engl J Med 320 (1989) 915-924.
40. Warren J., T. Higgenbottam. Caution with use of nitric oxide. Lancet 348 (1996) 629-630.
41. Finkel M., C. Oddis, T. Jacob et al: Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science 257 (1992) 387-389.
42. Nathan C., Q. Xie. Nitric oxide synthases: roles, tolls, controls. Cell 78 (1994) 915-918.
43. Braunwald E., R. Kloner. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 66 (1982) 1146-1149.
44. Dilsizian V., R. Bonow. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. Circulation 86 (1993) 1-20.
45. Finkel M., C. Oddis, B. Hattler, et al: Myocardial ischemia, stunning and hibernation. In: Iskandrian AS, van der Wall EE, eds. Myocardial viability. Dordrecht: Kluwer Academic Publishers, 1994: 5-18.
46. Xie Y., M. Wolin. Role of nitric oxide and its interaction with superoxide in the suppression of cardiac muscle mitochondrial respiration, involvement in response to hypoxia/reoxygenation. Circulation 94 (1996) 2580-2586.
47. Nathan C. Nitric oxide as a secretory product of mammalian cells. FASEB J 6 (1992) 3051-3064.
48. Moncada S., A. Higgs. The l-arginine-nitric oxide pathway. N Engl J Med 329 (1993) 2002-2012.

49. Niemeyer M., H. Kleinjans, R. De Ree et al: on behalf of the DUMQOL (DUtch Mononitrate Quality if Life) Study group. Comparison of multiple-dose and once-daily nitrate therapy in 1212 patients with stable angina pectoris: effects on quality-of-life indices. Angiology 48 (1997) 855-863.
50. Zwinderman A., T. Cleophas, H. van der Sluis et al: on behalf of the DUMQOL (Dutch Mononitrate Quality if life) Study group. Effects of 50 mg and 100 mg isosorbide mononitrate once daily on quality of life in 505 patients with stable angina pectoris. Angiology (in press).
51. Krepp H. Langzeitbehandlung der koronaren Herzerkrankung mit elantan®long. In Borchard U., W. Rafflenbeul, A. Schrey, editors. Mononitrat IV. Munich: Verlag Wolf & Sohn 1985: 176-183.
52. Heepe W., U. Gathman-Lewik. Antianginal efficacy and tolerability of 50 mg sustained-release isosorbide mononitrate in an open twelve-month observation study. Cardiology 74 (1987) S 34-39.
53. Ahmadinejad M., B. Eghbal, W. Sorgenicht. Slow-release isosorbide mononitrate: a new once daily therapeutic modility for angina pectoris. Eur Heart J 9 (1988) S 135-139.
54. Walker J., P. Curry, A. Bailey. A Comparison of nifedipine once daily, isosorbide mononitrate once daily, and isosorbide dinitrate twice daily in patients with chronic stable angina. Int J Cardiol 79 (1996) 117-126.
55. Cleophas T., M. Niemeyer, E. van der Wall. Nitrate-induced headache in patients with stable angina pectoris: beneficial effect of starting on a low dosage. Am J Ther 3 (1996) 802-806.
56. Parker J., J. Parker. Nitrate therapy for stable angina pectoris. N Engl J Med 338 (1998) 520-553.
57. Cleophas T., J. van der Meulen, M. Niemeyer et al: Mechanisms offsetting the beneficial effects of antihypertensive drugs. Perfusion 11 (1998) 373-380.
58. Münzel T., H. Sayegh, B. Freeman et al: Evidence for enhanced vascular superoxide anion production in nitrate tolerance. A novel mechanism underlying tolerance and cross-tolerance. J Clin Invest 95 (1995): 187-194.

59. Münzel T., E. Bassenge. Long-term angiotensin-converting inhibition with high-dose enalapril retards nitrate tolerance in large epicardial arteries and prevents rebound coronary vasoconstriction in vivo. Circulation 93 (1996) 2052-2058.

CHAPTER 3

Factors Influencing Efficacy of Nitrate Therapy for Stable Angina Pectoris:

a Multiple Linear Regression Analysis

(Angiology 2000; 51: 1007-12)

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Abstract

Background: Once-daily dosage regimens of isosorbide mononitrate provide better antianginal efficacy and quality of life in patients with stable angina pectoris than does the daily administration of multiple small doses of the compound. It is unknown whether certain patient characteristics contribute to this better benefit.

Objective: To determine independent factors contributing to this better benefit. Multiple linear regression analysis was performed of a self-controlled study of 1350 patients with stable angina pectoris. Quality of life was assessed by the Marquis-questionnaire for patients with angina and included the domains immobility, pain, and psychological distress. Individual scores were calculated as the pooled sums of the domain scores and were expressed on an ordinal scale of 10.

Results: Age did not influence the better benefit. Neither did gender, rhythmic disturbances, peripheral artery disease, or the concomitant use of calcium channel blockers or beta-blockers. New York Heart Association angina classification was an independent variable: patients with a class I or II benefited less than did patients with class III or IV (P=0.02). Obese patients as well as hypertensive patients benefited less (P=0.04 and 0.02), and smokers tended to benefit less (P=0.08). In contrast, cholesterolemia and diabetes mellitus improved the beneficial effect of nitrates on quality of life (P= 0.03 and 0.05).

Conclusions: Patients with severe angina pectoris benefit better from nitrate therapy than do patients with New York Heart Association class I-II. Also, patients with coronary artery disease and concomitant diabetes mellitus or cholesterolemia may better benefit from nitric oxide-donor therapy than patients without such concomitant conditions do. In contrast, patients with concomitant obesitas, hypertension, or smokers may benefit less.

Introduction

Asymmetric dosage regimens of isosorbide mononitrate (ISMN) are more effective antianginal treatments than daily administration of multiple small doses of the compound, because nitrate tolerance is less likely to develop [1]. Nitrates are nitric oxide (NO) donors. Patients with coronary artery disease (CAD) may or may not have endothelial dysfunction of coronary arteries and, thus, dysfunctional endogenous nitric oxide production [2,3]. Patients with dysfunctional endogenous NO production may better benefit from effective nitrate treatment than do others. However, this has not been tested. Patients with diabetes mellitus [4], hypertension [5], smoking [6], cholesterolemia [7], are particularly at risk of early endothelial dysfunction. The present paper tries to test the hypothesis that such patients might better benefit from effective NO donor therapy than do patients without such concomitant conditions.

For this purpose we performed a multiple linear regression analysis of a comparative study of 1,350 patients with stable angina pectoris (SAP) treated for 6 months with either 50 mg ISMN administered orally at 8 hours AM (asymmetric dosage regimen) or with standard multiple daily oral doses of the compound. In the univariate analysis of this study [8] the former modality improved New York Heart Association (NYHA) angina class and improved various quality of life indices compared to the latter modality. The objectives of the current study was to assess whether the presence of concomitant conditions, particularly those associated with early endothelial dysfunction, are independent determinants of the better benefit from effective nitrate therapy.

Subjects, Material and Methods

When the size of a study permits, important demographic or baseline characteristics for example age, gender, and the severity of condition, can be studied for influencing efficacy response [9]. Such analyses do not prove anything but may be helpful to refine questions for subsequent studies. Our intended treatment population consisted of 1,350 patients, which is large enough in size for such purposes. Patient characteristics are given in Table 1.

TABLE 1. Patient Characteristics of Intention to Treat Population (n=1350).

	n	(%)
Male gender	848	(63)
NYHA angina classification		
I	265	(20)
II	849	(63)
III	173	(13)
IV	14	(1)
Smokers	215	(16)
Hypercholesterolemia	407	(30)
Hypertension	400	(30)
Diabetes mellitus	143	(11)
Rhythm disturbances	195	(14)
Peripheral vascular condition	194	(14)

NYHA= New York Heart Association

All of these patients were treated for 3 months with ISMN immediate release multiple small daily doses and subsequently for another 3 months with 50 mg slow-release formulation. Primary efficacy data were estimated as anginal pain indices and quality of life (QOL) indices using the QOL-questionnaire of patients with angina pectoris by Marquis [10] and included the domains of immobility, pain, and psychological distress. For the purpose of this study, overall QOL was calculated as the pooled sums of the domain scores, scored on an ordinal scale of 0 to 10, and expressed as odds ratios (where the odds ratios are the mean scores during novel formulation divided by the mean scores during standard formulation doses). In brief, published results [8] show that the slow-release formulation of ISMN produced a 17% greater improvement in mobility, a 36% decrease of anginal pain index, a 35% greater reduction of anginal pain between the hours of 8 and 10 AM, a 13% greater improvement in psychological well-being, and a 50% greater improvement of patient compliance (P values were between P=0.03 and <0.001).
For the purpose of the multiple regression analysis, the summary odds ratios of QOL scores were added up and linearly transformed on a scale of 0 to 10, and subsequently used as dependent variable, otherwise called response variable.

Independent variables, otherwise called explanatory variables, included the nominal variables, gender, presence of arrhythmias, peripheral vascular disease, co-medications, NYHA class, smoking, hypertension, diabetes, and the continuous variables, age, body mass, plasma cholesterol levels. We did not try stepwise exclusion of non-significant independent variables, because all of the variables included studied important demographic characteristics, that we considered it necessary to adjust for them even if not statistically significant.

To test internal consistency and reliability of the data we used Cronbach's alpha [11]. SPSS statistical software was used to provide the best fit for the data as given, and to calculate regression coefficients beta1 to beta12, according to the following statistical model:

y = c + beta1.1 + beta2.2 +.....beta12.12

Odds ratio of quality of life scores = c + beta1(presence of hypertension) + beta2 (presence of diabetes) + …… beta12 (hypercholesterolemia)

where c is intercept and beta1, beta2, etc are the estimated slopes of the multiple linear regression equation. Regression coefficients were statistically tested with t-tests, and a P value of at least 0.05 was considered statistically significant. In a multiple regression analysis the x-variables should not tend to be highly related to each other, because most of the variance in one x-variable can be accounted for by the other x-variable. This problem known as multicollinearity was assessed by a correlation matrix of the x-variables.

Results

Our intention-to-treat population consisted of 1,350 patients (mean age ± standard deviation: 68 ±10 years), which is large enough a size for the purpose of a multiple regression analysis. CAD was confirmed by coronary angiography in 999 of the patients and in 351 of the patients on clinical grounds. Additional patient characteristics were shown in Table 1.

Table 2 gives a correlation matrix of the x-variables to be entered in the multiple regression analysis. As expected, there was a generally weak and insignificant correlation as estimated by Pearson correlation coefficient between the x-variables to be entered. Only the correlation between age and other variables appeared to be borderline significant, but in none of the comparisons adjustments for multicollinearity were required (correlation coefficient > 0.9).

TABLE 2. Correlation between factors contributing to benefit of nitrate therapy (Pearson correlation coefficients of >0.07 or <-0.07 were consistent with a P-value <0.05).

	Age	Gender	Rhythm	Vascdis	Ccb	Bb	NYHA	Smoke	Bmi	Chol	hypt
Gender	0.19										
Rhythm	0.12	ns									
Vasc dis	0.14	ns	ns								
Ccb	0.24	ns	0.07	ns							
Bb	0.33	ns	ns	ns	0.07						
NYHA	0.22	ns	ns	0.07	0.07	ns					
Smoking	-0.12	ns	0.09	0.07	0.08	ns	0.07				
Bmi	0.13	ns	ns	ns	ns	0.10	ns	-0.07			
Chol	0.15	ns	ns	0.12	0.09	ns	ns	0.08	0.09		
Hypt	0.09	ns	0.08	ns	0.10	0.09	0.07	0.09	0.09	0.07	
Diabetes	0.12	ns	0.09	0.10	ns	0.08	0.08	ns	0.11	0.12	0.10

Vasc dis= peripheral vascular disease; Ccb= concomitant calcium channel blocker therapy; Bb= concomitant beta-blocker therapy; Bmi= body mass index; Hypt= hypertension; ns= not statistically significantly correlated.

Table 3 gives the results of the multiple linear regression analysis. Age, obviously, did not influence the beneficial effect of nitrate therapy on QOL in our material. Neither did gender, rhythmic disturbances, peripheral artery disease, or the concomitant use of calcium channel blockers or beta-blockers. The NYHA angina classification, however, did influence the QOL outcome. Patients with a NYHA class I or II benefited less from nitrate therapy than did patients with NYHA class III or IV (P=0.02). Smokers tended to benefit less (P=0.08), and obese patients benefited less (P=0.04). In contrast, cholesterolemia and diabetes mellitus

improved the effect of nitrates on QOL (P=0.03 and P=0.02). Hypertension, finally, benefited again less (P=0.05).

TABLE 3. Regression Coefficients and Standard Errors for a Multiple Linear Regression of Odds Ratio for Quality of Life on Different Explanatory Variables.

Covariate	standardized regression coefficient (beta)	95 % CI	test statistic (T)	Significance level (P-value)
Age	-0.03	-0.11 to 0.05	0.8	ns
Gender	0.01	-0.09 to 0.11	0.5	ns
Rhythm disturbances	-0.04	-0.12 to 0.04	1.0	ns
Peripheral vascular disease	-0.00	-0.02 to 0.02	0.1	ns
Calcium channel blockers	0.00	-0.02 to 0.02	0.1	ns
Beta blockers	0.03	-0.05 to 0.11	0.7	ns
NYHA-classification I or II	-0.08	-0.14 to 0.02	2.3	0.02
Smoking	-0.06	-0.14 to 0.02	1.6	0.08
Body mass index	-0.07	-0.13 to –0.01	2.1	0.04
Cholesterolemia	0.07	0.01 to 0.10	2.2	0.03
Hypertension	-0.08	-0.14 to –0.02	2.3	0.02
Diabetes mellitus	0.06	0.00 to 0.12	2.0	0.05

NYHA= New York Heart Association; CI =confidence interval; ns= not statistically significant.

Discussion

The current study is a post-hoc analysis of a previously published [8] sequential study with the same order of treatments for all of the patients. One may speculate that carry-over effect may have influenced the treatment comparison. However, since the, presumably, more effective treatment was given after the less effective treatment, this risk may be less important.

Obviously, the levels of significance in the multiple regression analysis were not very low (between P=0.02 and 0.08), and so the chance of type I errors of finding a difference where there is none, cannot be ruled out. However, since the overriding

interest of our regression modelling was of exploratory nature, we decided to be liberal about including covariates in the model, at the risk of encountering some type I errors. Some statisticians even recommend to use P-values as low as 0.10 or even 0.20 for purpose of these kinds of analyses [9].

The current study, nonetheless, shows a significantly better benefit from effective nitrate therapy in patients with NYHA class III-IV angina pectoris than in patients with NYHA class I-II. Obviously, the more symptomatic the patients, the better the benefit from this symptomatic therapy. Second, we found that concomitant diabetes and cholesterolemia were associated with a better benefit. In diabetic and cholesterolemic patients with [4,5] or without [12,13,14,15,16] CAD, endothelial dysfunction, and, thus, dysfunctional endogenous NO production develops early. Although matter of speculation, the above mechanism would nicely explain the better benefit from NO donor therapy in these categories of patients in our study. Endothelial dysfunction and, thus, dysfunctional endogenous NO production is currently given particular emphasis in the pathogenesis of CAD in diabetic patients. Diabetes mellitus produces a two to threefold increased risk of coronary artery disease, and a twofold increased cardiac mortality [4]. Such greater risk could not be attributed to the presence of the three classic risk factors including smoking, hypertension, cholesterolemia: e.g., the large GISSI 2 [17], CONSENSUS II [18], GUSTO I [19], CORE [20], TRACE II [20] studies showed no difference in presence of such risk factors between diabetic and non-diabetic patients. Thrombolytic therapy, aspirin, ACE-inhibitors, and beta-blockers in diabetic patients were not particularly efficacious in diabetic patients in these studies. According to our study, this may be different with NO donor therapy: at least NO donors were particularly efficacious for symptomatic treatment of diabetic patients with CAD in our hands.

In contrast, hypertension and smoking, decreased or tended to decrease the benefit from effective nitrate therapy in our study. We have no obvious explanation for this unexpected finding, but the anginal complaints in such patients may sometimes have another mechanism than endothelial dysfunction. E.g., patients with hypertension may have increased peripheral resistance [5], and this may contribute to reduced exercise tolerance and angina-like complaints. Also nicotine

causes vasoconstriction of resistance arteries [6], and so, also in this category of patients, increased peripheral resistance may contribute to such symptoms. Increased peripheral resistance is negligibly influenced by NO donors [3]. It would explain why such patients benefit less from nitrate therapy. Finally, the patients with the highest body mass indices in our study, unlike healthy subjects, benefited less in our study from nitrate therapy than did their low body mass index counterparts. It can be explained as follows. Patients with mobility reducing obesity and a low NYHA classification-score have little anginal symptoms from the very start, and so, treatment may contribute little to their improvement of QOL.

Conclusions

The current study suggests that patients with angina NYHA class III-IV benefit better from effective nitrate therapy than do patients with angina NYHA class I-II. Patients with CAD and concomitant diabetes mellitus or cholesterolemia may better benefit from effective nitrate therapy than do patients without such concomitant conditions. Patients with smoking, high body mass index or hypertension may benefit less. The data are from a post-hoc study, and they are, therefore, speculative in nature.

References

1. Parker JD, Parker JO 1998 Nitrate therapy for stable angina pectoris. N Engl J Med 338:520-531.
2. Kinley S, Ganz P 1997 Role of endothelial dysfunction in coronary artery disease and implications for therapy. Am J Cardiol 80: 11-16-I.
3. Cleophas TJ, Van der Wall EE, Kalmansohn RB 1997 Nitrates and angina pectoris. More than just symptomatic treatment. Perfusion 10: 4-6.
4. Cleophas TJ 1999 Coronary artery disease in diabetes mellitus. Cardiologie 6: 16-17 s.
5. Higashi Y, Oshima T, Ozono R, Matsura H, Kajiyama G 1997 Aging and severity of hypertension attenuate endothelium-dependent vascular relaxation in humans. Hypertens 30 (Pt1): 252-258.
6. Cleophas TJ 1998 Mechanisms offsetting the beneficial effects of antihypertensive drugs. Am J Ther 5: 413-419.
7. Shimokawa H, Vanhoutte PM 1989 Impaired endothelium-dependent relaxation to aggregating platelets and related vasoactive substances in porcine coronary arteries in hypercholesterolemia and in atherosclerosis. Circ Res 64: 900-914.
8. Niemeyer MG, Cleophas TJ, Zwinderman AH, Kleinjans HA, Van der Wall EE, on behalf of the Dutch Mononitrate Quality Of Life (DUMQOL) Study Group 1997 Comparison of multiple dose and once-daily nitrate therapy in 1350 patients with stable angina pectoris; effects on quality of life. Angiology 48: 855-862.
9. Cleophas TJ, Cleophas AF, Zwinderman AH 1999 Statistics applied to clinical trials. Dordrecht, Neth, Kluwer Academic Publishers.
10. Marquis P, Fagol C, Joire JE 1995 Quality of life assessment in patients with angina pectoris. Eur Heart J 16: 1554-1559.
11. Bland JM, Altman DG 1997 Cronbach's alpha. Br Med J 314: 572-573.
12. O'Brien SF, Watts GF, Playford DA, Burke V, O'Neal DN, Best JD 1997 Low-density Lipoprotein size, high-density lipoprotein concentration, and

endothelial dysfunction in non-insulin-dependent diabetes. Diabetic Med 14: 974-978.

13. Timini FK, Henry HT, Haley EA, Roddy MA, Ganz P, Creager MA 1998 Vitamin C improves endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. J Am Coll Cardiol 31: 552-557.
14. Voors AA, Oosterga M, Buikema H, May JF, Grandjean JG, Van Buiten A 1997 Dyslipidemia and endothelium-dependent relaxation in internal mammary arteries used for coronary bypass surgery. Cardiovasc Res 34: 568-574.
15. Steinberg HO, Bayazeed B, Hook G, Johnson A, Cronin J, Baron AD 1997 Endothelial.
16. Tanaka S, Yashiro A, Nakashima Y, Ikeda M, Kurowa A 1997 Plasma nitrite/nitrate levels is inversely correlated with plasma low-density lipoprotein cholesterol levels. Clin Cardiol 20: 361-365.
17. Gruppo Italiano Per Lo Studio Della Sopravvivenza Nell'Infarto Miocadico 1990 GISSI-2: A multi-factorial trial of alteplase versus streptokinase and heparin among 12,490 patients with acute myocardial infarction. Lancet 336: 65-71.
18. Swedberg K, Kjekshus J, Rasmussen K, Ryden L, Wedel H, on behalf of the CONSENSUS II Study Group 1992 Effects of the early administration on mortality in patients with acute myocardial infarction. N Engl J Med 327: 678-684.
19. Topol EJ, Armstrong P, Van der Werf F 1992 Confronting the issues of patient safety investigator conflict of interest in an international clinical trial of myocardial reperfusion. Global Utilization of Streptokinase and Tissue Plasminogen Activator on occluded coronary arteries. GUSTO Steering committee. J Am Coll Cardiol 19: 1123-1128.
20. Pfeffer MA 1991 Angiotensin converting enzyme inhibition therapy following myocardial infarction: Rationale for clinical trials (GISSI-3, CORE, TRACE). Herz 16: 278-282.

CHAPTER 4

Once-daily versus multiple daily dose nitrate treatment:

an international quality of life study of 1045 patients with stable angina pectoris

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Abstract

Background: Chronic nitrate therapy administered once daily may be more convenient to patients and may better protect them from nitrate tolerance than multiple dose nitrate therapy. This is supported by a large Dutch study of patients with stable angina pectoris showing not only a better anginal class and patient compliance but also a better quality of life (QOL). Recent research has demonstrated that patients' self-rated satisfaction with disease state is an important additional indicator of QOL in these patients, and that chronic nitrate therapy may also benefit heart failure class in some of these patients.

Objective: To assess whether the Dutch data could be generalized across nations and times. To assess the effects on patients' satisfaction with disease state and on heart failure class.

Methods: Patients from hospitals in Germany, Portugal, and the Czech Republic were treated for 3 months with 2-4 times daily 10-20 mg isosorbide mononitrate/dinitrate and, subsequently, with once daily 50-120 mg isosorbide mononitrate/dinitrate for three more months. A QOL questionnaire, based on Wiklund's exercise tolerance index, Stewart's Short Form Questionnaire, and Dupuy's psychological well-being index, was completed after 3 and 6 month treatment. In addition, patients' self-rated satisfaction with the current disease state, their treatment preference, and their New York Heart Association (NYHA) anginal and heart failure class were assessed twice.

Results: Of the 1045 patients included, 1010 (97%) completed the study. After three months of once-daily nitrate therapy the QOL-scores showed a significantly better improvement in all of the domains addressed, than did multiple daily dose treatment ($p<0.0001$). In addition, anginal and heart failure classes improved significantly better($p<0.0001$). So did patient compliance as estimated by the percentages of patients forgetting to take their medication (59.6 versus 42.2%, $p<0.0001$), patients' self-rated satisfaction (30.5 versus 10.1%, $p<0.0001$), and patients' preference for the once-daily nitrate regimen (77.4 versus 3.6 %, $p<0.0001$).

Conclusions: Once-daily nitrate treatment provides better NYHA anginal class, patient compliance, and QOL than does multiple daily dose treatment. These better benefits can be observed across nations and times. In addition to QOL indexes, patients' self-rated satisfaction with disease state improved better, and so did NYHA heart failure class.

Introduction

Chronic nitrate therapy administered once-daily may be more convenient to patients and may better protect them from nitrate tolerance than multiple daily dose nitrate therapy. This is supported by a large Dutch study of patients with stable angina pectoris: once-daily therapy improved not only New York Heart Association (NYHA) anginal class and patient compliance but also quality of life (QOL) indexes significantly better [1]. Recent research has demonstrated that patients' self-rated satisfaction with disease state is an important indicator of QOL in this category of patients, in addition to the traditional QOL indexes like physical, social, and psychological indexes [2,3,4]. Also, it has been recently demonstrated by our group that many patients with stable angina pectoris have some degree of heart failure, and that not only their anginal class but also their heart failure class benefits from chronic nitrate treatment [5].

The primary objective of the current study was to assess whether the above Dutch study was reproducible, and could be generalized across nations / populations and across times. The secondary objective was to assess the effects of treatment modality on patients' satisfaction with their disease state, and on their NYHA heart failure class.

In order to reduce between subject variability of symptoms, and, thus, enhance the sensitivity of testing, a self-controlled study design was chosen with all of the patients starting on multiple dose nitrate therapy, and, after 3 months switching to once-daily nitrate therapy for three more months.

Patients were recruited from hospitals in Germany, Portugal, and the Czech Republic.

Patients and methods

Design

Because equivalent treatments were compared, the possibility of testing not only differences but also bioequivalence was included. For that purpose a statistically powerful comparison was required. A self-controlled comparison would provide adequate power. Based on prior data1 treatment was expected to improve QOL

indexes by 7%. Under the assumption of standard deviations of 25% and a correlation of + 0.6, the study would have to include 1000 patients. A crossover design would have enabled to randomize patients. However, such a design is at risk of psychological and physical carryover effects, particularly if a more efficacious is given prior to a less efficacious one. We, therefore decided to use a simple self-controlled design with all of the starting on the, presumably less efficacious, multiple dose nitrate therapy changing over after three months to the, presumably more efficacious, once daily treatment. This design closely met the rest of our criteria including those involving medical ethics and recruitment methods.

Multiple dose nitrate therapy consisted of 2 to 4 times daily 10-20 mg of isosorbide mononitrate or isosorbide dinitrate while once-daily nitrate therapy consisted of 50 mg of isosorbide mononitrate in Portugal and the Czech Republic and of 120 mg of isosorbide dinitrate in Germany.

Quality of life was assessed after three months of multiple dose and after three months of once daily nitrate therapy by self-administered questionnaires. In addition, patients' satisfaction with the current disease state and treatment preference was assessed. NYHA classification for coronary heart disease and congestive heart failure as well as information on nitrate therapy were documented by the physicians. A placebo control was not included in the protocol because it was not considered ethical to withdraw symptomatic patients from active therapy.

Patients

Out-patients from hospitals in three European community countries were sampled. Inclusion criteria included: presence of coronary artery disease documented either by coronary arteriogram and / or by myocardial infarction or by clinical signs only, presence of symptoms of stable angina pectoris treated by beta-blockers and / or calcium channel blockers and / or sublingual nitrates ad libitum so far. Exclusion criteria included the presence of serious diseases other than coronary heart disease, hospitalization within one month of enrolment especially for myocardial infarction, coronary bypass surgery or angioplasty. An adequate knowledge of the language was required.

Methods of evaluation

Patients completed twice a validated 24-item quality of life questionnaire in local language. The items of the questionnaire were based on the Short-Form 36 questionnaire of Stewart [6] , the exercise tolerance index of Wiklund [7], the pain index of Marquis [2] for patients with angina, the psychological well being index of Dupuy [8], and the distress scale of Testa and Simonson [3]. The following domains were assessed: functional dependence (8 items), side effects (7 items), anginal pain (5 items), and psychological distress (4 items). For each item the individual response was scored on a 5-point scale from 0 to 4. The sum of scores was used for further evaluation. Higher scores indicated worse quality of life. In addition, patients' satisfaction with regard to the current disease state (2 items) and the patients' own estimation of their compliance (2 items) were assessed on 5-point scales. The first and second QOL questionnaires were identical except for an additional question in the second form requesting the patient to give his/her preference either for the multiple dose or for the once-daily regimen.

On an additional form physicians reported the individual patient characteristics such as demographics, eligibility criteria, cardiovascular risk factors, cardiac history, concomitant therapies, and the current NYHA anginal and heart failure class. In case the patient did not continue the study the reasons for withdrawal were documented. Also information on adverse events was collected.

Statistical analysis

Qualitative characteristics were described by absolute and relative frequencies (percentages). Variables which could be observed after three and after 6 month treatment were cross-classified. Quantitative and the scored qualitative characteristics as well as the differences between before and after change-over of therapies were described by mean, standard deviation, median, lower and upper quartile, minimum, and maximum. For statistical analysis were used two-sided statistical tests: changes of the sum of scores were analyzed by paired t-tests, changes of frequencies regarding the qualitative characteristics Bowker's

symmetry tests and McNemar's tests. 95% confidence intervals (95% CI) and standard deviations (SDs) are given, a $p<0.05$ was considered significant.

Results

1045 patients were enrolled at 200 centres. 1010 patients (96.6%) completed the study. The majority of patients was male. Age ranged from 34 to 100 years with a mean of 66.4 years. All of the patients suffered from coronary artery disease. Angina pectoris was classified as NYHA class II in the majority of patients (57.4%) and class III in 25.6% of all patients. For congestive heart failure NYHA class II was most frequent (37.1%), followed by class I (29.9%). Patient characteristics are given in table 1, NYHA classifications in table 2. The cardiovascular risk factors were typically those of this patient population. Hypertension was found in 64.0% (n=669), hyperlipidemia in 54.6% (n=571) of the patients. Familial coronary artery disease was present in 38.5% of the patients (n=402). According to their physicians 38.4% of the patients were obese (n=401) and 30.6% were smokers (n=320). A history of diabetes was given in 25.7% (n=268). 136 patients (13.0%) suffered from peripheral vascular problems.

TABLE 1. Patient characteristics.

	Total	Germany	Portugal	Czech Republic
Centres (n)	200	132	65	3
Patients (n)	1045	606	379	60
Males (%)	64.4	64.7	63.6	66.7
Age (years, mean ± SD)	66.4 ± 10.2	67.6 ± 10.2	65.2 ± 10.0	64.2 ± 10.8
Previous angiography (n)	300 (28.7%)	220 (36.6%)	62 (16.4%)	18 (30.0%)
Previous MI (n)	271 (26.0%)	152 (25.1%)	95 (25.0%)	24 (40.0%)

MI = myocardial infarction, SD = standard deviation

TABLE 2. 1045 patients suffered from angina, 833 in addition from congestive heart failure. The NYHA classifications at baseline are given (%).

	Class I	Class II	Class III	Class IV
Angina pectoris	15.5%	57.4%	25.6%	0.6%
Congestive heart failure	29.9%	37.1%	12.2%	0.5%

NYHA = New York Heart Association

Table 3 gives an overview of the results of the QOL assessments. After three month treatment with the once-daily nitrate regimen, improvements both of the average score sums and of the separate items of all of the domains were observed. No major differences between the countries were observed (country-specific data not shown). For the domain "functional dependence" the overall score change was most pronounced by -4.3 ± 0.2, followed by the change for the domains "anginal pain" by -2.4 ± 0.1, "side effects" by -2.3 ± 0.1, and "psychological distress" by -1.6 ± 0.1, all of them highly significant at p<0.0001.

TABLE 3. Mean quality of life (QOL) scores. For functional dependence, side effects, anginal pain, and psychological distress maximal scores are respectively 40, 35, 25, and 20. Higher scores indicate worse QOL.

	Multiple dose	Single dose	Difference multiple - single dose		
	mean ± SD	mean ± SD	mean	95% CI	p
Functional dependence	16.1 ± 6.5	11.8 ± 6.2	-4.3	-4.6 to -4.0	< 0.0001
Side effects	11.6 ± 5.4	9.3 ± 5.1	-2.3	-2.5 to -2.0	< 0.0001
Anginal pain	6.8 ± 4.2	4.4 ± 3.6	-2.4	-2.6 to -2.2	< 0.0001
Psychological distress	8.6 ± 3.7	6.9 ± 3.7	-1.6	-1.8 to -1.5	< 0.0001

95% CI = 95% confidence interval, SD = standard deviation

Figure 1 shows the effect of treatment on NYHA anginal and heart failure class. Once-daily nitrate regimen improved both of the classes in a highly significant manner ($p<0.0001$). Particularly, the percentages of patients in anginal class I raised from 16 to 45%, in heart failure class from 40 to 47%. Similar effects were observed in the data of the separate countries (country-specific data not shown).

Figure 1a. Improvement of New York Heart Association anginal class (based on 1045 patients, no data available for 0.9% and 11.1% of the patients on multiple and single dose, respectively)

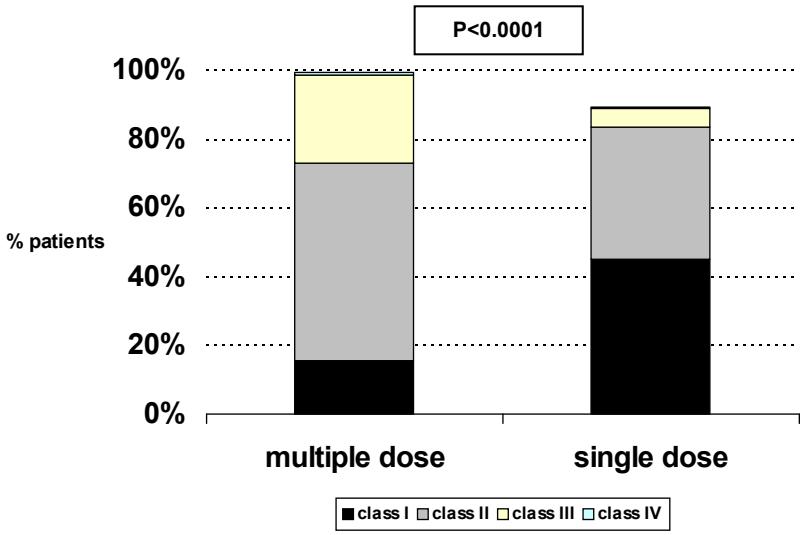
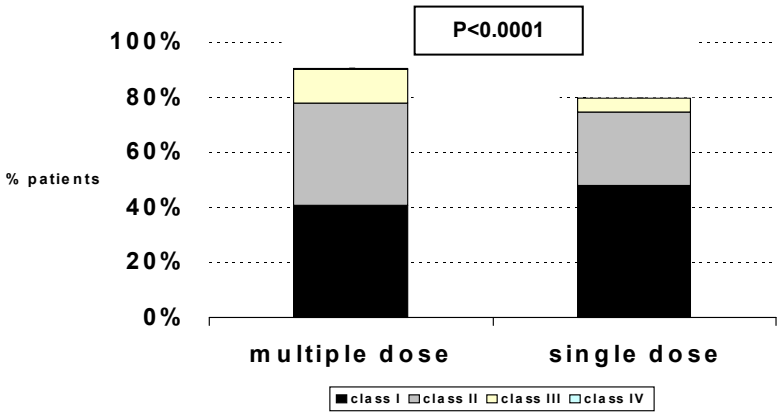
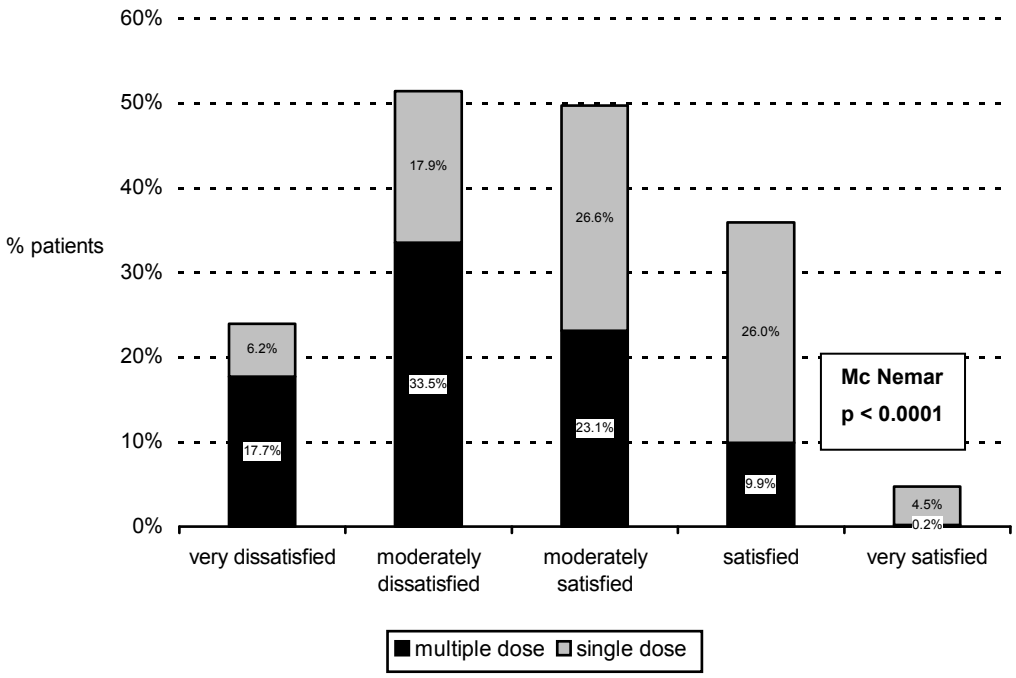


Figure 1b. Improvement of New York Heart Association congestive heart failure class (based on 1045 patients)



Improvement of satisfaction with current disease state as estimated by the question: “If you had to live with your present heart problem, how satisfied would you then be?” is shown in Figure 2. Instead of add-up sums of scores, here separate scores for each point of the 5-point scale were assessed (% of patients). Obviously, many more patients were satisfied with single dose than they were with multiple dose.

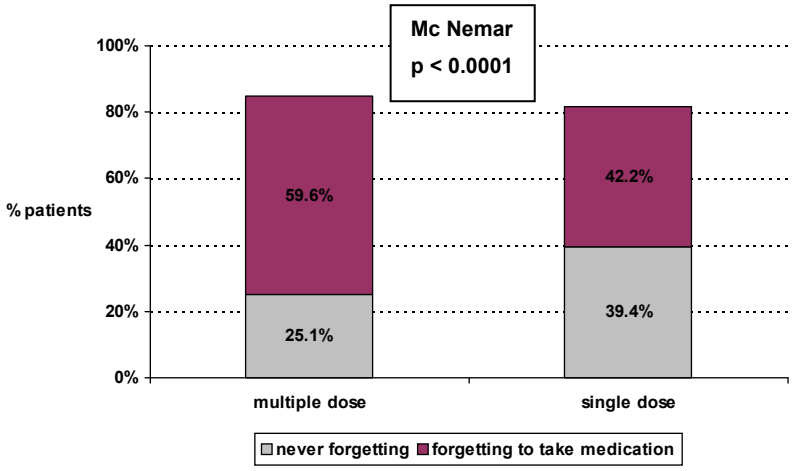
Figure 2. Improvement of satisfaction with current disease state as estimated by the question: “If you had to live with your present heart problem, how satisfied would you then be?” Instead of add-up sums of scores, here separate scores for each point of the 5-point scale are given (% of patients).



Patient compliance improved better with once daily nitrate (Figure 3) as estimated by a significantly lower percentage of patients forgetting to take their medication ($p<0.0001$). Also patients had fewer swallowing problems (25.7% versus 20.2%,

p<0.05). 77.4% preferred once-daily to multiple dose for future treatment while only 3.6% preferred the opposite (19% unknown).

Figure 3. Improvement of patient compliance, based on the question: "Do you forget to take your medication?" and future preference.



Discussion

The current study shows that long-term once daily nitrate treatment provides a significantly better anginal class, patient compliance, and quality of life than does multiple dose nitrate treatment. These results are in line with the results of the Dutch study [1], and further support that once daily treatment is more convenient to patients and better protects them from nitrate tolerance. Also the present study shows that patients' self-rated satisfaction [2,3,4] with disease state, currently considered as the most important indicator of quality of life, is significantly higher with once daily than it is with multiple daily dose treatment. Finally, the data confirm not only that patients with stable angina pectoris often suffer from concomitant heart failure but also that the heart failure class is beneficially influenced by nitrate treatment, and significantly better so by a once daily than by a multiple daily dose regimen.

The limitations of the current study include that it did not control carryover effects and time effects. However, carryover effects mainly occur if a more efficacious treatment is given prior to a less efficacious treatment [9] , while in our study the order of treatment was opposite. This was a study of patients with stable disease, and we presumed, therefore, that the risk of major time effects may be negligible. Another limitation of the study includes that it did not control placebo effects. Indeed, placebo effects may occur with quality of life assessments. However, this has been demonstrated to be particularly so in the physical symptom and pain domains, rather than in the functional dependence and distress domains [10,11]. Moreover, it was not considered ethical to replace nitrate therapy with placebo in these symptomatic patients for such a long period of time.

We conclude that once-daily nitrate treatment provides better NYHA anginal class, patient compliance, and QOL than does multiple daily dose treatment. These better benefits can be observed across nations and times. Not only traditional QOL indexes improved better, but also patients' self-rated satisfaction with disease state. So did NYHA heart failure class.

References

1. Niemeijer MG, Kleinjans HA, De Ree R et al. Comparison of multiple-dose and once-daily nitrate therapy in 1212 patients with stable angina pectoris: effects on quality of life indexes. Curr Ther Res 1996; 57: 927-36.
2. Marquis P, Fayol C, Joire JE. Clinical validation of a quality of life questionnaire in angina pectoris patients. Eur Heart J 1995; 16:1554-60.
3. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996; 334:835-40.
4. Albert SM, Frank L, Murri R, Hyland ME, Apolone G, Leplege A. Defining and measuring quality of life. JAMA 1998; 279: 429-31.
5. Zwinderman AH, Cleophas TJ, Niemeijer MG, Van der Wall EE. Effects of 50 mg and 100 mg isosorbide mononitrate once daily on quality of life in patients with stable angina pectoris. Curr Ther Res 1998; 59 : 511-20.
6. Stewart AL, Hays RD, Ware JE. The MOS short form general health survey. Reliability and validity in a patient population. Med Care. 1988; 26:724-35.
7. Wiklund I, Comerford MB, Dimenas E. The relationship between exercise tolerance and quality of life in angina pectoris. Clin Cardiol 1991; 14:204-8.
8. Dupuy HJ. The psychological general well being index. In: Wenger NK, Matson ME, Furberg CD, Elinson J, eds. Assessment of Quality of Life in Clinical Trials of Cardiovascular Therapies. New York: Le Lacq Publishing 1984:170-83.
9. Cleophas TJ. A simple analysis of crossover studies with one-group interaction. Int J Clin Pharmacol Ther 1995; 32: 322-8.
10. Hunt S, McKenna SP, McEwen J. The Nottingham Health profile user's manual. Manchester, Galen Research and Consultancy, 1989.
11. Brazier JE, Harper B, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionaaire: new outcomes measure for primary care. Br Med J 1992; 305: 160-4.

CHAPTER 5

Chronic nitrate therapy in Patients with Angina with Comorbidity

(Am J Ther 2006; 13: 188-91)

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Abstract

Background: In a retrospective study from the Dutch Mononitrate Quality of Life (DUMQOL) Study Group, the authors found that anginal patients with concomitant diabetes or hypercholesterolemia derived more benefit from changing over to a once-daily nitrate treatment regimen, than did anginal patients without.

Objective: To assess this issue prospectively.

Methods: In an open-label study patients with stable angina pectoris (SAP) from facilities in Germany, Portugal, and the Czech Republic were treated for 3 months with multiple daily dosages and subsequently for 3 more months with once daily isosorbide mono-/dinitrate (ISMN/DN). After the first and second 3 month period they were assessed by a validated QOL-battery including the domains, mobility, side-effect, life-satisfaction, anginal-pain, and psychological-distress.

Results: In the 1045 patients who participated in the study mean summary domain-scores varied from 5-16 points, score improvements from 1.6 to 4.3 points. In the patients with concomitant hypertension and the smokers domain-scores improved less than they did in the patients without, with differences in domain-score improvements up to 1.0 points ($p<0.001$), which is substantial considering the range of improvement being between 1.6 and 4.3 points. In the patients with diabetes mellitus or hypercholesterolemia a reversed pattern was observed with differences in domain-score improvements up to 0.4 points ($p<0.05$).

Conclusions: Anginal patients with diabetes or hypercholesterolemia derived more benefit from a once-daily regimen of isosorbide mono/dinitrate than did patients without. Anginal patients with hypertension or smokers did less so. Differences in endothelial function may be involved.

Introduction

Once daily dosage regimens of isosorbide mononitrate/dinitrate (ISMN/ISDN) are more effective antianginal treatments than multiple daily dosages, because nitrate tolerance is less likely to develop.[1] In a retrospective study the authors found that anginal patients with concomitant diabetes or hypercholesterolemia derived more benefit from changing over to a once daily regimen than did patients without.[2] In contrast, anginal patients with concomitant hypertension or smokers derived less benefit.[2] Retrospective studies are at risk of confounding and recall bias, and have to be confirmed by prospective data. The IQOLAN (International Quality Of Life ANgina study)[3] , an international survey with a focus on quality of life (QOL) in nitrate-treated patients with angina pectoris gave us the opportunity to assess this issue prospectively.

Thus, we assumed that anginal patients with comorbidities may better benefit from a once daily dosage regimen than patients without. For that purpose we compared improvements of QOL after 3 month multiple dose and after 3 month once daily treatment in patients with and without comorbidities. For assessment a validated QOL battery was used.

Methods

Patients

Out-patients were recruited from 200 facilities in three European community countries (Germany, Portugal , and the Czech Republic). Inclusion criteria included: coronary artery disease (CAD) documented either by coronary arteriogram or by a coronary event, presence of symptoms of stable angina pectoris (SAP) treated by beta-blockers, calcium channel blockers and / or sublingual short-acting nitrates ad libitum. Exclusion criteria included: serious diseases other than coronary heart disease, hospitalization within one month of enrollment, coronary bypass surgery or angioplasty.

Design

This was an open-label evaluation study performed according to the Safety Assessment of Marketed Medicines guidelines.[4] After oral informed consent, patients were treated for 3 months with 2 to 4 times daily 10-20 mg ISMN/ISDN, and, subsequently, for 3 more months with once daily 50 mg ISMN in Portugal and the Czech Republic and 120 mg of ISDN in Germany. QOL was assessed after 3 and 6 month treatment. The primary endpoints were (1) effects on QOL of different nitrate dosage regimens and (2) review of the effects of comorbidities. The effects on QOL of different nitrate dosages have been reported separately.[5] For the effects of comorbidities subgroup QOL-domain-scores were analyzed separately from Germany and from the other European countries.

QOL-battery

QOL was measured by a test battery based on the Stewart's[6] and Marquis's[7] questionnaires, adapted to current standards[8-10], and consisted of five QOL-domains: mobility-, side-effect-, life-satisfaction-, anginal-pain-, and psychological-distress-domain (24 items all-in). Items were linearly scored on 5 point scales. Mean summary scores were used for evaluation. The study was approved by the ethic committees of all of the participating centres.

Statistical analysis

Paired and unpaired t-tests for quantitative data, and McNemar's and Bowker's tests for qualitative data were used. A p-value<0.05 was considered statistically significant, standard deviations (SDs) or standard errors (SEMs) were presented. Intention to treat analysis was given. For the calculation of the pooled differences the correlation coefficients were expected to be at least +0.5 (+0.6 in the DUMQOL study).[11] The statistical analysis was performed independently of the sponsor by X-act Statistical Service, Cologne, Germany.

Results

Enrolled were 1045 patients, 1010 completed the study, 12 were lost for follow-up, 23 required more intensive therapy. Mean age was 66.4 (SD 10.2) years, 64.4% were males, 64.0% suffered from hypertension, 54.6% from hypercholesterolemia, 25.7% from diabetes, and 30.6% were smokers, 57.4% were in New York Heart Association anginal class II, 25.6%, in class III, 15.5% in class I. No statistically significant differences in characteristics were observed between Germany and the other European countries. Mean summary domain- scores varied from 4.4 to 16.1 points, domain-score improvements varied from 1.6 to 4.3 points.

TABLE 1. Differences in domain-score improvements between anginal patients with and without comorbidities (subtractions), indicating better score improvements without comorbidities.

	Germany	Europe	Germany	Europe
	Hypertension		Smoking	
	Differences in domain-score improvements (means (SEMs))			
Mobility-domain	-1.0(0.4)**	-0.6(0.3)**	-0.1(0.4)	0.4(0.5)
Side-effect-domain	-0.3(0.4)	-0.1(0.3)	-0.2(0.3)	0.1(0.4)
Life-satisfaction-domain	-0.3(0.2)*	-0.2(0.1)*	-0.1(0.3)	0.0(0.2)
Anginal-pain-domain	-0.6(0.3)**	-0.3(0.1)*	-0.5(0.4)	-0.1(0.3)
Psychological-distress-domaine	-0.6(0.3)**	-0.5(0.2)***	0.0(0.4)	0.1(0.3)
Pooled	-0.6(0.1)***	-0.3(0.1)***	-0.2(0.1)**	0.1(0.1)

** 0.05<p<0.10, **p<0.05, ***p<0.01*

Table 1 shows the effects of comorbidities. Differences in domain-score improvements between patients with and without comorbidities are shown (subtractions). In Germany mobility-domain improved significantly less in the patients with hypertension than it did in the patients without. A difference of -1.0

points is substantial considering the range of observed score improvements between 1.6 and 4.3 points. Also life-satisfaction-domain improved significantly less, as did anginal-pain- and psychological-distress-domain. The pooled difference was significant at p<0.001. The other European countries gave similar results but less substantial. Also in the smokers from Germany, domains improved generally less than it did in non-smokers, although not significantly. However, the pooled difference was significant at p<0.05. This was not true for the smokers from the other European countries, but no deterioration was observed either. In the subgroups with diabetes or hypercholesterolemia a reversed pattern was observed (Table 2).

TABLE 2. Differences in domain-score improvements between anginal patients with and without comorbidities (subtractions), indicating better score improvements with comorbidities.

	Germany	Europe	Germany	Europe
	Diabetes mellitus		Hypercholesterolemia	
	Differences in domain-score improvements (means (SEMs))			
Mobility-domain	0.3(0.4)	0.0(0.3)	0.2(0.5)	0.3(0.4)
Side-effect-domain	0.4(0.4)	0.1(0.2)	0.3(0.4)	0.2(0.2)
Life-satisfaction-domain	0.1(0.2)	0.1(0.1)	0.1(0.2)	0.1(0.1)
Anginal-pain-domain	0.0(0.3)	0.2(0.2)	0.1(0.4)	0.2(0.2)
Psychological-distress-domaine	0.0(0.3)	0.1(0.2)	-0.1(0.3)	-0.2(0.2)
Pooled	0.2(0.1)**	0.1(0.1)	0.2(0.1)*	0.1(0.1)

** 0.05<p<0.10, **p<0.05*

In Germany domains generally improved better in the patients with diabetes with a pooled difference statistically significant at p<0.05. Also a trend to better improvement (0.05<p<0.10) was observed in the hypercholesterolemic patients

from Germany. The other countries showed no significant improvements, but, again, no significant deterioration was observed either.

Discussion

Patients with CAD and comorbidities like diabetes, hypercholesterolemia, or hypertension may less benefit from symptomatic treatment with nitrates, because their heart condition may be more severe.[1] In contrast, a retrospective study from our group showed that this was not true for anginal patient with diabetes or hypercholesterolemia.[2] Retrospective data are at risk of confounding and have to be prospectively assessed. The current study used the same protocol and drug regimens, but is otherwise entirely new and prospective in nature. In spite of this, the results are remarkably similar: patients with hypertension and smokers benefited less from nitrates, while those with diabetes or hypercholesterolemia benefited or tended to benefit better. The differences in domain-score improvements were more substantial in the patients from Germany, than they were in the patients from the other European countries. This is probably due to higher dosages of nitrates used. The results of this study confirm that a real effect is involved. There are two possible explanations. First, hypertensives and smokers may, indeed, represent a category with more advanced CAD, and may, consequently, benefit less from nitrates. However, there are no data to support that CAD is less advanced in patients with diabetes or hypercholesteremia. Second, the difference in nitrate efficacy between comorbidities may be related to differences in endothelial dysfunction. Patients with diabetes or hypercholesterolemia are at risk of endothelial dysfunction.[12-14] Such patients lack endogenous NO-release, and may, therefore, particularly benefit from nitrates, being NO-donors. Endothelial dysfunction is difficult to assess and systematic studies are lacking. For that purpose studies are currently at progress in our department.

Conclusions

1. Anginal patients with diabetes or hypercholesterolemia derived more benefit from an once-daily regimen of isosorbide mono/dinitrate than did patients without.
2. Anginal patients with hypertension or smokers did less so.
3. Differences in endothelial function may be involved.

References

1. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. N Engl J Med 1998; 338: 520-31.
2. Jansen R.M.G., Cleophas TJ, Zwinderman AH, Niemeijer MG. Factors influencing efficacy of nitrate therapy: a multiple linear regression. Angiology 2000; 51: 1007-13.
3. Cleophas TJ, Jansen R, Niemeijer MG, et al. International quality of life study in patients with angina pectoris on nitrate therapy. Br J Clin Pharmacol 2002; 54: 553-4 (abstract).
4. Safety Assessment of Marketed Medicines SAMM guidelines. Br J Clin Pharmacol 1994; 38: 95-7.
5. Cleophas TJ, Jansen R, Niemeijer MG, et al. Once daily and multiple daily dose nitrate treatment: an international quality of life study of 1045 patients with stable angina pectoris. Perfusion 2004; 17: 36-72.
6. Stewart AL, Hays RD, Ware JE. The MOS short form general health survey. Reliability and validity in a patient population. Med Care 1988; 26:724-35.
7. Marquis P, Fayol C, Joire JE. Clinical validation of a quality of life questionnaire in angina pectoris patients. Eur Heart J 1995; 16:1554-60.
8. Dupuy HJ. The psychological general well being index. In: Wenger NK, Matson ME, Furberg CD, Elinson J, eds. Assessment of Quality of Life in Clinical Trials of Cardiovascular Therapies. New York: Le Lacq Publishing 1984:170-83.
9. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996; 334:835-40.
10. Bland JM, Altman DG. Cronbach's alpha. Br Med J 1997; 314: 572-3.
11. Cleophas TJ, Niemeijer MG, Zwinderman AH, et al. Assessment of quality of life in patients with angina pectoris. Neth Heart J 2002; 10: 13-9.
12. Niemeijer MG, Kleinjans HA, De Ree R et al. Comparison of multiple-dose and once-daily nitrate therapy in 1212 patients with stable angina pectoris: effects on quality of life indexes. Angiology 1997; 48: 855-63.

13. Cleophas TJ. Coronary artery disease in diabetes mellitus. Neth Heart J 1999; 6: 16-8, s1.
14. Shimokawa H, Vanhoutte PM, Impaired endothelium-dependent relaxation to aggregating platelets and related vasoactive substances in porcine coronary arteries in hypercholesterolemia and in atherosclerosis. Circ Res 1999; 64: 900-14.
15. Voors AA, Oosterga M, Buikema H, et al. Dyslipidemia and endothelium-dependent relaxation in internal mammary arteries used for coronary bypass surgery. Cardiovasc Res 1997; 34: 568-74.

CHAPTER 6

Replacement of Multiple Daily with Once-Daily Nitrate Therapy:

an International Quality of Life Assessment of 2675 Patients with Stable Angina Pectoris

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on behalf of the IQOLAN investigators

Abstract

Background: Once-daily nitrate dosages provided better therapeutic efficacy in patients with stable angina pectoris, than did multiple daily dosages. Anginal patients with cardiovascular comorbidities may particularly benefit from nitric-oxide-(NO) donor therapy due to the underlying impairment of endothelium-dependent NO-activity.

Objectives:

1. To compare QOL and exercise capacity before and after replacement of multiple daily with once-daily nitrate therapy.
2. To investigate the influence of cardiovascular comorbidities on the observed changes.

Methods: Out-patients with stable angina pectoris and at least three months pre-treatment with 3 times daily 20-40 mg of isosorbide mono-or dinitrate were switched to the equivalent single daily dose of the compound early in the morning. We assessed predefined QOL-indices, painfree walking distances, New York Heart Association (NYHA) anginal class, and the influence of cardiovascular risk factors and comorbidities. Standard multi- and univariate methods were applied.

Results: Of 2675 patients included, 2574 (96.2%) completed the study. After three months once-daily nitrate mean QOL-scores improved from 10 to 19% ($p<0.0001$ for all of the QOL-domains). The percentage of patients in NYHA anginal class I increased by 23.4% ($p<0.0001$), while exercise capacity increased from a median painfree walking distance of 300 to 500 m ($p<0.001$). In patients with concomitant hypertension or hypercholesterolemia anginal class improved better (27.4 and 24.6 %, both $p<0.001$). Young age, advanced NYHA anginal class, hypercholesterolemia and coronary artery disease (CAD) in the family were important independent determinants of the improved QOL.

Conclusions: Replacement of multiple-dose with once-daily nitrate treatment resulted in an improved QOL, anginal NYHA class, and exercise capacity. Patients with concomitant hypertension or hypercholesterolemia particularly benefited from the asymmetric dosage regimen.

Introduction

Chronic nitrate treatment is safe and efficacious for the symptomatic treatment of stable angina pectoris. Asymmetric dosages regimens provided better therapeutic efficacy than did multiple daily dosages [1]. Possible explanations include (1) less risk of nitrate tolerance with nitrate low periods for several hours per day, (2) better patient compliance with once daily dosages, and (3) better protection from the circadian peak frequencies of angina pectoris during daytime.

Nitrates release nitric oxide (NO) from the nitrate molecule. NO has a vasoprotective potential, because it has vasodilatory, anticoagulant, and antioxidative properties, antagonizes leukocyte-adhesion, and smooth-muscle-proliferation. These effects are assumed to be clinically relevant, substantiated by the fact that a variety of cardiovascular conditions such as hypertension, diabetes, hypercholesterolemia, and cigarette smoking are associated with an impairment of endothelium-dependent NO activity [2.] This could mean that anginal patients with such comorbidities might better benefit from nitrate therapy than their counterparts without.

The international survey IQOLAN (International Quality Of Life assessment of patients with Angina pectoris on Nitrate therapy) was designed as a multinational study, evaluating the effect of a switch from multiple daily to a once-daily nitrate treatment on the QOL and anginal symptoms of patients with stable angina pectoris. The first objective was to compare predefined quality of life indices and New York Heart Association (NYHA) anginal class before versus after replacement of multiple daily with once-daily nitrate therapy, and to assess whether the results of previous research [3,4] were reproducible in a larger study and across countries. The second objective was to investigate the influence of cardiovascular risk factors and comorbidities on the observed changes in QOL and NYHA anginal class.

Patients and methods

Design

Patients were enrolled in Germany, Portugal and the Czech Republic, Latvia, Russia, and China. They were switched from multiple daily nitrate (3 times daily 20-40 mg of isosorbide mono-or dinitrate) to the equivalent single daily dose of the compound administered early in the morning (isosorbide dinitrate 120mg in Germany, isosorbide mononitrate 50mg in the other countries). A QOL questionnaire was completed by each patient before and after the change in therapy. In addition, patient satisfaction with the current disease state and treatment preference were noted. The physicians assessed exercise capacity, and documented the NYHA anginal class as well as information on nitrate therapy before and after three months of once-daily nitrate therapy.

Patients

Outpatients with stable angina pectoris on the above multiple daily dosage nitrate therapy for at least three months prior to enrolment were eligible for the survey. An adequate knowledge of the local language was required. Patients presenting with unstable angina pectoris or myocardial infarction within the last month before enrolment, concomitant severe diseases with a possible impact on quality of life, or hospitalization within the last month before enrolment were not eligible.

Methods of evaluation

Prior to and after 3 month once-daily nitrate treatment all of the patients completed a validated [5] and previously successfully applied [3,4] 24-item English QOL questionnaire translated in local language. The items of the questionnaire were based on the Short-Form 36 questionnaire of Stewart et al. [6] , the exercise tolerance index of Wiklund et al. [7], the pain index of Marquis et al for patients with angina [8], the psychological well being index of Dupuy [9], and the distress scale of Testa and Simonson [10]. From the single items the following domains were defined: functional dependence (8 items), anginal pain (5 items), side effects (7 items), and psychological distress (4 items). For each item the individual response was scored

on a 5-point scale from 0 to 4. The sum of score values of each domain was used for further evaluation. Higher scores indicated worse quality of life. In addition, data on satisfaction with current disease state, the presence of swallowing problems, and preference for either the multiple daily or once-daily treatment were collected.
Patients were also assessed for exercise capacity indicated by the distance a man could walk on the flat at a normal pace without anginal pain [11] , and the duration of anginal attacks. The physicians reported the individual patient characteristics including demographics, eligibility criteria, presence of cardiovascular risk factors, cardiac history, the initial nitrate therapy for angina pectoris, as well as concomitant therapies. Angina pectoris was classified according to the NYHA class before and after 3 month once-daily nitrate treatment. In case the patient did not continue the study, the reasons for withdrawal were documented. Information on adverse events was collected.

Statistical analysis

The statistical analysis was performed independently of the sponsor by Xact Vieth and Partners, Cologne Germany, using SAS (Statistical Analysis System) version 6.12. Intention to treat analysis is given. Although all of the indices used in the QOL assessment have been demonstrated to have acceptable within-subject test retest variability in untreated patients5 , we considered it matter of course to assess internal consistency of the multi-item scales and used for that purpose the ratios of within- and between-item variances (Cronbach's alphas) [12]. Single data entry was performed. Data were submitted to several checks of plausibility before the start of the evaluation. Data entry errors were corrected. Before the start of the survey it was agreed that no queries were generated, not even in the case of inconsistency or incompleteness.
Variables observed before onset of the once-daily nitrate regimen and three months later were cross-classified. Qualitative variables were described by absolute and relative frequencies (percentages), and tested by the symmetry test of Bowker or the test of McNemar, whenever appropriate. Quantitative and the scored qualitative variables, as well as the differences between before and after

change-over were described as means, standard deviations / errors, 95% CIs (confidence intervals), medians, lower and upper quartiles, minimums and maximums, and tested by the paired t-test. The accumulated data were analyzed with and without country-factor as a separate variable. For the latter analysis ANCOVA (analysis of covariance) was used. Subgroups were analyzed in an exploratory manner using backward multiple regression analysis, and for the variable NYHA anginal class by Mantel-Haenszl test, stratified by country. Only cases without missing items of the corresponding domain were taken into consideration for the latter assessment (complete cases).

Results

In total, 2675 patients were enrolled, with 784 patients (29.3%) in Russia, 606 (22.7%) in Germany, 605 (22.6%) in China, 379 (14.2%) in Portugal, 241 (9.0%) in Latvia, and 60 (2.2%) in the Czech Republic. Of these, 96.2% of all patients (n=2574) completed the study (preliminary data from Germany, Portugal, and the Czech Republic have been reported [14]). Of the withdrawals, 30% were lost for follow-up, 68% needed more intensive therapy. Coronary artery disease was confirmed by angiography and/or previous myocardial infarction in 69.6% of all patients. The patient characteristics are shown in Table 1.

TABLE 1. Patient characteristics.

	n= 2675
Mean age (years, range)	63.6 (39-99)
Males (%)	62.1
Mean body mass index (range)	26.93 (19.47-39.06)
Previous coronary arteriography and/ or previous myocardial infarction(%)	69.6
NYHA anginal class I (%)	10.1
II	49.1
III	33.9
IV	3.9
Hypertension (n, %)	1872 (70.0)
Hypercholesterolemia (n,%)	1624 (60.7)
Smoking (n,%)	950 (35.5)
Adipositas (BMI>2.5 kg/m2 ,n,%)	928 (34.7)
Familial coronary disease (n,%)	918 (34.3)
Diabetes mellitus (n,%)	618 (23.1)
Peripheral vascular disease (n,%)	419 (15.7)

NYHA= New York Heart Association, BMI = body mass index

FIGURE 1. Improvement in NYHA anginal class based on n=2675 patients, no data available for 2.6% and 6.8% of all patients with multiple- and single-dose, respectively.

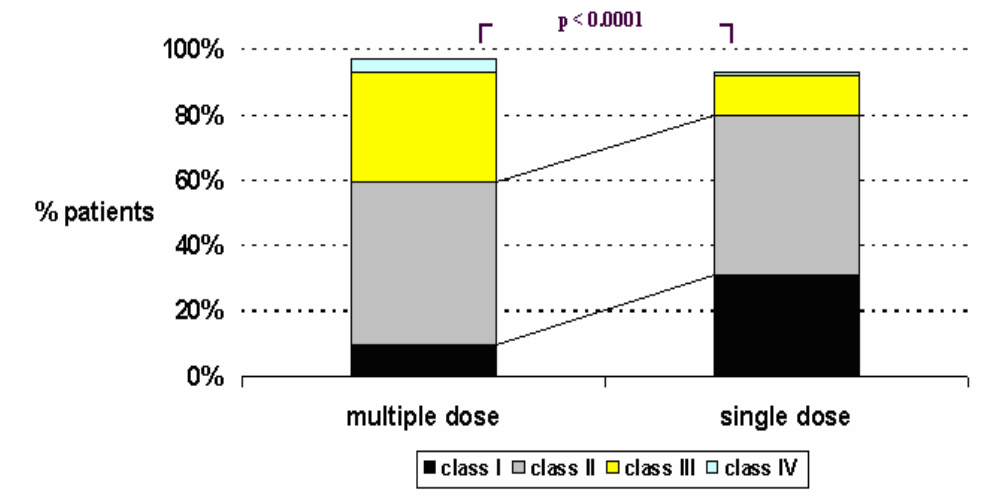
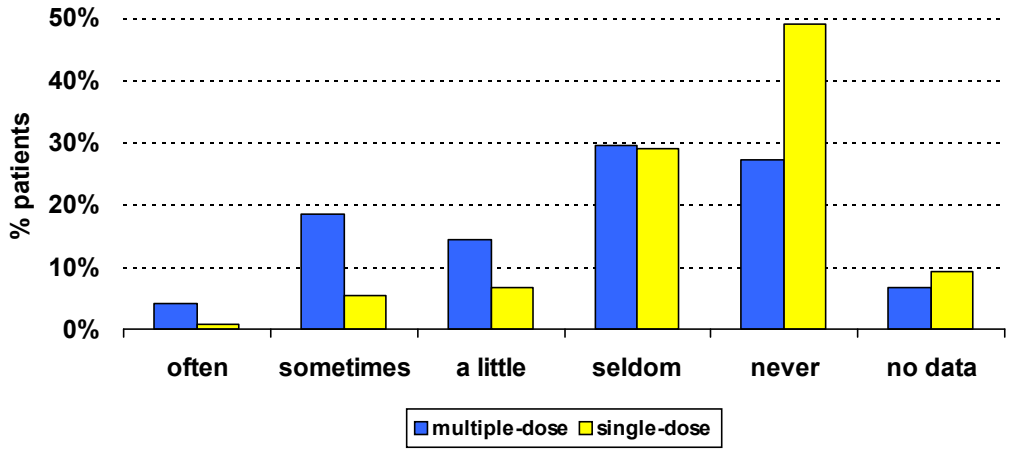


FIGURE 2 . Patient compliance as estimated by the answer to the question: did you ever forget to take your medication (p<0.0001 multiple-dose versus single-dose).



The number of patients in NYHA anginal class I increased by 23.4% ($p<0.0001$, Figure 1).

Other benefits included an improved self-reported patient compliance (Figure 2, $p<0.0001$), fewer swallowing problems ($p<0.001$), less need for additional short-acting sublingual nitroglycerin ("often" 22.1 and 4.4% of the patients, "never" 8.7 and 20.2%, multiple and once-daily, respectively, $p<0.001$), and preference for once-daily nitrate in 75.3% of the patients (Figure 3, $p<0.0001$). The painfree walking distance increased from a median of 300 meter (25% quartile: 150 meter, 75% quartile: 800 meter) to 500 meters (250 and 1000 meter, respectively, $p<0.001$). The duration of anginal pain decreased from a median of 5.0 minutes (25% quartile: 2.5 minutes, 75% quartile: 8.0 minutes) to 3.0 minutes (2.0 and 5.0 minutes, respectively, $p<0.001$).

FIGURE 3. Preference for future therapy as expressed by the patients at the completion of the study ($p<0.0001$ multiple-dose versus single-dose).

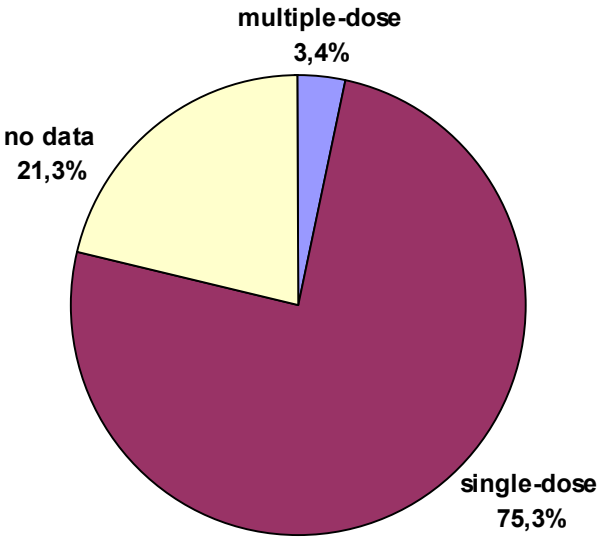
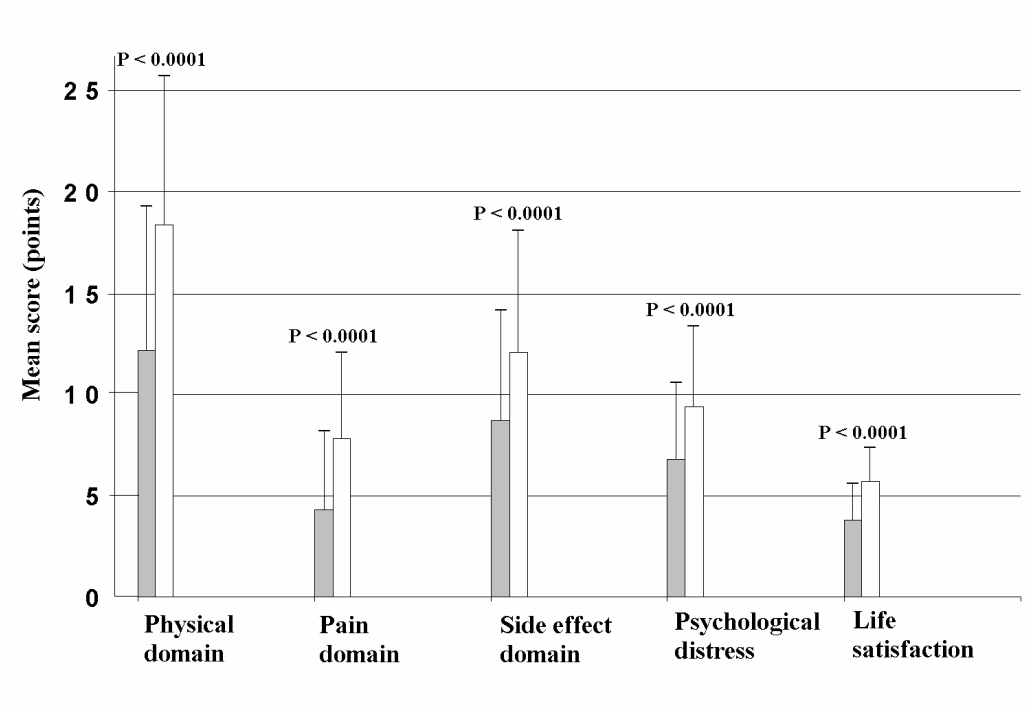


Figure 4 gives the main results of the QOL-assessments. Cronbach's alphas were >0.7 for all of the QOL-domains indicating that internal consistency of the multi-item scales were acceptable. So was test-retest reliability with duplicate standard errors of the QOL-domains from 1.6 to 2.9%. When the analysis of these QOL-data was performed including the country factor as a separate variable, the results were virtually the same indicating no major effect of nationality on the variability of these data (analysis not shown).

FIGURE 4. Quality of life scores after 3 month multiple daily and after 3 month once daily nitrate treatment(means and standard deviations).



The subgroup analyses are shown in Tables II and III. In patients with concomitant hypertension or hypercholesterolemia NYHA anginal class improved significantly better than it did in their counterparts without (Table II, p<0.001). In contrast, in patients with adipositas or CAD in the family it did significantly less so (p<0.001). The multiple regression analysis with QOL improvement as dependent and various patient characteristics as independent variables showed that age and NYHA anginal class were strong independent determinants of QOL score improvements (Table III). In all of the QOL-domains the younger the patients, and the more advanced the NYHA anginal class prior to switch, the better the QOL-benefit from the once-daily nitrate treatment was observed. Also hypercholesterolemia, and CAD in the family was associated with a better QOL-benefit in most of the QOL-domains, and a trend to better benefit in the accumulated QOL-scores (p<0.07, both). The remainder of the subgroup variables including hypertension, diabetes, smoking were not strongly associated with better benefit from once-daily nitrate.

TABLE 2. Subgroup analysis: improvement of NYHA anginal class after 3 month once daily regimen as estimated by new patients in NYHA class I (%).

	Mean Improvement (%)	95% CI	p-value	
Accumulated data	23.4	21.2-25.6	<0.0001	vs zero
Patients with diabetes	23.6	21.6-25.5	ns	vs non-diabetics
" " smoking	22.9	20.7-25.0	ns	vs no-smokers
" " Hypercholesterolemia	24.6	21.6-27.4	<0.001	vs noncholesterolemics
" " CAD in family	22.0	19.9-24.0	<0.001	vs patients without
" " hypertension	27.4	24.0-30.7	<0.001	vs patients without
" " PVD	24.4	22.5-26.3	ns	vs patients without
" " adipositas	22.4	20.3-24.5	<0.001	vs patients without
Males	24.5	22.2-26.7	ns	vs females
Elderly (>70 years)	24.6	21.0-28.3	ns	vs patients <70 years

NYHA=New York Heart Association, CI=confidence intervals, vs= versus, CAD=coronary artery disease, PVD=peripheral vascular disease.

TABLE 3. Subgroup analysis: independent determinants of QOL-score improvements (backward multiple regression analysis).

	1. physical domain		*2. pain domain*		*3. side effect domain*		*4. psychological distress*		*5. life satisfaction*		*6. add-up score*	
	b se	p-value	b se	p-value	b se	p-value	b se	p-value	b se	p-value	b se	p-value
Age	-0.04 0.01	0.0004	-0.03 0.01	<0.0001	-0.03 0.01	<0.002	-0.03 0.01	<0.0001	-0.03 0.01	<0.0001	-0.13 0.03	<0.0001
Gender		ns		ns	0.41 0.22	0.05		ns	0.19 0.09	0.03		ns
NYHA	1.85 0.18	<0.0001	1.67 0.11	<0.0001	0.63 0.15	<0.0001	0.52 0.10	<0.0001	0.43 0.06	<0.0001	5.72 0.53	<0.0001
Diabetes		ns		ns		ns		ns		ns		ns
Smoking		ns		ns		ns		ns		ns		ns
Cholesterol		ns		ns	0.05 0.02	0.03	0.33 0.15	0.03		ns	1.43 0.79	<0.07
CAD in family		ns		ns	0.06 0.02	0.09	0.30 0.15	<0.05	0.33 0.09	<0.0001	1.43 0.79	<0.07
Hypertension		ns		ns		ns		ns	-0.22 0.01	0.02		ns
PVD		ns		ns	0.58 0.29	0.05		ns		ns		ns
Adipositas		ns		ns		ns		ns		ns		ns
Concomit.BBs	0.52 0.25	<0.04		ns		ns	0.26 0.15	0.07		ns		ns
Concomit.CCB		ns		ns	0.57 0.24	<0.02	0.30 0.16	0.06		ns		ns

QOL= quality of life, b = regression coefficient, se = standard error, ns= not statistically significant, NYHA= New York Heart Association, CAD=coronary artery disease, PVD=peripheral artery disease, concomit.=concomitant, BBs=beta-blockers, CCBs=calcium channel blockers

Discussion

Nitrates are commonly used for the treatment of stable angina pectoris. However, so far, little is known about their net effects on QOL. In the current study 3-month-replacement of multiple daily dose nitrate with a once-daily dosage regimen not only improved clinical symptoms but also QOL in all of the domains and in every single item. The study was not placebo-controlled, because symptomatic patients would have to be withdrawn from active and, generally, recognized treatment, and because a double-dummy was not feasible due to the varied dosages. Yet the data are in agreement with previous studies [1,2,3] , and the improvements of the exercise parameters support the validity of the QOL-assessment. The improvements can be explained by less risk of nitrate tolerance. However, better patient compliance has to be accounted: higher average plasma levels of NO due to a better patient compliance could also explain the improvements observed. Zwinderman et al. [4] observed similar improvements in 453 patients with stable angina pectoris after replacement of 50 mg of isosorbide mononitrate once-daily with 100mg of the same compound. Plasma concentrations were not determined in the current study.

The subgroup analyses showed that QOL improved better in two subgroups: (1) the younger, and therefore presumably, more energetic patients, and (2) those with advanced NYHA anginal class, and therefore presumably, more symptomatic patients. The main purpose of the subgroup analysis was to assess whether patients with cardiovascular comorbidities would particularly benefit from NO-donor therapy due to the underlying impairment of endothelium-dependent NO- activity. In a post-hoc analysis of the DUMQOL data [14], indeed, a slightly better benefit was observed in patients with hypercholesterolemia and those with diabetes than in their counterparts without. Also, in the current study patients with hypercholesterolemia displayed better improvement of anginal class and of most of the QOL indices. Better QOL indices and anginal class improvements were also observed in patients with CAD in the family and hypertension respectively. However, no consistent pattern was observed, and, in particular, the presence of diabetes did not influence either anginal class or QOL indices. Of course, the linear

model assumed in our multivariate assessment may not have been sensitive to detect some independent determinants.

The duplicate standard errors of the QOL-domains from 1.6 to 2.9% suggested an acceptable test-retest reliability. A general problem with QOL assessments is its lack of sensitivity with heterogeneous populations. Even, small differences like language differences are often a major obstacle for such purpose [15]. The current study shows that it is not impossible to estimate QOL by statistical methods even in extremely heterogeneous populations. We should admit that a statistically powerful treatment comparison was provided by the self-controlled design which largely removed between-subject variability from the treatment comparison, as it was based on within-subject comparisons.

In summary, the results of the IQOLAN survey show, that a switch from a multiple daily to a once-daily nitrate treatment regimen resulted in an improvement of QOL and anginal NYHA class in patients with stable angina pectoris. These improvements were mirrored by an increased patient compliance, increases in the painfree walking distance, and a reduced use of additional sublingual nitroglycerin. The results support the use of once-daily treatment regimens for long-term nitrate therapy for maximized patient compliance and therapeutic benefit. Patients with concomitant hypertension, hypercholesterolemia or with CAD in the family particularly benefited from an asymmetric dosage regimen, suggesting that an underlying impairment of endothelium-dependent NO activity may be involved in these subgroups.

References

1. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. N Engl J Med 1998; 338: 520-31.
2. Gewaltig MT, Kojda G. Vasoprotection by nitric oxide: mechanisms and therapeutic potential. Cardiovasc Res 2002; 55: 250-60.
3. Niemeyer MG, Kleinjans HAJ, De Ree R et al: Comparison of multiple-dose and once-daily nitrate therapy in patients with stable angina pectoris: effects on quality of life indices. Current Therapeutic Research 1996; 57: 927-36.
4. Zwinderman AH, Cleophas TJ, van der Sluijs H et al: Comparison of 50-mg and 100-mg sustained-release isosorbide mononitrate in the treatment of stable angina pectoris: effects on quality-of-life indices. Angiology 1999, 50: 963-9.
5. Cleophas TJ, Niemeijer MG, Zwinderman AH, et al. Assesssment of quality of life in patients with angina pectoris. Progress made by the Dutch Mononitrate Quality of life Study Group. Neth Heart J 2002 ; 10 : 13-8.
6. Stewart AL, Hays RD, Ware JE: The MOS short form general health survey. Reliability and validity in a patient population. Med Care 1988; 26: 724-35.
7. Wiklund I, Comerford MB, Dimenas E: The relationship between exercise tolerance and quality of life in angina pectoris. Clin Cardiol 1991; 14: 204-8.
8. Marquis P, Fayol C, Joire JE: Clinical validation of a quality of life questionnaire in angina pectoris patients. Eur Heart J 1995; 16:1554-60.
9. Dupuy HJ: The psychological general well being index. In: Wenger NK, Matson ME, Furberg CD, Elinson J, eds. Assessment of Quality of Life in Clinical Trials of Cardiovascular Therapies. New York: Le Lacq Publishing 1984: 170-83.
10. Testa MA, Simonson DC: Assessment of quality-of-life outcomes. N Engl J Med 1996; 334: 835-40.

11. Guyatt GH, Sullivan MJ, Thompson PJ, et al. Walking distance: a new measure of exercise capacity in patients with coronary artery disease. Can Med Assoc J 1985; 132: 919-23.
12. Bland JM, Altman DG. Cronbach's alpha. Br Med J 1997; 314: 572-3.
13. Jansen RMG, Niemeijer MG, Cleophas TJ, et al. Once daily and multiple daily dose nitrate treatment in 1045 patients with stable angina pectoris. Perfusion 2004; 17: 36-42.
14. Jansen R, Niemeyer MG, Cleophas TJ et al. Factors influencing efficacy of nitrate therapy for stable angina pectoris: a multiple linear regression analysis. Angiology 2000, 51: 1007-12.
15. Aaronson NK, Muller M, Cohen PD. Translation, validation, and norming of the English language version of the Short-Form-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51: 1055-68.

CHAPTER 7

Quality of life with heart failure:

psychosocial determinants to be considered by cardiologists

(Neth Heart J 2003; 11: 337-40)

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Abstract

Background: Independent determinants of QOL (quality of life) with heart disease have been recognized and include factors like severity of medical condition, comorbidity, and concomitant medication. Psychosocial factors, like “ability to cope with the unpleasantness of the medical condition”, “want of information”, and “social identification” have important influence on self-perceived well-being, but their influence on health-related QOL domains and self-perceived QOL in patients with heart failure have not been systematically studied.

Objective: to assess correlation between such psychosocial factors and QOL in patients with heart failure.

Methods: Patients from the outpatient heart failure clinic of the Martini Hospital , a 1000-bed community hospital in the city of Groningen, Netherlands, were included if their ejection fractions were <40% and their medical diagnosis according to their cardiologists was stable chronic congestive heart failure. The following QOL-estimators were applied: Pearlin’s Mastery Scale, Stewart’s Short Form 36 Quality of Life Questionnaire, Dupuy’s Index of Well-being, Cantrill’s Self-perceived Quality of Life Scale, Mester’s Want of Information Scale. Internal consistency of the multi-item scales were estimated by Cronbach’s alphas. Linear and multiple linear regression analyses were performed of the data.

Results: Sixty patients were enrolled, 41 males and 19 females, average age 68 years (range 51-84 years). “Ability to cope with the unpleasantness of the medical condition” was not only an independent determinant of self-perceived and health-related QOL(both $p<0.001$), but also of each domain of health related QOL separately ($p<0.001$ for each domain). Lack of “adequate medical information” and “negative social identification” (the identification with counterparts who are doing worse) were negative predictors of “ability to cope” ($p<0.01$ and <0.001 resp). “Negative social identification” also was an independent determinant of self-perceived QOL, both unadjusted and after adjustment for “ability to cope” and “adequate medical information”.

Conclusions: Relevant recommendations from this paper to be considered by cardiologists during everyday office-hours could include:

1. Patients who express having difficulties to cope with the unpleasant aspects of their underlying heart condition, have low health-related QOL as well as low self-perceived QOL.
2. Adequate medical information given is a significant contributor to both better “ability to cope” and better self-perceived QOL.
3. Avoiding to identify oneself with counterparts who are doing worse, and, instead, starting to identify oneself with counterparts who are doing better, are significant contributors to both better “ability to cope” and better self-perceived QOL.

Introduction

Patients able to cope with all of the unpleasant aspects of their medical condition, generally, have better levels of well-being than those unable to cope [1,2,3]. Also the correlation between levels of well-being and QOL (quality of life) has been demonstrated to be strongly positive [4,5]. What are determinants of "ability to cope"? It has been suggested that adequate objective information of patients on their physicomedical condition is an important factor [3,6]. Also, social identification of patients with their counterparts has been suggested as a possible contributory factor [7,8,9]. This may be particularly true for patients from moderate or low social class, as not infrequently observed in patients with heart failure [10]. We hypothesized that in patients with heart failure "inability to cope" would be associated not only with low QOL, but also with lack of adequate medical information and lack of social identification with the patients' counterparts. We also assumed that the latter factors may be direct contributors to low QOL. In order to assess these hypotheses we studied 60 patients with stable chronic heart failure. All of the patients were assessed by a test battery consisting of validated questionnaires. Linear and multiple linear regression analyses of the data were performed.

Methods

Patients from the Outpatient Heart Failure Clinic of the Martini Hospital , a 1000-bed community hospital in the city of Groningen, Netherlands, were included if their ejection fractions were <40% and their medical diagnosis according to their cardiologists was stable chronic congestive heart failure. Patients were assessed by the following battery of validated questionnaires. The Mastery Scale of Pearlin and Schooler [11] was used to estimate ability to cope with the unpleasantness of the medical condition. The scale consisted of 7 items scored on five point ordinal Likert scales ranging from "completely untrue" to "completely true". Scores were added up and divided by numbers of items in order to indicate "ability to cope". Health-related QOL was assessed by a validated test battery based on the Short Form 36 Quality of Life Questionnaire of Stewart [12] and the Index of Psychological Well-

being of Dupuy [13]. The adapted form as used by Niemeijer [14] and Zwinderman [15] consisted of 19 items also scored on 5 points: 8 items addressing the physical domain, 7 items the pain domain, and 4 items the psychological domain of QOL. As the above QOL battery was developed for patients with coronary heart disease in general, 3 items were added to address specific symptoms of heart failure, including shortness of breath at rest, shortness of breath with exercise, and (ankle) oedema. Also 3 items were added to address social problems rising from the medical condition. Again scores were added up and divided by numbers of items to estimate overall scores in different QOL domains.

Self-perceived QOL was assessed by Cantrill's Stair Diagram [16].It was scored on a 10 point scale: number 0 for the worst , number 10 for the best self-perceived QOL.

Lack of adequate medical information was assessed by Mester's Want of Information Scale [17]. Six items were scored on 5 point scales.

Social identification, either positive (identification with counterparts who are doing better) or negative (identification with counterparts who are doing worse) were assessed by two scales of 8 items each and again scored on 5 point scales. The scales were developed by one of the authors who is a recognized expert in the field of social comparisons [7,8,9].

Internal consistency of the multi-item scales were estimated by Cronbach's alphas. This coefficient represents the proportion of variance due to the true scores as compared to the overall variance in the data including measurement error. It has a maximal value of 1.0 whereas a value above 0.7 is recommended to ensure acceptable reliability.

All of the patients answered their questionnaires without assistance of the physician. Linear and multiple linear regression analyses of the accumulated data were performed. Under the assumption of pooled scores of at least 50% and differences between pooled scores of at least 10%, and clinically relevant within-group correlations of at least +0.6, the study would have to include 61 patients to obtain a statistical power of 80% and a 5% significance level. The study was approved by the institutional ethic committee.

TABLE 1. Internal consistency of the questionnaires as estimated by Cronbach's alpha.

	Number of items	Cronbach's alpha
The Mastery Scale of Pearlin and Schooler	7	0.73
Health-related QOL Questionnaire:		
Physical domain	8	0.91
Pain domain	7	0.75
Psychological domain	4	0.74
Symptoms of heart failure	3	0.69
Social domain	3	0.91
Mester's Want of Information Scale	6	0.87
Positive social identification	8	0.91
Negative social identification	8	0.87

Results

Sixty patients were enrolled, 41 males and 19 females. Average age 68 years (range 51-84 years).

Table 1 gives an overview of levels of internal consistency of the various questionnaires, which were adequate without exception. "Ability to cope with the unpleasantness of the medical condition" was not only an independent determinant of self-perceived and health-related QOL but also of each domain of health-related QOL separately ($p<0.001$ for each domain, Table 2).

TABLE 2. Linear regression analysis of the determinant "ability to cope with the unpleasantness of the heart condition" on health-related QOL and self-perceived QOL.

	R square	Regression coefficient	P-value
Self-perceived QOL	0.46	1.62	<0.001
Health-related QOL:			
Overall	0.44	0.65	<0.001
Physical domain	0.20	1.0	<0.001
Pain domain	0.21	0.29	<0.001
Psychological domain	0.29	0.54	<0.001
Symptoms of heart failure	0.23	0.55	<0.001
Social domain	0.44	0.55	<0.001

Table 3 shows that lack of “adequate medical information” and “negative social identification” (the identification with counterparts who are doing worse) were strong negative predictors of “ability to cope” (p<0.01 and <0.001 resp). Table 4 shows that “negative social identification” also was an independent determinant of self-perceived QOL. This was so both unadjusted and after adjustment for “ability to cope” and “adequate medical information”.

TABLE 3. Linear regression analysis of the determinants “adequate medical information”, “positive social identification”, and “negative social identification” on “ability to cope with the unpleasantness of the heart condition”.

	R square	Regression coefficient	P-value
“Adequate medical information”	0.15	-0.36	<0.01
“Positive social identification”	0.04	0.28	ns
“Negative social identification”	0.20	-0.59	<0.001

TABLE 4. Linear regression analysis of the determinants (1) “positive social identification” and (2) “negative social identification” on self-perceived QOL.

	R square	Regression coefficient	P-value
“Positive social identification”	0.04	0.36	ns
“Negative social identification” *	0.34	-0.58	<0.001

** The “negative social identification” remained a statistically significant determinant of self-perceived QOL (p<0.01) after adjustment for “ability to cope” and “adequate medical information”.*

Discussion

As expected, “ability to cope with the medical condition” largely determined QOL. No less than 46% of the variance in the self-perceived QOL was determined by the variance in the “ability to cope” (Table 2). Adequate medical information improved both “ability to cope” and self-perceived QOL. While a “positive social identification” (social identification with counterparts who are doing better) did not change self-perceived QOL or “ability to cope”, a “negative social identification” (social identification with counterparts who are doing worse) deteriorated both factors,

either tested separately or simultaneously. It is remarkable that the negative influence of “negative social identification” was a lot stronger than the positive influence of “positive social identification”. Possible explanations for this unexpected discrepancy include: (1) negative events and experiences, generally, have a more profound impact on personal life than positive ones [18] ; (2) patients with heart failure are, particularly, at risk of being depressed and, maybe therefore, less able to identify themselves with those who are doing better [19].

A limitation of the present study is that it did not test all of the correlations simultaneously. For such purpose LISREL’s method [20] should be used. However, our sample size did not provide enough power to apply this method reliably. Nonetheless, our results are impressive and largely confirm our prior hypotheses. They will be used by our group for the development of an intervention program to improve QOL with heart failure, currently in progress at our departments. In the meantime, relevant recommendations to be considered by cardiologists for their everyday office-hours could include:

Patients who express having difficulties to cope with the unpleasant aspects of their underlying heart condition, have low health-related QOL as well as self-perceived QOL.

Adequate medical information given is a significant contributor to both better “ability to cope” and better self-perceived QOL.

Avoiding to identify oneself with counterparts who are doing worse, and, instead, starting to identify oneself with counterparts who are doing better, are significant contributors to both better “ability to cope” and better self-perceived QOL.

References

1. Cohen F. Coping with surgery: Information, psychological preparation, and recovery. In: L.W.Poon (Ed.). Aging in the 1980's: Psychological issues (pp. 375-382). Washington, D.C.: American Psychological Association, 1980.
2. Cohen S, Edwards JR. Personality characteristics as moderators of the relationship between stress and disorder. In: R.W. Neufeld (Ed.). Advances in the investigation of psychological stress (pp. 235-283). New York: John Wiley & Sons, 1989.
3. Cohen F, Lazarus RS. Coping with the stress of illness. In: G. Stone, F. Cohen, & N. Adler (Eds.). Health Psychology. San Fransisco: Jossey-Bass, 1979.
4. Abbey A, Andrews FM. Modelling the psychological determinants of life quality. Social Indicators Research. 1985; 16: 1-34.
5. Taylor SE, Brown JD (1988). Illusion and well-being: A social psychological perspective on mental health. Psychological Bulletin. 1988; 103: 193-210.
6. Felton BJ, Revenson TA (1984). Coping with chronic illness: A study of illness controllability and the influence of coping strategies on psychological adjustment. Journal of Consulting and Clinical Psychology. 1984; 52: 343-53.
7. Buunk BP, Collins RL, Taylor SE, VanYperen NW, Dakof GA (1990). The affective consequences of social comparison: Either direction has its ups and downs. Journal of Personality and Social Psychology. 1990; 59: 1238-49.
8. Buunk BP, Ybema JF. Social comparison and occupational stress: The identification contrast model. In: B.P. Buunk, & F.X. Gibbons (Eds.). Health, coping and well-being: Perspectives from social comparison theory (pp. 359-388). Mahwah, NY: Lawrence Erlbaum Associates, 1997.
9. Van der Zee K, Buunk B, Sanderman R, Botke G, Van den Bergh F. Social comparison and coping with cancer treatment. Personality and individual differences. 2000; 28: 17-34.
10. Westlake C, Dracup K. Predictors of quality of life for patients with advanced heart failure. Circulation. 1998; 97: 482 (Suppl 1).

11. Bland JM, Altman DG. Statistics notes. Cronbach's alpha. Br Med J . 1997; 314: 572-3. Pearlin LI, Schooler C. The structure of coping. Journal of Health and Social behavior. 1978; 19: 2-21.
12. Stewart AH, Hays RD, Ware JE. The MOS short-form general health survey: reliability and validity in a patient population. Medical Care. 1995; 26: 724-35.
13. Dupuy HJ. The psychological well-being index. In: N.K. Wenger, M.E. Matson, C.D. Furberg, & J. Elinson (Eds.). Assessment of quality of life in clinical trials of cardiovascular therapies (pp. 170-183). Le Jaq Publishing, 1984.
14. Niemeijer MG, Kleinjans HAJ, De Ree R, Zwinderman AH, Cleophas TJM, Van der Wall EE. Comparison of multi-dose and once-daily nitrate therapy in 1212 patients with stable angina pectoris: Effects on quality of life indices. Angiology. 1997; 48: 855-62.
15. Zwinderman AH, Cleophas TJ, Niemeijer MG, Van der Wall EE. Effects of 50 mg and 100 mg isosorbide mononitrate once daily on quality of life in patients with stable angina pectoris. Angiology. 1999; 50: 949-65.
16. Cantril H. The pattern of human concerns. New Brunswick, NJ, Rutgers University Press, 1965.
17. Nederlandse Hartstichting. Brochure: Hartfalen. Mouthaan Grafisch bedrijf, Papendrecht, 2000. [Dutch Heart Foundation, (2000). Information Pamflet: Heart Failure.].
18. Taylor SE, Helgeson VS, Reed GM, Skokan LA. Self-generated feelings of control and adjustment to physical illness. Journal of Social Issues. 1991; 47: 91-109.
19. Sykes DH, Hanley M, McC Boyle D, Higginson JDS, Wilson C. Socioeconomic status, social environment, depression and postdischarge adjustment of the cardiac patient. Journal of Psychosomatic Research. 1999; 46: 83-98.
20. Jöreskog KG, Sörbom D. LISREL 8: User's reference guide. Mooresville, IN: Scientific Software, 1993.

CHAPTER 8

Quality of life of patients on the waiting list for coronary angiography

(Neth Heart J 2006; 14: 292-96)

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Summary

Background: Providing adequate medical information and avoiding patients to identify themselves with fellow-sufferers were significant contributors to better quality of life (QOL) in cardiac patients. Gender and level of psychic tension were significant predictors of QOL in cardiac patients. We don't know (1) whether we can improve QOL by increasing patients' ability to cope with the unpleasant aspects of the underlying condition, (2) whether gender and level of psychic tension interact or act independently.

Objective: to assess both questions.

Methods: 38 patients on the waiting list for coronary angiography were assessed with validated test batteries. To increase the patients' ability to cope, they were randomly assigned to read either (1) the comments of a patient previously successfully treated or (2) general information about the procedure. The former information, unlike the latter, was assumed to improve coping ability and, thus, provide better QOL. Homogeneity of the patient group was estimated by Cronbach's alphas. For analysis linear regression and general factorial analyses of variance were applied.

Results: The group was psychologically homogeneous as indicated by Cronbach's alphas being, generally, over 75%. There was a significant or close to significant association of presence of coping information with a better mobility, social performance and self-perceived QOL ($p<0.05$, $p<0.06$, and $p = 0.10$).High levels of psychic tension were associated with low self-perceived QOL and low psychological scores (both $p<0.02$). Female gender was associated with lower mobility, lower psychological scores and lower overall QOL ($p<0.05$, $p<0.02$ and $p<0.05$). A significant or close to significant interaction was observed between gender and psychic tension as combined determinants of self-perceived QOL, mobility index, and overall QOL index ($p<0.03$, $p<0.09$, and $p<0.05$). Separate assessments of these determinants showed that the female gender was the strongest determinant of low QOL.

Conclusions:

1. In patients on the waiting list for coronary angiography, an increased ability to cope with the unpleasant aspects of a possible underlying heart condition improves QOL.
2. Female gender and a high level of psychic tension places patients at risk of low QOL.

It is to be hoped that this paper raises the physicians' awareness of such psychological mechanisms, and that, particularly, future female patients will receive adequate attention for that purpose.

Introduction

Therapeutic interventions have been demonstrated to beneficially influence quality of life of patients with cardiovascular conditions. E.g. once-daily dosage schedules of nitrates significantly improved quality of life (QOL) in patients with stable angina pectoris.[1,2] In the past few years also psychological interventions have been successfully employed. Particularly, providing adequate medical information[3] and avoiding patients to identify themselves with fellow-sufferers who are doing worse, and , instead, identifying themselves with those who are doing better, were significant contributors to both better ability to cope with the unpleasant aspects of the underlying condition and better self-perceived quality of life.[4-8] However, we don't know whether we can improve QOL by increasing patients' ability to cope.

Gender [9-12] and psychic tension [13,14] have been recently recognized as important determinants of QOL. Females, unlike males, underestimated their level of health, suffered more than their male counterparts from health problems and chronic conditions, used more medicines [9,10] , and felt sicker than men.[8] Females with cardiovascular disease had lower QOL than had their male counterparts.[15] Psychic tension influences QOL, probably, because it induces a negative mood which is a strong predictor of symptoms and health complaints.[13,14] However, we don't know whether these two factors interact or act independently.

Patients on the waiting list for coronary angiography are, of course, somatically heterogeneous, but psychologically they are less so. We assumed that a group of patients meeting the Cronbach's criterium for consistency [16] would qualify for assessing the following questions:

1. Can we improve QOL by increasing the patients' ability to cope with the unpleasant aspects of a possible underlying heart condition?
2. Are gender and psychic tension independent determinants of QOL in this category of patients, and do these two factors interact or act independently?

To assess these questions we studied 38 patients all of whom were to be assessed by test batteries consisting of validated questionnaires. Linear regression and general factorial analyses of variance were used.

Methods

In the period between May and August 2004 38 patients gave their informed consent. Each patient had been examined at the outpatient Cardiology Clinic of the Martini Hospital, a 1000 bed teaching hospital in the city of Groningen, Netherlands, and was included if his/her knowledge of the Dutch language was adequate. The protocol was approved by the institutional ethic committee.

Patients were assessed by the following battery of validated questionnaires.

Health related QOL was assessed by the DUMQOL (Dutch Mononitrate Quality of Life) Questionnaire.[1,2] It consisted of 19 items scored on 5 points: seven items addressed the physical domain, six the pain domain, four the psychological domain, and three the social domain. Self- perceived QOL was assessed by Cantril's Stair Diagram.[17] It was scored on a ten-point scale: number 0 for worst, number 10 for the best self-perceived QOL.

Social identification with fellow sufferers who are doing worse or better was assessed by the Iowa-Netherlands Comparison Orientation Measure (INCOM).[18] The scale consisted of 11 items scored on 5 points.

In order to increase the patients' ability to cope with the unpleasant aspects of a possible underlying heart condition, patient were randomly assigned to read either (1) the comments of a patient previously successfully treated or (2) general information about the procedure. We assumed that the former information, unlike the latter, would improve coping ability and, thus, provide better QOL, and defined the assigned subgroups as respectively the coping-information-subgroup and the neutral-information-subgroup.

Finally, the presence of psychic tension was assessed by a standard questionnaire routinely used for that purpose at our department and consisting of three items scored on 7 points (1= no, 7 maximal psychic tension). All of the scores were added linearly and divided by the numbers of items in order to obtain overall scores.

Statistical analysis

Internal consistency of the multi-item scales was estimated by Cronbach's criterium of consistency.[16]

Cronbach´s alpha $$\text{alpha} = \frac{k}{(k-1)} \cdot \left(1 - \sum \frac{s_i^2}{s_T^2}\right)$$

k = number of items

s^2_i = variance of *i*th item

s^2_T = variance of total score obtained by summing up all of the items

This criterium represents the proportion of variance due to the true scores as compared to the overall variance in the data including the measurement error. It has a maximal value of 1.0 whereas a value above 0.7 indicates an acceptable reliability and reproducibility in the data. For analysis we used linear regression analyses and general factorial analyses of variance using the groups means as main effects and the combined effects of the factors as interactive effects. If a significant interaction effect was demonstrated, differences in the subgroups were, subsequently, assessed separately by linear regression. We used Excel data files[19] and SPSS Statistical Software.[20]

TABLE 1. Cronbach's criterium of consistency[16] of the multi-item DUMQOL and the other questionnaires as calculated from the current study data indicating, generally, a good reproducibility.

		Cronbach's alpha*
1. DUMQOL questionnaire	**Mobility domain**	0.91
2.	**Pain domain**	0.82
3.	**Psychological domain**	0.60
4.	**Social domain**	0.75
5. Social Comparison Orientation Measure		0.77
6. Psychic Tension questionnaire		0.76

**A value above 0.7 indicates acceptable reliability and reproducibility in the data.*

Results

The study group consisted of 21 males and 17 females, mean age 68 (standard deviation 7.9) years, range 46 to 82 years. Of the patients 34 (90%) had a partner, 14 (37%) were underwent the intervention for the second time. Except for the psychological domain of the DUMQOL questionnaire, the internal consistency and reliability of the questionnaires was adequate, underscoring both the reproducibility of the questionnaires and the homogeneity of the study group (Table 1).

TABLE 2. Linear regression analyses of the associations between QOL estimators and the ability to cope as estimated by the presence of coping-information or neutral-information.

	Independent variable **Coping***	
	R^2	**p-value**
1. Mobility domain	0.39	<0.05
2. Pain domain	-	ns
3. Psychological domain	-	ns
4. Social domain	0.26	<0.06

**The significant association was lost after adjustment for social comparison orientation (linear regression); R2 = Pearson's correlation coefficient squared.*

Table 2 assesses the strength of the associations between the QOL estimators and the ability to cope as estimated by the presence of coping-information or neutral-information. There was a significant and close to significant association between the presence of coping-information with both a better mobility and a better social performance. The presence of coping-information may indeed produce better QOL, at least in these two domains of the DUMQOL battery. A similar trend was observed with the Cantril's Self-perceived Quality of Life Scale, although significance was not obtained here (p=0.10). The significant associations were lost after adjustment for social comparison orientation using factorial analysis of variance with the INCOM Questionnaire as second dependent variable.

Table 3 gives the results of the factorial analyses of variance of the effects of the determinants gender and psychic tension on various QOL estimators.

TABLE 3. General factorial analyses of variance of the associations of gender, psychic tension and their interaction with various QOL estimators.

	Gender		Psychic tension		Interaction gender x psychic tension	
	b	**p-value**	**b**	**p-value**	**b**	**p-value**
1. Cantril's Self- perceived Quality of life Scale	-0.57	ns	-0.92	<0.02	-1.13	<0.03
2. Mobility domain	-0.71	<0.05	0.07	ns	-0.53	<0.09
3. Pain domain	-0.15	ns	-0.21	ns	-0.19	ns
4. Psychological domain	-0.45	<0.02	-0.35	<0.02	-0.05	ns
5. Social domain	0.05	ns	-0.23	ns	0.01	ns
6. Overall (2-6)	-0.46	<0.05	-0.01	ns	-0.04	<0.05

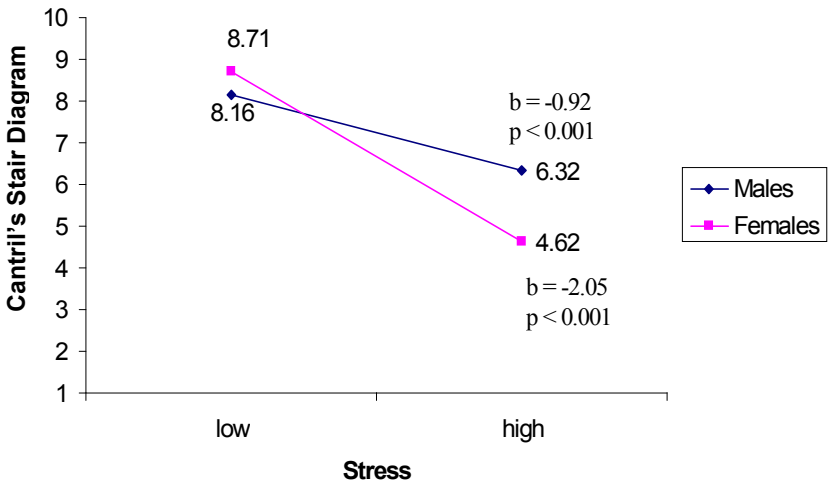
b = regression coefficient

Psychic tension was inversely correlated with Cantril's Self-perceived QOL Scale; the lower the psychic tension the better the QOL. Female gender was correlated with the lower scores in the mobility, psychological and overall QOL of the DUMQOL battery, while high psychic tension was correlated with lower scores in the psychological domain. As indicated in the Table 3, a significant or close to significant interaction was observed between gender and psychic tension as combined determinants of the Cantril's QOL scores, mobility DUMQOL and overall DUMQOL scores. Because a significant interaction overrules the conclusion of independence of the separate determinants, we performed simple linear regression analyses of these determinants for either gender. The figures 1-3 show that psychic tension is a stronger determinant of QOL estimators in females than it is in males. Obviously, in males, unlike females, QOL estimators are little influenced by psychic tension.

Discussion

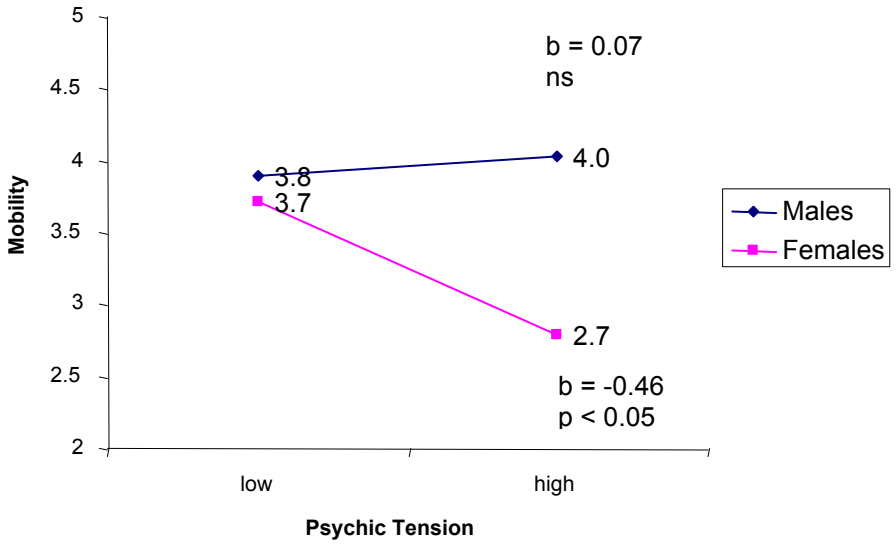
The study showed a significant ($p<0.05$) and close to significant ($p<0.06$) association of the presence of coping-information with mobility and social indices of QOL, and a similar trend was observed with the Cantril's self-perceived QOL Scale. This suggests that a better ability to cope may indeed improve some QOL estimators. However, the magnitude of these effects is less impressive than it was in our previous study where an association of coping ability was found at $p<0.001$ with all of the QOL estimators.[3] There are several explanations for this difference: (1) a study with a small sample size can hardly produce low p-values, (2) a different evaluation / assessment of coping ability was applied. Also (3) the difference could be explained by the presence of more females in the present study: 45% compared to 30 % of the patients in the previous study. To date no studies showing gender differences in coping ability have been published, but gender differences of other psychological factors like psychic tension have been established before. Despite the less impressive result, the two studies are in line, and support the findings of investigators who studied other medical conditions for the effects of coping on QOL.[21-24]

FIGURE 1. Mean effects of level of psychic tension on Cantril's Self-perceived QOL scale; b = regression coefficient.



The current study found a significant association of psychic tension, gender as well as their combination with various QOL estimators. When females and males were assessed separately, psychic tension was a much stronger determinant of QOL estimators in females than it was in males. Obviously, in females a high level of psychic tension reduces QOL more than it does in males. The present study can not only confirm that females at the waiting list for coronary angiography are more tense than males, but can also conclude that their QOL is lower, possibly as a consequence of being more tense. The price of women's longer life expectancy has to be paid in terms of a life with more psychic tension and less QOL. The current paper provides, thus, further support for Nathanson's legendary statement: "women get sick, men die".[11]

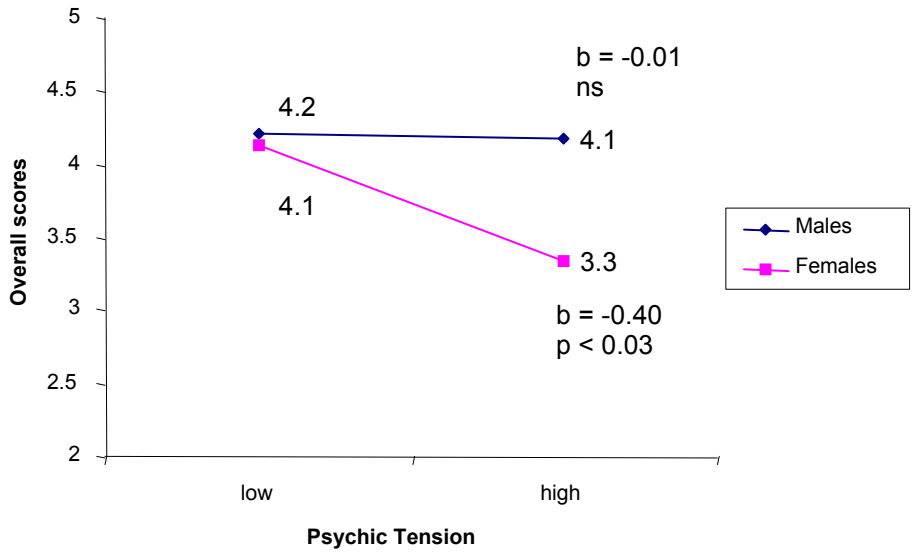
FIGURE 2. Mean effects of level of psychic tension on mobility index (DUMQOL Battery); b= regression coefficient.



Many differences have been recognized to exist between women and men with coronary heart disease.[25,26] Usually, women will develop a heart attack about 10 years later than men, probably because they are protected by a higher HDL

cholesterol premenopausally, but at the same time suffer from more risk of diabetes due to associated obesity, higher frequency of metabolic syndrome, twice the risk of heart attack due to smoking. Women may not experience the crushing chest pain that is a classic symptom of a heart attack in men, and also have smaller coronary arteries, making various intervention more difficult to do. They may not talk to their physicians about coronary risks and may not recognize the symptoms, mistaking them for signs of panic disorder, psychic tension or hypochondria. The current paper demonstrates psychological mechanisms that are obviously different between males and females, and may contribute to the above differences in behaviour patterns.

FIGURE 3. Mean effects of psychic tension on overall QOL scores (DUMQOL Battery); b = regression coefficient.



We conclude that:

1. In patients at the waiting list for coronary angiography, an increased ability to cope with the unpleasant aspects of a possible underlying heart condition improves QOL.

2. Female gender and a high level of psychic tension places patients at risk of low QOL.

It is to be hoped that this paper raises the physicians' awareness of such psychological mechanisms, and that, particularly, future female patients will receive adequate attention for that purpose.

Appendix

DUMQOL questionnaire

A self-administered questionnaire comprising of 21 items of five point scales on three important areas of quality of life, based on the Short Form 36 questionnaire of Stewart[27], the exercise tolerance index of Wiklund[28], the pain index for patients with angina pectoris of Marquis[29], the psychological well-being index of Dupuy[30], as well as the distress scale of Testa[31].

Cantril's stair diagram

A diagram shaped like stairs, with number one at the bottom and number ten at the top. People have to place themselves on the stairs according to their current well-being. When they place themselves at the bottom it means that they rate their well-being as bad. The more they place themselves towards the top, the more they feel their well-being is good.

INCOM questionnaire

The Iowa-Netherlands Comparison Orientation Measure. A validated measure of the tendency to make social comparisons. Assuming that the tendency toward social comparison is universal, the scale was constructed so as to be appropriate to and comparable in 2 cultures: American and Dutch[18].

Cronbach's alpha

Cronbach's alpha measures how well a set of items (or variables) measures a single unidimensional latent construct. When data have a multidimensional structure, Cronbach's alpha will usually be low. Technically speaking, Cronbach's alpha is not a statistical test - it is a coefficient of reliability (or consistency) [16].

References

1. Zwinderman AH, Cleophas TJ, Niemeijer MG, Van der Wall EE. Effects of 50 and 100 mg isosorbide mononitrate once daily on quality of life in patients with stable angina pectoris. Angiol 1999; 50: 949-65.
2. Niemeijer, MG, Kleinjans HA, De Ree R, Zwinderman AH, Cleophas TJ, Van der Wall EE. Comparison of multiple-dose and once-daily nitrate therapy in 1212 patients with stable angina pectoris: effects on quality of life indices. Angiol 1997; 48: 855-62.
3. Jansen R, Vos S, Cleophas TJ, Niemeijer MG, Zwinderman AH, Buunk B. Quality of life with heart failure: psychosocial determinants to be considered by cardiologists. Neth Heart J 2003; 11: 337-41.
4. Buunk BP, Gibbons FX, Visser A (2002). The relevance of social comparison processes for prevention and health care. Patient education and Counseling 2002; 47: 1-3.
5. Dixon T, Lim LL, Heller RF (2001). Quality of life: an index for identifying high-risk cardiac patients. Journal of clinical epidemiology 2001; 54: 952-60.
6. Grady KL, Jalowiec A, White-Williams C. (1995). Predictors of quality of life in patients with advanced heart failure awaiting transplantation. Heart Lung Transplant 1995; 14; 2-10.
7. Helgeson VS, Taylor SE (1993). Social comparisons and adjustment among cardiac patients. J Appl Soc Psychol, 23, 1171-1195.
8. Hou N, Chui MA, Eckert GJ, Oldridge NB, Murray MD, Bennett SJ (2004). Relationship of age and sex to health-related quality of life in patients with heart failure. Am J Crit Care 2004; 13: 153-61.
9. Gijsbers van Wijk CM, Kolk AM. Sex differences in physical symptoms: the contribution of symptom perception theory. Social Sciences & Medicine 1997; 45: 231-46.
10. Gijsbers van Wijk CM, Huisman H, Kolk AM. Gender differences in physical symptoms and illness behavior: a health diary study. Sciences & Medicine 1999; 1061-74.

11. Nathanson CA. Sex, illness, and medical care. A review of data, theory, and method. Social Sciences & Medicine 1977; 11: 13-25.
12. Riedinger MS, Dracup KA, Brecht ML, Padilla G, Sarna L. (2001). Quality of life in patients with heart failure: do gender differences exist? Heart & Lung 2001; 30, 105-16.
13. Kulik JA, Moore PJ, Mahler HI. Stress and affiliation: hospital roommate effects on preoperative anxiety and social interaction. Health psychology 1993; 12: 118-224.
14. Kulik JA, Mahler HI. (1998). Stress and affiliation in a hospital setting: preoperative roommate preferences. Personality and Social Psychology Bulletin 1998; 15: 183-93.
15. Van Jaarveld CH, Sanderman R, Ranchor AV, Ormel J, Van Veldhuisen DJ, Kempen GI. Gender- specific changes in quality of life following cardiovascular disease: a prospective study. J Clin Epidemiol 2002; 55: 1105-12.
16. Bland JM, Altman DG. Statistical notes. Cronbach's alphas. Br Med J 1997; 314: 572-3.
17. Cantril H. The pattern of human concerns. New Brunswick, NJ, Rutgers University Press, 1965.
18. Gibbons FX, Buunk BP. (1999). Individual differences in social comparison: development of a scale of social comparison orientation. Journal of Personality and Social Psychology 1999; 76: 112-42.
19. www.excel.com
20. www.spss.com
21. Bennenbroek FT, Buunk BP, Van der Zee KI, Grol B. Social comparison and patient information: what do cancer patients want? Patient education and Counseling 2001; 47: 5-12.
22. Bennenbroek FT, Buunk BP, Stiegelis HE, Hagedoorn M, Sanderman R, Van den Bergh AC, Botke G. (2003). Audiotaped social comparison information for cancer patients undergoing radiotherapy: differential effects

of procedural, emotional and coping information. Psycho-Oncology 2003; 12: 567-79.

23. Kulik JA, Mahler HI. Social comparison, affiliation, and coping with acute medical threats. In: Buunk BP, Gibbons FX. Health, coping, and well-being. Perspectives from social comparison theory. Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc, Publishers, 1997: 227-62.
24. Kulik JA, Mahler HI, Moore PJ. Social comparison and affiliation under threat: effects on recovery from major surgery. Journal of Personality and Social Psychology 71:5, 967-979.
25. Anonymous. Gender Matters: heart disease in women. www.health.harvard.edu/newsweek/gender_matters_Heart
26. Anonymous. Heart disease in women. www.menopause-online.com/heart.html
27. Stewart AH, Hays RD,Ware JE.The MOS Short-Form General Health Survey: reliability and validity in a patient population. Med Care 1988; 26: 724-35.
28. Wiklund J, Comerfold MB, Dimenas E.The relationship between exercise tolerance and quality of life in angina pectoris. Clin Cardiol 1991; 14: 204-8.
29. Marquis P, Fagol C, Joire JE. Clinical validation of a quality of life questionnaire in angina pectoris patients. Eur Heart J 1995; 16: 1554-60.
30. Dupuy HJ.The psychological general wellbeing index. In:Wenger NK, Matson ME, Furberg CD, Elinson J eds.Assessment of quality of life in clinical trials of cardiovascular therapies. Le Jaq Publishing Inc. 1984:170-83.
31. Testa MA, Simonson DC. Assessment of quality of life outcomes.N Engl J Med 1996; 334: 835-40.

CHAPTER 9

Early discharge (24-36 hours) after primary angioplasty for acute myocardial infarction:

feasibility and Quality of life

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Summary

Objective: The objective of this study is to investigate the feasibility of a short-stay protocol after myocardial infarction (MI) and primary percutaneous transluminal coronary angioplasty (PTCA) in a selected low-risk population and to evaluate Quality of life (QOL).

Methods: patients eligible for the study had acute MI, treated successfully with primary PTCA. Inclusion criteria included single vessel disease, TIMI 3 flow after the procedure combined with a good myocardial blush and absence of heart failure. Patients meeting the inclusion criteria were discharged 24 to 36 hours after admission, and visited the outpatient clinic (where they were seen by a specialised nurse) on the third and fourth day. Consecutively, they were enrolled in the standard rehabilitation program. We evaluated re-infarction, re-admission or visits to the emergency department in the follow-up period of three months. Furthermore, we evaluated quality-of-life scores and secondary prevention goals at the end of the follow-up period.

Results: 46 patients were included in the study. Mean age was 55 yrs (37-73 yrs), 26 patients (57%) were current smokers, 4 patients (9%) had diabetes mellitus and 13 patients (28%) were known with hypertension. There were 12 patients with anterior infarction (26%). Mean CK was 1016 U/L (range 95-4333), CK-MB 118 U/L (range 13-374). Mean left ventricular ejection fraction 1 week after infarction was 59% (range 39%-77%). Patients were discharged after a mean of 29 hours (standard deviation 6.6, range 20-48 hours). During the follow-up period, there were no re-infarctions or re-admissions. After three months 17 of the 26 patients who smoked on admission had not resumed smoking. Mean total cholesterol was 3.9 (on admission 5.4) and mean blood pressure 127/75 (on admission 138/83). On exercise testing, none of the patients showed signs of myocardial ischemia and mean performance was 97% of the expected value. QOL scores on 3 scales (emotional, physical and social well being), taken both 1 week after discharge and after 3 months, were excellent.

Conclusion: After acute MI and primary PTCA, hospital discharge on the day after admission in combination with outpatient visits and a rehabilitation program is feasible and offers a safe and patient-friendly alternative to the usual 3 to 4 days of in hospital care, without any apparent negative effect on quality of life or secondary prevention goals.

Introduction

The last decade's considerable improvement has occurred in the process of care for patients with ST-elevation myocardial infarction (STEMI). Primary percutaneous coronary intervention has become the preferred (first choice) therapy for acute myocardial infarction with ST elevation in most developed countries. It has demonstrated to be more effective than thrombolysis in restoring TIMI 3 flow and thus decreasing mortality and morbidity [1,2,3]. This also has a consequence on the length of stay of patients with ST elevation myocardial infarction. In 1988 A randomised trial of early discharge by Topol [4] showed the safety of discharge on the third day after infarction in selected patients (thrombolysis and angioplasty patients). In recent years there have been suggestions that an even shorter hospital stay may be safe for some STEMI patients. However, a difficulty in introducing early discharge after myocardial infarction is the identification of patients who have uncomplicated disease or are at low risk of death. This assessment is needed very early after admission so that the patients can be given appropriate treatment and health education in the few time that they spend in hospital. Although several scores have been introduced as useful tools for bedside risk stratification for patients with STEMI [5,6,7,8,9,10] they can not be fully be applied to patients treated successfully with angioplasty. Therefore we recently described an easy and practical score for early risk stratification in patients with ST-segment elevation treated with primary angioplasty [11]. This score reliably identifies a large group of patients at very low risk, who may safely be discharged early after primary angioplasty. The score is based on coronary anatomy and flow parameters and can be applied immediately after the percutaneous coronary intervention. As a consequence, we developed a pilot study that evaluates a short-stay protocol after myocardial infarction (MI) and primary percutaneous transluminal coronary angioplasty (PTCA) in a selected low-risk patient population. This protocol included intensive out-patient follow up and cardiac rehabilitation for secondary prevention therapies.

Methods

We evaluated a short stay protocol after myocardial infarction that included an intensive out patient follow up conducted by specially trained cardiac rehabilitation nurses at our hospital.

Patients eligible for the study had acute myocardial infarction treated successfully with primary PTCA. Procedural success was assessed by the physician and defined as an uncomplicated procedure resulting in TIMI 3 flow with a good myocardial blush in the infarct related vessel. In addition, eligible patients had single vessel disease and no signs of heart failure (defined as KILIP class I). These inclusion criteria reflect a Zwolle risk score of 3 or less [11]. This score is a practical and useful index for risk stratification after primary angioplasty for STEMI. Total score can range from 0 to 16, reflecting respectively a low and high risk for 30 day mortality. Patients with a score of 3 or less are at a very low risk for mortality (0.1% at 2 days, 0.2% at 3 to 10 days, and 0.5% at 30 days) after treatment with PTCA for STEMI. An outline of the Zwolle risk score is given in figure 1.

After informed consent was obtained, the patient was seen by the research nurse of the cardiac rehabilitation department. Patients received discharge instructions about recognizing acute cardiac symptoms and appropriate actions to take into response to ensure early evaluation and treatment should symptoms occur. Depending on the time of admittance, patients were discharged from the hospital 24 to 36 hours after admittance. The first and the second day after discharge, patients were seen by the research nurse of the cardiac rehabilitation department. During these out-patient visits, an ECG and laboratory samples were taken. Also a physical examination was performed. If necessary, medication was adjusted. Standard medication included beta-blocker, aspirin, statins, clopidogrel and if appropriate ace inhibition. After 1 week, nuclear ejection fraction measurement was performed. Immediately after discharge, the patients were also enrolled in the rehabilitation program. This rehabilitation program focused on education and actively involves patients in planning for adherence to lifestyle changes and drug therapies that are important for the secondary prevention of cardiovascular diseases. Patients were also given the possibility of supervised exercise training at

our hospital. We evaluated re-infarction, re-admission or visits to the emergency department in the follow-up period of three months. Furthermore, we evaluated quality-of-life scores and secondary prevention goals at the end of the follow-up period. For QOL evaluation, we used the Dutch translation of the "Quality of Life after Myocardial infarction instrument" (QLMI) [12]. This questionnaire consists of 24 questions to measure health-related quality of life for patients after myocardial infarction. QOL is measured on three subdomains, the emotional domain, the physical domain, and the social domain. The sum of the score on the various domains gives the total quality of life score. The higher the score is, the better the QOL. The maximum total score is 168, reflecting the best possible QOL status, the minimum score is 20.

FIGURE 1. Zwolle risk score for STEMI.

	Points
Killip class	
1	0
2	4
3	9
TIMI flow post	
3	0
2	1
0-1	2
Age	
<60	0
> or = 60	2
3 vessel disease	
No	0
Yes	2
Anterior Infarction	
No	0
Yes	1
Ischemia time (> 4 hours)	
No	0
Yes	1
Total score	**16**

Results

From July 2004 to September 2005, 46 patients were included in the study. Mean age was 55 yrs (37-73 yrs), 26 patients (57%) were current smokers, 4 patients (9%) had diabetes mellitus and 13 patients (28%) were known with hypertension. There were 12 patients with anterior infarction (26%). Mean CK was 1016 U/L (range 95-4333), CK-MB 118 U/L (range 13-374). Mean left ventricular ejection fraction (nuclear measurement, using the enigma protocol) was 59% (range 45%-77%). Patients were discharged after a mean of 29 hours (SD 6.6, range 20-48 hours). The demographics are also represented in table 1. During the follow-up period, there were no re-infarctions or re-admissions. 6 patients visited the emergency department within the 3 months after discharge; however, in these patients there were no signs of cardiac ischemia and these patients were discharged from the emergency department.

TABLE 1. Demographics.

Total	N = 46	%
Male	36	78
Female	10	22
Known CAD	3	7
Prior infarction	2	4
DM	4	9
Hypertension	13	28
Anterior infarction	12	26
Stent	43	94

The medication use at discharge and follow up is given in table 2. After three months 17 of the 26 patients who smoked on admission had not resumed smoking (table 3). Mean total cholesterol was 3.9 (on admission 5.24) and mean blood pressure 127/75 (on admission 138/84). On exercise testing, none of the patients showed signs of myocardial ischemia and the mean performance was 97% of the expected value. QOL scores were evaluated in 25 patients. 1 week after discharge, the sum of the QOL score was 146, which reflects the 9th deciles as compared tot

404 Dutch cardiac patients with different types of cardiac incidents (Myocardial infarction, CABG and PTCA). QOL at 3 months was better than baseline for all of the three subscales, with a total score of 161, reflecting an excellent QOL state in this selected patient population.

TABLE 2. Medication.

Medication	Discharge	3 months
Aspirine (%)	100%	97.8%
ACE/I (%)	56.5%	52.2%
Beta Blocker (%)	100%	80.4%
Clopidogrel (%)	100%	50%
Statin (%)	100%	91.3%

TABLE 3. Secundary prevention.

	Admission	3 months
Smoking (%)	56.5%	19.6%
Smoking ever (%)	67.4%	
Cholesterol (mean)	5.4	3.9
Blood Pressure (mean)	138/84	127/75

TABLE 4. Quality of life scores, hihger scores indicate better QOL.

Domain	*1 week*	*3 months*
Physical	42	48
Social	42	47
Emotional	62	66
Total*	**146****	**161*****

** These scores reflect excellent QOL state compared to 404 Dutch cardiac patients with different types of cardiac incidents*

*** 9th percentile*

**** 10th percentile*

Discussion

Despite extensive research there is still a lot of variation between countries in length of stay patterns in patients treated for acute myocardial infarction [13]. This supports the statement that length of stay after an acute myocardial infarction is, as for many medical conditions, more a consequence of historical precedent than medical evidence. The consequence of this is care without any incremental medical benefit but considerable expense. According to the guidelines of the ACC/AHA, STEMI patients originally admitted to the coronary car unit who demonstrate 12 to 24 hours of clinical stability (absence of recurrent ischemia, heart failure or hemodynamically compromising dysrhythmias), should be transferred to the step-down unit were mostly there is no possibility for rhythm monitoring. Since compromising dysrhythmias are most concerning for the physician, these step down units are not necessarily safe places to stay.

A difficulty for showing that an early discharge strategy has safety equal to a routine hospital discharge strategy is the very large sample size required. This is presumably why there are only a few relatively small randomized trials concerning early discharge strategy. In the PAMI 2 trial [14], 471 low risk patients (<50% of screened patients; age < 70 years, no persistent arrhythmia, no triple vessel disease, ejection fraction > 45%, and successful reperfusion) were randomly assigned to early discharge or conventional care. Early discharge was applied to 60% of the randomly assigned patients because of physician preference or patient refusal. Safety of early discharge was demonstrated by the very low 6-month mortality rate. Further review of the literature [15,16] shows that there is no evidence for improved outcomes with lengths of stay of more than 72 hours in low risk patients after myocardial infarction. In addition, patients with non ST-elevation myocardial infarction (NSTEMI) without complications can even be discharged on the day after coronary intervention [17.] Since the mechanism underlying both STEMI an NSTEMI is presumably the same, it is likely that for selected low-risk STEMI patients, an equal discharge protocol as for NSTEMI patients is safe.

As described earlier, another problem with early discharge is to determine which STEMI patient is sufficiently low risk to go home. As stated before, there have been

introduced several bedside scores for risk stratification of patients with STEMI However, these risk scores have been developed in patients treated with medical therapy, with or without thrombolysis, without taking into account the procedural variables that significantly affect the outcome of these patients. In our study, we used the Zwolle risk score. This score is only based on coronary anatomy and flow parameters and can be applied immediately after the PTCA procedure and therefore is suitable for early identification of a patient that is a possible candidate for early discharge.

As a consequence of earlier discharge, the demand for an intensive cardiac rehabilitation programs increases. In our study, patient counselling by the cardiac rehabilitation department started the day after discharge and continues at intensive follow up visits. Patient counselling focussed on information supply, compliance with taking medication, and smoking cessation. The cardiac rehabilitation program provided counselling on risk factor modification in the secondary prevention of ischemic heart disease, such as smoking, blood pressure, lipid management, physical activity, weight and DM management. In addition patients were included in an exercise program that consist of weekly ECG-monitored exercise sessions for 8 to 12 weeks. The goals of these sessions were to develop and teach an individualized exercise prescription that is both safe and effective, to initiate interventions aimed at reducing coronary risk factors, and to identify and manage the psychosocial problems that commonly affect the cardiac patient. If necessary, additional individual psychosocial intervention was performed.

The demand for these services should continue to increase as hospital stays become shortened, the population ages, and more advanced cardiac interventions become routinely available.

In addition, it is known that even a short course of cardiac rehabilitation program is cost effective in improving long-term quality of life in patients with recent myocardial infarction or percutaneous coronary intervention [18].

As coronary disease in its various forms of presentation is associated with a reduction in the patients' own perception of their QOL, QOL is an important measure of effectiveness of treatment. In our study we used the QLMI . The QLMI

was developed and tested to evaluate a comprehensive cardiac rehabilitation programme for patients after myocardial infarction. It comprises 24 items that were selected after being rated as important by patients and clinicians. Two questions from QLMI (illustrating its disease specific nature) are: "In the past two weeks, how much time did you feel very confident that could deal with your heart problem?" and "During the last two weeks how much have you been limited in doing sports or exercise as a result of your heart problem?". These represent three subscales with scores ranging from 0-7, where higher scores represent higher functioning. In our study we found excellent QOL scores as compared tot 404 Dutch patients in who the same questionnaire was taken after myocardial infarction, CABG or PTCA. This might be explained by the young age and limited infarction size with good left ventricular rest function in our population. This contributes to a good prognosis, especially with the right secondary prevention, in these patients with one vessel disease.

Conclusion

We conclude that by using the proposed prognostic index, patients may be stratified into an appropriate low risk group soon after admission to a coronary care unit. In these patients hospital discharge on the day after admission in combination with outpatient visits and a revalidation programme is feasible and offers a safe and patient-friendly alternative to the usual 3 to 4 days of in hospital care. This strategy at least doesn’t have any apparent negative effect on quality of life or secondary prevention goals and presumably has a positive effect. For future purposes we will continue “early discharge” in selected patients at our hospital and we will investigate possible inclusions of other hospitals.

References

1. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med*. 1993;328:680–684.
2. Grines CL, Browne KF, Marco J. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med*. 1993;328:673–679.
3. Weaver WD, Simes RJ, Betriu A. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA*. 1997;278:2093–2098.
4. Topol EJ, Burek K, O'Neil WW et al. A randomized controlled trial of hospital discharge three days after myocardial infarction in the era of reperfusion. *N Engl J Med.* 1988;318:1083-8.
5. Morrow DA, Antman EM, Charlesworth A, et al. TIMI Risk Score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation. *Circulation.* 2000; 102: 2031–2037.
6. Lee KL, Woodlief LH, Topol E, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. *Circulation.* 1995; 91: 1659–1668.
7. Hillis LD, Forman S, Braunwald E. Risk stratification before thrombolyitic therapy in patients with acute myocardial infarction: the Thrombolysis in Myocardial Infarction (TIMI) Phase II co-investigators. *J Am Coll Cardiol.* 1990; 16: 313–315.
8. Rouleau JL, Talajic M, Sussex B, et al. Myocardial infarction patients in the 1990s: their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) Study. *J Am Coll Cardiol.* 1996; 27: 1119–1127.
9. Normand ST, Glickman ME, Sharma RG, et al. Using admission characteristics to predict short-term mortality from myocardial infarction in

elderly patients: results from the Cooperative Cardiovascular Project. *JAMA*. 1996; 275: 1322–1328.

10. Jacobs DR Jr, Kroenke C, Crow R, et al. PREDICT: a simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina: the Minnesota Heart Survey. *Circulation.* 1999; 100: 599–607.
11. De Luca G, Suryapranata H, van't Hof AW, de Boer MJ, Hoorntje JC, Dambrink JH, Gosselink AT, Ottervanger JP, Zijlstra F. Prognostic assessment of patients with acute myocardial infarction treated with primary angioplasty: implications for early discharge. *Circulation*. 2004 Jun 8;109(22):2737-43.
12. Hillers TK, Guyatt GH, Oldridge N, Crowe J, Willan A, Griffith L, Feeny D. Quality of life after myocardial infarction. *J Clin Epidemiol.* 1994 Nov;47(11):1287-96.
13. Kaul P, Newby LK, Fu Y, Mark DB, Califf RM, Topol EJ, Aylward P, Granger CB, Van de Werf F, Armstrong PW. International differences in evolution of early discharge after acute myocardial infarction. *Lancet*. 2004 Feb 14;363(9408):511-7.
14. Grines CL, Marsalese DL, Brodie B, et al. Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction: PAMI-II Investigators, Primary Angioplasty in Myocardial Infarction. *J Am Coll Cardiol*. 1998; 31: 967–972.
15. Kandzari DE, Tcheng JE, Cohen DJ, et al. CADILLAC Investigators: feasibility and implications of an early discharge strategy after percutaneous intervention with abciximab in acute myocardial infarction (the CADILLAC Trial). Am J Cardiol. 2003; 92: 779–784.
16. ACC/AHA guidelines.
17. Wiviott SD, Braunwald E. Unstable angina and non-ST-segment elevation myocardial infarction: part II. Coronary revascularization, hospital discharge, and post-hospital care. *Am Fam Physician*. 2004 Aug 1;70(3):535-8. Review.

18. Yu CM, Lau CP, Chau J, McGhee S, Kong SL, Cheung BM, Li LS. A short course of cardiac rehabilitation program is highly cost effective in improving long-term quality of life in patients with recent myocardial infarction or percutaneous coronary intervention. *Arch Phys Med Rehabil*. 2004 Dec;85(12):1915-22.

CHAPTER 10

Summery and conclusions

In chapter 2, the beneficial effects of nitrates were discussed. We concluded that, based on previous studies with nitrates, nitrates can effectively control symptoms of angina pectoris and can be safely used for long term treatment. IR-SR isosorbide mononitrate has a rapid onset of action, is clinically efficient, and might provide better quality of life than the conventional ISMN/ISDN. However, tolerance with continued use of the formulation has not yet been reported and long-term efficacy data both of isosorbide mononitrate IR-SR and conventional ISMN/ISDN are limited so far. Therefore, we performed relatively large studies in patients with angina pectoris, the DUtch Mononitrate Quality of Life (DUMQOL) and International Quality Of Life assessment of patients with Angina pectoris on Nitrate therapy (IQOLAN) study. These studies are discussed in chapter 3 to 6.

The purpose of chapter 3 was to compare the effects of a multiple and once daily formulation of nitrate therapy on the quality of life and to identify the influence of certain patient characteristics on the quality of life. In this retrospective study from the Dutch Mononitrate Quality of Life (DUMQOL) Study Group, the effects of multiple-dose (2 to 3 times daily 10 to 20 mg) and once-daily nitrate therapy (sustained-release isosorbide mononitrate 50 mg) on the quality of life were evaluated in 1350 patients with stable angina pectoris. Patients were requested to complete a self-administered quality of life questionnaire after three months and after 6 months of treatment. The physician reported the actual patient characteristics. A multiple regression analysis was performed to assess which patient characteristics significantly influenced the overall quality of life. The results of this analysis showed that age did not influence the better benefit. Neither did gender, rhythmic disturbances, peripheral artery disease, or the concomitant use of calcium channel blockers or beta-blockers. New York Heart Association angina classification was an independent variable: patients with a class I or II benefited less than did patients with class III or IV (P=0.02). Obese patients as well as hypertensive patients benefited less (P=0.04 and 0.02), and smokers tended to benefit less (P=0.08). In contrast, cholesterolemia and diabetes mellitus improved the beneficial effect of nitrates on quality of life (P= 0.03 and 0.05). We concluded

that patients with severe angina pectoris benefit better from nitrate therapy than do patients with New York Heart Association class I-II. Also, patients with coronary artery disease and concomitant diabetes mellitus or cholesterolemia may better benefit from nitric oxide-donor therapy than patients without such concomitant conditions do. In contrast, we concluded that patients with concomitant obesitas, hypertension, or smokers may benefit less.

In chapter 4 we assessed whether the DUMQOL data could be generalized across nations and times. In addition, we assessed the effects on patients' satisfaction with disease state and on heart failure class. Therefore, patients from hospitals in Germany, Portugal, and the Czech Republic were treated for 3 months with 2-4 times daily 10-20 mg isosorbide mononitrate/dinitrate and, subsequently, with once daily 50-120 mg isosorbide mononitrate/dinitrate for three more months. A QOL questionnaire, based on Wiklund's exercise tolerance index, Stewart's Short Form Questionnaire, and Dupuy's psychological well-being index, was completed after 3 and 6 month treatment. In addition, patients' self-rated satisfaction with the current disease state, their treatment preference, and their New York Heart Association (NYHA) anginal and heart failure class were assessed twice. Of the 1045 patients included, 1010 (97%) completed the study. After three months of once-daily nitrate therapy the QOL-scores showed a significantly better improvement in all of the domains addressed, than did multiple daily dose treatment ($p<0.0001$). In addition, anginal and heart failure classes improved significantly better ($p<0.0001$). So did patient compliance as estimated by the percentages of patients forgetting to take their medication (59.6 versus 42.2%, $p<0.0001$), patients' self-rated satisfaction (30.5 versus 10.1% , $p<0.0001$), and patients' preference for the once-daily nitrate regimen (77.4 versus 3.6 %, $p<0.0001$). We concluded that once-daily nitrate treatment provides better NYHA anginal class, patient compliance, and QOL than does multiple daily dose treatment. These better benefits can be observed across nations and times. In addition to QOL indexes, patients' self-rated satisfaction with disease state improved, and so did NYHA heart failure class.

As stated in chapter 3, we found in a retrospective study from the Dutch Mononitrate Quality of Life (DUMQOL) Study Group that anginal patients with concomitant diabetes or hypercholesterolemia derived more benefit from changing over to a once daily nitrate treatment regimen, than did anginal patients without. In Chapter 5 we assessed this issue prospectively. In an open-label study, patients with stable angina pectoris (SAP) from facilities in Germany, Portugal, and the Czech Republic were treated for 3 months with multiple daily dosages and subsequently for 3 more months with once daily isosorbide mono-/dinitrate (ISMN/DN). After the first and second 3 month period they were assessed by a validated QOL-battery including the domains, mobility, side-effect, life-satisfaction, anginal-pain, and psychological-distress. In the 1045 patients who participated in the study mean summary domain-scores varied from 5-16 points, score improvements from 1.6 to 4.3 points. In the patients with concomitant hypertension and the smokers domain-scores improved less than they did in the patients without, with differences in domain-score improvements up to 1.0 points ($p<0.001$), which is substantial considering the range of improvement being between 1.6 and 4.3 points. In the patients with diabetes mellitus or hypercholesterolemia a reversed pattern was observed with differences in domain-score improvements up to 0.4 points ($p<0.05$).
We concluded that anginal patients with diabetes or hypercholesterolemia derived more benefit from an asymmetric regimen of isosorbide mono/dinitrate than did patients without. Anginal patients with hypertension or smokers did less so. The results are in line with the findings of chapter 3. We suggest that differences in endothelial function may be involved.

From the previous chapters we concluded that asymmetric nitrate dosages provided better therapeutic efficacy in patients with stable angina pectoris, than did multiple daily dosages. Anginal patients with cardiovascular comorbidities may particularly benefit from nitric-oxide- (NO) donor therapy due to the underlying impairment of endothelium-dependent NO-activity. The objective of chapter 6 was to compare QOL and exercise capacity before and after replacement of multiple

daily with once-daily nitrate therapy and to investigate the influence of cardiovascular co morbidities on the observed changes in a larger, international study group. Out-patients with stable angina pectoris and at least three months pre-treatment with 3 times daily 20-40 mg of isosorbide mono-or dinitrate were switched to the equivalent single daily dose of the compound early in the morning. We assessed predefined QOL-indices, painfree walking distances, New York Heart Association (NYHA) anginal class, and the influence of cardiovascular risk factors and comorbidities. Standard multi- and univariate methods were applied. Of 2675 patients included, 2574 (96.2%) completed the study. After three months once-daily nitrate mean QOL-scores improved from 10 to 19% ($p<0.0001$ for all of the QOL-domains). The percentage of patients in NYHA anginal class I increased by 23.4% ($p<0.0001$), while exercise capacity increased from a median painfree walking distance of 300 to 500 m ($p<0.001$). In patients with concomitant hypertension or hypercholesterolemia anginal class improved better (27.4 and 24.6 %, both $p<0.001$). Young age, advanced NYHA anginal class, hypercholesterolemia and coronary artery disease (CAD) in the family were important independent determinants of the improved QOL.
We concluded that replacement of multiple-dose with once-daily nitrate treatment resulted in an improved QOL, anginal NYHA class, and exercise capacity. Patients with concomitant hypertension or hypercholesterolemia particularly benefited from the asymmetric dosage regimen. However, the results of the multivariate analysis are not in line with the findings in chapter 3 and 5. Further research is needed to asses this discrepancy.

Chapter 7 focussed on QOL and social comparison in patients with stable chronic congestive heart failure. Independent determinants of QOL in these patients have been recognized and include factors like severity of medical condition, comorbidity, and concomitant medication. Psychosocial factors, like “ability to cope with the unpleasantness of the medical condition”, “want of information”, and “social identification” have important influence on self-perceived well-being, but their influence on health-related QOL domains and self-perceived QOL in patients with

heart failure have not been systematically studied. In this chapter we assessed correlation between such psychosocial factors and QOL in patients with heart failure. Therefore, patients from the outpatient heart failure clinic of the Martini Hospital , a 1000-bed community hospital in the city of Groningen, Netherlands, were included if their ejection fractions were <40% and their medical diagnosis according to their cardiologists was stable chronic congestive heart failure. The following QOL-estimators were applied: Pearlin's Mastery Scale, Stewart's Short Form 36 Quality of Life Questionnaire, Dupuy's Index of Well-being, Cantrill's Self-perceived Quality of Life Scale, Mester's Want of Information Scale. Internal consistency of the multi-item scales were estimated by Cronbach's alphas. Linear and multiple linear regression analyses were performed of the data. In total, sixty patients were enrolled, 41 males and 19 females, average age 68 years (range 51-84 years). "Ability to cope with the unpleasantness of the medical condition" was not only an independent determinant of self-perceived and health-related QOL(both $p<0.001$), but also of each domain of health related QOL separately ($p<0.001$ for each domain). Lack of "adequate medical information" and "negative social identification" (the identification with counterparts who are doing worse) were negative predictors of "ability to cope" ($p<0.01$ and <0.001 resp). "Negative social identification" also was an independent determinant of self-perceived QOL, both unadjusted and after adjustment for "ability to cope" and "adequate medical information".

Relevant recommendations from this chapter to be considered by cardiologists during everyday office-hours could included: 1. Patients who express having difficulties to cope with the unpleasant aspects of their underlying heart condition, have low health-related QOL as well as low self-perceived QOL. 2. Adequate medical information given is a significant contributor to both better "ability to cope" and better self-perceived QOL. 3. Avoiding to identify oneself with counterparts who are doing worse, and, instead, starting to identify oneself with counterparts who are doing better, are significant contributors to both better "ability to cope" and better self-perceived QOL.

From the previous chapter it was concluded that providing adequate medical information and avoiding patients to identify themselves with fellow-sufferers were significant contributors to better quality of life in patients with stable chronic congestive heart failure. In previous studies, gender and level of psychic tension were significant predictors of QOL in cardiac patients. We don't know (1) whether we can improve QOL by increasing patients' ability to cope with the unpleasant aspects of the underlying condition, (2) whether gender and level of psychic tension interact or act independently. In chapter 8 we assessed both questions. For that purpose, 38 patients on the waiting list for coronary angiography were assessed with validated test batteries. To increase the patients' ability to cope, they were randomly assigned to read either (1) the comments of a patient previously successfully treated or (2) general information. The former information, unlike the latter, was assumed to improve coping ability and, thus, provide better QOL. Homogeneity of the patient group was estimated by Cronbach's alphas. For analysis linear regression and general factorial analyses of variance were applied. We found that the group was psychologically homogeneous as indicated by Cronbach's alphas being, generally, over 75%. There was a significant or close to significant association of presence of coping information with a better mobility, social performance and self-perceived QOL ($p<0.05$, $p<0.06$, and $p = 0.10$).High levels of psychic tension were associated with low self-perceived QOL and low psychological scores (both $p<0.02$). Female gender was associated with lower mobility, lower psychological scores and lower overall QOL ($p<0.05$, $p<0.02$ and $p<0.05$). A significant or close to significant interaction was observed between gender and psychic tension as combined determinants of self-perceived QOL, mobility index, and overall QOL index ($p<0.03$, $p<0.09$, and $p<0.05$). Separate assessments of these determinants showed that the female gender was the strongest determinant of low QOL. We concluded that in patients on the waiting list for coronary angiography, an increased ability to cope with the unpleasant aspects of a possible underlying heart condition improves QOL. In addition, female gender and a high level of psychic tension places patients at risk of low QOL.

Chapter 9 refers to a feasibility study concerning early discharge and QOL evaluation after acute myocardial infarction. The objective of this study was to investigate the feasibility of a short-stay protocol after myocardial infarction (MI) and primary PTCA in a selected low-risk population and to evaluate QOL. Patients eligible for the study had acute MI, treated successfully with primary PTCA. Inclusion criteria included single vessel disease, TIMI 3 flow after the procedure combined with a good myocardial blush and absence of heart failure. Patients meeting the inclusion criteria were discharged 24 to 36 hours after admission, and visited the outpatient clinic (where they were seen by a specialised nurse) on the third and fourth day. Consecutively, they were enrolled in the standard revalidation programme. We evaluated re-infarction, re-admission or visits to the emergency department in the follow-up period of three months. Furthermore, we evaluated quality-of-life scores and secondary prevention goals at the end of the follow-up period. In total, 46 patients were included in the study. Mean age was 55 yrs (37-73 yrs), 26 patients (57%) were current smokers, 4 patients (9%) had diabetes mellitus and 13 patients (28%) were known with hypertension. There were 12 patients with anterior infarction (26%). Mean CK was 1016 U/L (range 95-4333), CK-MB 118 U/L (range 13-374). Mean left ventricular ejection fraction 1 week after infarction was 59% (range 39%-77%). Patients were discharged after a mean of 29 hours (standard deviation 6.6, range 20-48 hours). During the follow-up period, there were no re-infarctions or re-admissions. After three months 17 of the 26 patients who smoked on admission had not resumed smoking. Mean total cholesterol was 3.9 (on admission 5.4) and mean blood pressure 127/75 (on admission 138/83). On exercise testing, none of the patients showed signs of myocardial ischemia and mean performance was 97% of the expected value. Quality-of-life scores on 3 scales (emotional, physical and social wellbeing), taken both 1 week after discharge and after 3 months, were excellent. We concluded that after acute MI and primary PTCA, hospital discharge on the day after admission in combination with outpatient visits and a revalidation programme is feasible and offers a safe and patient-friendly alternative to the usual 3 to 4 days of in hospital

care, without any apparent negative effect on quality of life or secondary prevention goals.

CHAPTER 11

Samenvatting in het Nederlands

Belangrijke doelstellingen bij de behandeling van coronaire hartziekten zijn niet alleen de primaire en secundaire preventie van een myocardinfarct, maar ook afname van pijn en de toename van inspanningstolerantie van de patiënt: om die toename te bereiken kunnen bij deze patiëntengroep organische nitraten worden gebruikt. Een prototype daarvan is nitroglycerine. Hoewel vele andere vormen van anti-ischemische therapie, zoals beta-blokkerende middelen en calcium-antagonisten, hun waarde bewezen hebben, vormen nitraten de hoeksteen van anti-angineuze therapie. De effectiviteit van deze middelen staat al meer dan 100 jaar vast. Alfred Nobel (1833-1896), een Zweedse chemicus, was de eigenaar van het patent op de productie van nitroglycerine, een stof die aanvankelijk als explosief werd gebruikt. Hij beschreef de stof als volgt: “Het is een reukloze, bruinige vloeibare substantie die geproduceerd wordt door de nitrilatie van glycerine. Het is stabiel bij kamertemperatuur, maar het kan exploderen in het geval van push or hit.” De eerste experimenten met nitroglycerine waren nogal traumatiserend. In 1884 explodeerde een van de fabrieken van Alfred Nobel. Daarbij kwam zijn broer om het leven. In die dagen werden ook de eerste symptomen van nitraattolerantie gerapporteerd bij arbeiders in de nitroglycerine fabrieken. Zij hadden typische hoofdpijnklachten, vooral op maandag, wanneer ze na een vrij weekend weer aan het werk gingen. Alfred Nobel doneerde zijn gehele vermogen aan de “Nobel Foundation”, die sinds 1901 elk jaar de Nobelprijzen ter beschikking stelt aan de wetenschap. De eerste die de gunstige effecten van nitroglycerine bij de mens beschreef, was Lauder Brunton in 1867. Hij gebruikte destijds een nitraatzetmeel-verbinding om angineuze klachten te behandelen. In de laatste decennia is de kennis over de functie en de werking van nitroglycerine drastisch toegenomen. Stikstofoxide (NO) blijkt het actieve molecuul te zijn dat verantwoordelijk is voor vasodilatatie. Dit oxide wordt ook door het endotheel zelf geproduceerd (endothelian derived relaxation factor (EDRF) = nitric oxide (NO).

In **hoofdstuk 2** van dit proefschrift werden de effecten van nitraten besproken. Hierbij werd geconcludeerd dat, gebaseerd op eerdere studies, nitraten effectief zijn in het verlichten van symptomen van angina pectoris en dat ze veilig gebruikt

kunnen worden voor een chronische behandeling. Isosorbidemononitraat eenmaal daags met een 30% snelle afgifte gecombineerd met een 70% langzame afgifte blijkt klinisch efficiënt te zijn en kan wellicht leiden tot een betere kwaliteit van leven bij mensen met angina pectoris dan de meermaaldaagse toedieningsvorm van nitraten. Daarnaast is er nog weinig bekend over de lange termijn effecten van zowel de nitraten met eenmaaldaagse gereguleerde afgifte als de conventionele nitraten met meermaal daagse toediening. Derhalve zijn er twee relatief grote studies opgezet bij patiënten met stabiele angina pectoris, de Dutch Mononitrate Quality of Life (DUMQOL) en de International Quality Of Life assessment in patients with Angina pectoris on Nitrate therapy (IQOLAN) studie. De resultaten van deze studies werden besproken in de hoofdstukken 3 tot en met 6.

Het doel van **hoofdstuk 3** was het vergelijken van de effecten van meermaal daagse toediening en eenmaal daagse dosering op de kwaliteit van leven en het identificeren van bepaalde patiëntkarakteristieken die hier van invloed op zijn. Hiertoe werden de effecten van meermaaldaagse toediening (2 tot 3 maal daags 10-20 mg) en eenmaaldaagse toediening (sustained release isosorbidemononitraat 50 mg) op de kwaliteit van leven bij 1350 patiënten met stabiele angina pectoris bekeken. Patiënten werden gedurende drie maanden behandeld met de meermaaldaagse vorm van nitraat. Vervolgens werden patiënten drie maanden behandeld met een eenmaaldaagse vorm. Patiënten werd gevraagd een kwaliteit van leven vragenlijst na drie en na zes maanden in te vullen. De vragenlijst was gebaseerd op de “Wiklund`s exercise tolerance index”, “Stewart`s Short Form Questionnaire” en “Dupuy`s psychological well-being index”. Daarnaast werden de voorkeur van behandeling van de patiënt, de NYHA angina pectoris klasse en de NYHA hartfalen klasse geëvalueerd. De actuele patiëntkarakteristieken werden door de behandelend cardioloog verzameld. Er werd een multipele regressie-analyse toegepast om te evalueren welke patiëntkarakteristieken een significante invloed hadden op de kwaliteit van leven. Leeftijd, geslacht, voorkomen van ritmestoornissen, perifeer vaatlijden en co-medicatie (bètablokkerende middelen of calciumantagonisten) hadden geen significante invloed, maar een aantal andere

factoren had dat wel. Zo bleek de NYHA klasse een onafhankelijke variabele te zijn: patiënten met NYHA klasse III of IV bleken extra baat te hebben bij een eenmaaldaagse dosering en dus een grotere verbetering van de kwaliteit van leven te krijgen met monotherapie dan patiënten met NYHA klasse I of II (p=0.02). Zowel obesitas (p=0.02), hypertensie (p=0.04) als roken (p=0.08) gaven een significante verslechtering van de kwaliteit van leven. Dit in tegenstelling tot mensen met hypercholesterolaemie en diabetes mellitus (p=0.04 en 0.02), deze patiënten bleken juist weer meer baat te hebben bij een eenmaaldaagse nitraattherapie. We concludeerden dan ook dat patiënten met ernstige angina pectoris meer baat hebben bij eenmaaldaagse nitraattherapie dan patiënten met angina pectoris NYHA klasse I of II. Dit geld tevens voor patiënten met coronaire hartziekten en bijkomende diabetes mellitus of hypercholesterolaemie. Dit in tegenstelling tot patiënten met obesitas, hypertensie en roken als risicofactor: deze patiënten profiteerden minder van de wisseling van meermaaldaagse naar eenmaaldaagse nitraattherapie.

In **hoofdstuk 4** evalueerden we of de data van het DUMQOL onderzoek reproduceerbaar waren in andere Europese landen. Hiertoe werden patiënten met stabiele angineuze klachten uit ziekenhuizen in Duitsland, Portugal en de Tsjechische republiek gedurende drie maanden behandeld met een meermaaldaagse nitraattherapie. Vervolgens werd gedurende drie maanden overgegaan op de behandeling van de angineuze klachten met een eenmaal daagse dosering van nitraat met gereguleerde afgifte. Een kwaliteit van leven vragenlijst werd afgenomen na drie en zes maanden. Van de 1045 geïncludeerde patiënten waren er 1010 (97%) die de follow-up voltooiden. Na drie maanden behandeling met een eenmaaldaagse nitraattherapie was er een significante verbetering van kwaliteit van leven zichtbaar (p<0.0001). Tevens was er een significante verbetering van zowel de NYHA angina pectoris als de NYHA hartfalen klasse (p<0.0001). De compliantie met betrekking tot het nemen van de medicatie nam toe, daar de patiënten aangaven minder vaak hun medicatie te vergeten (59.6% versus 42.2%). Daarnaast bleek het algeheel welbevinden significant beter

te zijn bij eenmaaldaagse nitraattherapie. Patiënten gaven hier dan ook de voorkeur aan (77.4% voorkeur aan eenmaaldaagse dosering, 3.6% voorkeur aan meermaal daagse dosering). We concludeerden dat eenmaaldaagse nitraattherapie leidt tot een verbetering van de NYHA angina pectoris klasse, een verbetering van de patiënt-compliantie en een verbetering van de kwaliteit van leven. Deze bevindingen zijn vergelijkbaar tussen verschillende Europese bevolkingsgroepen. Daarnaast verbeterden het algemeen welbevinden en de NYHA hartfalen klasse bij het overgaan van meermaaldaagse op eenmaaldaagse toediening van nitraten.

Zoals vermeld in hoofdstuk 3, liet de analyse van de DUMQOL data zien dat patiënten met stabiele angineuze klachten en diabetes mellitus of hypercholesterolaemie meer baat hadden bij de omzetting van meermaaldaagse nitraattherapie naar eenmaaldaagse nitraattherapie dan patiënten zonder diabetes mellitus of hypercholesterolaemie. In **hoofdstuk 5** werd dit prospectief onderzocht. In een open-label onderzoek werden patiënten met stabiele angina pectoris uit Duitsland, Portugal en Tsjechië gedurende drie maanden behandeld met meermaaldaagse doseringen nitraat. Vervolgens werd overgegaan op een eenmaaldaagse behandeling met gereguleerde afgifte. Na de eerste en tweede periode van drie maanden werd kwaliteit van leven gemeten. De kwaliteit van leven werd gemeten aan de hand van verschillende domeinen. Deze domeinen waren: mobiliteit, bijwerkingen, algeheel welbevinden, angina pectoris en psychische druk. De gemiddelde scores op ieder domein varieerden van 4 tot 16 punten. De scores namen toe van 1.6 tot 4.3 punten. Bij patiënten met hypertensie en bij rokers verbeterde de score significant minder dan bij patiënten zonder hypertensie of niet-rokers. Het verschil bedroeg maximaal 1.0 punt ($p<0.001$), hetgeen aanzienlijk is daar de range van verbetering zich tussen de 1.6 en 4.3 punten bevond. Dit verschil was vooral te zien bij patiënten uit Duitsland. Bij patiënten met diabetes mellitus of hypercholesterolaemie werd een tegenovergesteld patroon gezien. De verbetering van kwaliteit van leven met betrekking tot de verschillende domeinen bedroeg tot 0.4 ($p<0.05$) ten opzichte van patiënten zonder diabetes mellitus of

hypercholesterolaemie. We concludeerden dat patiënten met diabetes mellitus of hypercholesterolaemie meer baat hadden bij het overgaan van meermaaldaagse op eenmaaldaagse nitraattherapie. Voor patiënten met hypertensie en rokers gold het omgekeerde. De bevindingen kwamen overeen met de bevindingen in hoofdstuk 3. Wellicht dat verschillen in endotheelfunctie hierbij betrokken zijn.

Uit de voorgaande hoofdstukken concludeerden we dat eenmaaldaagse nitraattherapie een beter therapeutisch effect had bij patiënten met stabiele angineuze klachten dan meermaaldaagse nitraattherapie. Patiënten met angineuze klachten en co-morbiditeit hadden wellicht extra baat bij een eenmaaldaagse nitraattherapie door onderliggende disfunctie van het endotheel. Het doel van **hoofdstuk 6** was om de kwaliteit van leven en inspanningstolerantie voor en na de vervanging van de meermaaldaagse door de eenmaaldaagse vorm van nitraat te vergelijken en hierbij tevens te kijken naar de invloeden van de cardiovasculaire co-morbiditeit op de waargenomen veranderingen in kwaliteit van leven. Dit alles in een grotere en internationale patiënten populatie. De landen die meededen aan het onderzoek zijn: Duitsland, Portugal, Tsjechië, Letland, Rusland en China. Poliklinische patiënten met stabiele angina pectoris die tenminste drie maanden behandeld waren met een meermaaldaagse dosering nitraat, werden omgezet naar een eenmaaldaagse dosering nitraat in de ochtend. Van te voren gedefinieerde kwaliteit van leven indices als pijnvrije loopafstand, angina pectoris NYHA klasse en de invloed van cardiovasculaire risicofactoren en co-morbiditeit werden geëvalueerd. Standaard uni-variate en multi-variate analyses werden toegepast. Van de 2675 patiënten die werden geïncludeerd waren er 2574 (96.2%) die de complete follow-up doorliepen. Na drie maanden behandeling met eenmaaldaagse nitraattherapie verbeterden de kwaliteit van leven scores 10-19% ($p<0.001$ voor alle kwaliteit van leven domeinen). Het percentage patiënten met NYHA angina pectoris klasse I nam toe met 23.4% ($p<0.001$), de pijnvrije inspanningstolerantie nam toe van 300 naar 500 meter ($p<0.001$). Bij patiënten met hypertensie en hypercholesterolaemie was er sprake van een significant grotere verbetering (resp. 27.4 en 24.6% meer patiënten in NYHA klasse I, $p<0.001$).

Zowel een jongere leeftijd, hogere NYHA klasse, hypercholesterolaemie en een positieve familie-anamnese voor hart- en vaatziekten waren onafhankelijke determinanten van een betere kwaliteit van leven. We concludeerden dat het vervangen van meermaaldaagse behandeling met nitraten door een eenmaal daagse behandeling resulteerde in een verbetering van de kwaliteit van leven, de NYHA klasse en de inspanningstolerantie. Uit dit onderzoek bleek dat patiënten met hypercholesterolaemie of hypertensie extra baat hebben bij een eenmaal daagse behandeling. Dit is echter niet geheel in overeenstemming met de bevindingen in de hoofdstukken 3 en 5. De multivariate analyse van de DUMQOL 50, zoals beschreven in hoofdstuk 3, is tamelijk grof omdat scores van verschillende domeinen zijn opgeteld. Bij patiënten met adipositas bijvoorbeeld zal het mobiliteitsdomein grotere problemen geven dan bij slanke mensen. Echter de bevindingen van de IQOLAN met data uit Duitsland, Portugal en Tsjechië laten dezelfde resultaten zien als bij de DUMQOL multivariate analyse. Een verklaring voor het niet bevestigen van deze data in het uiteindelijke IQOLAN onderzoek, zoals beschreven in dit hoofdstuk, is mogelijk het genetische verschil tussen de bevolkingsgroepen in de verschillende landen. Daarnaast bestaat er ook een groot verschil in medisch handelen tussen de cardiologen in de verschillende landen. Verder spelen cultuurgebonden factoren mogelijk een rol. Niettemin leverden de huidige analyses van de resultaten interessante conclusies op. Patiënten met een hogere NYHA klasse of hypercholesterolaemie lijken extra gebaat te zijn bij een eenmaal daagse nitraattherapie. Dat overige patiëntengroepen dit extra voordeel mogelijk missen, is op zichzelf geen reden om aan hen de optimale nitraattherapie te ontzeggen.

In **hoofdstuk 7** werd gekeken naar de kwaliteit van leven en sociale vergelijking bij patiënten met stabiel chronisch hartfalen. Er werd onderzocht hoe deze patiënten hun kwaliteit van leven beoordeelden en door welke psychologische factoren de kwaliteit van leven beïnvloed werd. De psychologische factoren die geëvalueerd werden zijn “het ervaren van controle over de medische conditie”, “behoefte aan objectieve medische informatie” en “sociale vergelijking”. Hiertoe werden

opeenvolgende patiënten met stabiel chronisch hartfalen op de polikliniek van het Martini Ziekenhuis te Groningen geïncludeerd. De volgende kwaliteit van leven instrumenten werden gebruikt: Pearlin`s Mastery Scale, Stewart`s Short Form 36 Quality of Life questionnaire, Dupuy`s Index of Well-being, Cantrill`s Self perceived QOL Scale en de Mester`s want of information scale. Interne consistentie van de multi-item domeinen werd bepaald middels Cronbach`s alphas. Lineaire en multipele lineaire regressie analyses werden verricht. In totaal werden 60 patiënten geïncludeerd. De “ervaren controle op de medische conditie“ was een sterke onafhankelijke voorspeller voor de kwaliteit van leven. Gebrek aan “objectieve medische informatie” en “negatieve sociale vergelijking” (de identificatie met lotgenoten die er slechter aan toe zijn) waren negatieve voorspellers voor “de ervaren controle”. “Negatieve sociale vergelijking” was ook een onafhankelijke voorspeller voor kwaliteit van leven. Belangrijke conclusies uit dit onderzoek waren: 1. Patiënten die aangeven weinig controle te hebben op de ongunstige effecten van hartfalen hebben een mindere kwaliteit van leven 2. Het geven van goede medische informatie draagt bij aan een betere controle op de ongunstige effecten van hartfalen en zodoende tot een betere kwaliteit van leven 3. Het vermijden van vergelijken met lotgenoten die er slechter aan toe zijn en in plaats daarvan vergelijken met lotgenoten die er beter aan toe zijn draagt bij patiënten met hartfalen bij aan een significant betere kwaliteit van leven.

Uit het vorige hoofdstuk werd onder meer geconcludeerd dat het geven van goede medische informatie en sociale vergelijking significant bijdragen aan de kwaliteit van leven bij patiënten met stabiel chronisch hartfalen. Eerder onderzoek heeft laten zien dat geslacht en psychische spanningen significante voorspellers zijn van kwaliteit van leven bij cardiale patiënten. In **hoofdstuk 8** onderzochten we 1) of door het verbeteren van de coping de kwaliteit van leven verbeterd kan worden en 2) of geslacht en psychische spanning een interactie vertonen dan wel of zij onafhankelijke variabelen voor kwaliteit van leven zijn. Hiervoor werden 38 achtereenvolgende patiënten die werden aangemeld voor electieve diagnostische coronairangiografie geïncludeerd. Om de coping van de patiënten te verbeteren

werden ze gerandomiseerd naar het lezen van 1) het commentaar van een patiënt die eerder een ongecompliceerde coronairangiografie had ondergaan, dan wel 2) algemene informatie. De veronderstelling was dat patiënten in de eerste groep een betere coping hadden en derhalve een betere kwaliteit van leven. Er bleek sprake van een borderline significante relatie tussen de “coping informatie” en een betere score op een drietal domeinen van kwaliteit van leven. Verhoogde psychische spanning ging gepaard met een mindere kwaliteit van leven. Een borderline significante interactie werd gezien tussen geslacht en psychische spanning. Univariate analyse liet zien dat het vrouwlijk geslacht de sterkste determinant was van een mindere kwaliteit van leven. We concludeerden dat bij patiënten op de wachtlijst voor coronairangiografie een toename van coping leidde tot een betere kwaliteit van leven. Daarnaast zijn vrouwelijk geslacht en hoge psychische spanningen een risicofactor voor een mindere kwaliteit van leven. Opgemerkt dient te worden dat de hoofdstukken 7 en 8 analyses betreffen in relatief kleine populaties, zodat de resultaten voorzichtig geïnterpreteerd moeten worden. Reproduceerbaarheid dient in een groter onderzoek getoetst te worden.

In **hoofdstuk 9** wordt een onderzoek beschreven waarbij patiënten met een doorgemaakt acuut myocardinfarct, die een ongecompliceerde primaire percutane coronaire interventie (PCI) ondergingen, reeds 24 tot 36 uur na opname werden ontslagen en daarna direct opgenomen in een hartrevalidatietraject. Het doel van het onderzoek was om het opgestelde protocol te evalueren. Hierbij werd tevens de kwaliteit van leven gemeten. Patiënten die in aanmerking kwamen voor het onderzoek waren door middel van een ongecompliceerde primaire PCI met goed resultaat behandeld voor een acuut myocardinfarct. Zij werden 24 tot 36 uur na opname ontslagen en direct opgenomen in een hartrevalidatieprotocol. Er werd gekeken naar recidief infarcten, heropnames en opnames op de Eerste Harthulp. Tevens werden kwaliteit van leven en secundaire preventiedoelen geëvalueerd. In totaal werden 46 patiënten geïncludeerd. De gemiddelde leeftijd bedroeg 55 jaar (37-73). Er waren twaalf patiënten met een voorwand-myocardinfarct (26%). De gemiddelde CK-piek bedroeg 1016 U/L (range 95-4333) en de gemiddelde CKMB-

piek 118U/L (range 13-374). De gemiddelde linkerventrikel-ejectiefractie 1 week na het infarct was 59%. Na 3 maanden waren 17 van de 26 rokers nog steeds gestopt met roken. Ook de streefwaarden voor bloeddruk en cholesterol werden bereikt. Fietsergometrie liet in de gehele groep een goede inspanningstolerantie zonder aanwijzingen voor recidief ischemie zien. De kwaliteit van leven scores, verdeeld over 3 domeinen (emotioneel, psychisch en sociaal welbevinden) en geevalueerd 1 week en 3 maanden na ontslag, waren uitstekend. We concludeerden dan ook dat, in een selecte patiëntengroep, na een myocardinfarct waarvoor behandeling is geweest middels primaire PCI, ontslag 24 tot 36 uur na opname een patiëntvriendelijk alternatief is voor de normale 3 tot 4 dagen opname, zonder ongunstige effecten op de kwaliteit van leven of secundaire preventiedoelen

CURRICULUM VITAE

Rutger Marcel Gerard Jansen werd op 24 oktober 1974 te Nijmegen geboren. Hij behaalde in 1993 zijn eindexamen Atheneum aan het Ludger college te Doetinchem. In hetzelfde jaar begon hij met de studie Geneeskunde te Groningen. In 1998 werd het doctoraalexamen afgelegd. Na het behalen van zijn artsexamen in 2000 was hij als arts-assistent werkzaam op de afdeling cardiologie van de Isala klinieken te Zwolle. Daar werkte hij tevens van 2000 tot 2006 aan zijn promotieonderzoek. In 2001 begon hij in Zwolle aan de opleiding tot cardioloog. Verder bleef hij betrokken bij verschillende onderzoeken op het gebied van kwaliteit van leven in het Martini ziekenhuis te Groningen. Hij is getrouwd met Roos Zwetsloot en verwacht binnenkort voor het eerst vader te worden.