

Therapies for improving walking distance in intermittent claudication.

PhD dissertation

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Papers

This PhD-thesis is based on the following studies:

Paper I:

Drug therapy for improving walking distance in intermittent claudication. A systematic review and meta-analysis of robust randomized controlled studies.

Anne-Mette Hedeager Momsen MPH, Martin Bach Jensen MD, PhD, Charlotte Buchard Norager MD, PhD, Torben Vestersgaard-Andersen MD, Jes Sanddal Lindholt MD PhD

Eur J Vasc Endovasc Surg. 2009 Oct;38(4):463-74

Paper II:

Caffeine improves walking distance in patients with intermittent claudication. A randomized, double-blind, placebo-controlled crossover study.

Anne-Mette Hedeager Momsen MPH, Martin Bach Jensen MD, PhD, Charlotte Buchard Norager MD, PhD, Mogens Rorbæk Madsen MD, Torben Vestersgaard-Andersen MD, Jes Sanddal Lindholt MD PhD

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Paper III:

Quality of life and functional status after revascularization or conservative treatment in patients with intermittent claudication. Results from a combined follow-up study and randomized, double-blinded, placebo-controlled crossover study.

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List of abbreviations

ABI – ankle brachial index
BMI – body mass index
CI – confidence interval
CONSORT – Consolidated Standards of Reporting Trials
CNS – central nervous system
CRF – Case Record File
GCP – Good Clinical Practice
IC – intermittent claudication
MVC – maximal voluntary contraction
MWD- maximal walking distance
NYHA – New York Heart Association (class)
PAD – peripheral arterial disease
PWD – pain-free walking distance
QUOROM – Quality of Reporting of Meta-analyses
WIQ – Walking Impairment Questionnaire
RCT – randomized controlled trial
RPE – rate of perceived effort
SD – standard deviation
SF-36 – Short Form 36 Health Survey

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Part 1: Background

Atherosclerosis

Atherosclerosis-related complications remain the primary cause of death in the Western World, and the major cause of morbidity worldwide.

Atherosclerosis is a systemic, chronic, cholesterol-fuelled inflammatory disease affecting large and medium-sized elastic and muscular arteries¹. It is characterised by arterial-wall thickening and loss of elasticity. The generic term arteriosclerosis includes several diseases: atherosclerosis, arteriolosclerosis, Mönckeberg's media sclerosis.

The term is derived from the Greek words *athere* (gruel) and *sclerosis* (hardening), and it is not only a disease of modern affluence, Egyptian and Alaskan mummies have shown sclerotic artery changes thousands of years ago.

Through history, the understanding of atherosclerosis has evolved and changed, and there has been several theories. As it is a heterogeneous disease, the theories are not necessarily mutually exclusive, but may play different roles in aspects of atherosclerosis:

The "Inflammatory theory" by Rudolf Virchow (1856), and "the lipid hypothesis" by Nikolai N. Anitschkow (1913) who identified foam cells and advanced plaques in an egg yolk-fed rabbit model and coded cholesterol was the causative agent.

In 1973 two theories emerged "Monoclonal proliferation theory" by Benditt and Benditt, and "Response to injury hypothesis" by Russell Ross and John Glomset based on the discovery of platelet-derived growth factor. This led to updating of hypothesis by Ross (1976), acknowledging the inflammatory nature instead of mechanical endothelial injury.

The latest hypothesis, "Response to retention hypothesis", by Williams and Tabas (1995) was supported by Skalen in 2002. The central pathogenic process in atherogenesis is sub endothelial retention of atherogenic lipoproteins, leaving other contributory processes either not individually necessary or not sufficient.

Atherosclerosis alone is a relatively benign disease, it is the acute complications which account for most fatalities and disease, like coronary syndromes, ischemic stroke, transient ischemic attacks, mesenterial or lower extremity gangrene and aneurysm rupture².

Among the most important chronic complications are:

Angina pectoris, heart failure, sudden cardiac death, mesenterial angina, renovascular hypertension and IC.

Cardiovascular diseases (including stroke) are responsible for most deaths in Denmark, with a dramatic decline from 46% (1985) to 32% in 2005 (Sundhedsstyrelsen 2006, rapport 18).

Epidemiology

Atherosclerosis can present itself as hemodynamically-significant arterial stenosis in the leg. Peripheral arterial disease (PAD) of which IC is the most common symptom is an important public health issue. The prevalence of asymptomatic PAD is based on non-invasive hemodynamic measurement of ankle-brachial systolic pressure index (ABI). A resting ABI of <0.90 is caused by significant arterial stenosis, and is approximately 95% sensitive in detecting arteriogram-positive PAD and almost 100% specific in identifying healthy individuals. The prevalence of PAD ranged from 2.5% in the age group 50-59 years to 14.5% in subjects >70 years³.

The majority of PAD patients have limited exercise performance and walking ability. Consequently PAD is associated with reduced physical functioning and quality of life.

The classical symptom of PAD is IC, which is muscle discomfort in the lower limb reproducibly produced by exercise and relieved by rest within 10 minutes. IC patients' exercise performance peaks at a mere 50% of that of age-matched controls. Typical claudication occurs in up to one third of all patients with PAD. The prevalence increases from about 3% in patients aged 40 to 6% in patients aged 60 years. To sum up there are three to four subjects with symptomatic PAD who do not meet the clinical criteria for IC. Population-screening studies have shown that 10-50% of patients with IC have never consulted a doctor ³. Patients with established PAD have a highly increased risk of cardiovascular event and mortality caused by the systemic atherosclerotic burden, therefore identification and prevention of complications are important⁴. In the near future, we will face an increasing number of elderly patients with more advanced PAD and higher co morbidity levels⁵. The differences in risk factor patterns related to different stages of the epidemiological transition (changes in disease pattern as a consequence of economic development etc.) are the main cause to global differences in atherosclerosis-related mortality and morbidity⁶.

Risk factors of PAD/IC

Epidemiological studies, such as the Framingham study, have demonstrated that a probability of development of coronary artery disease, stroke or peripheral artery disease could be predicted years in advance by measuring risk factors (individual characteristics). However, in most cases the evidence is only for an association³. Yusuf categorised risk factors into those that have proved to be causal, and others that show associations.

Table 1: Risk factors for cardiovascular disease

Modifiable, direct:	Smoking
	Hypertension
	Diabetes
	Dyslipidemia
Predisposing:	Lack of exercise
	Diet
	Obesity
	Low social status
Non-modifiable	Age
	Family history
	Male history

The predisposing (obesity) factor may work through raising blood pressure, glucose and lipids. Relationship between obesity and arteriosclerosis is multifactorial including changes in blood pressure, alterations in the composition and plasma level of lipoproteins, coagulation and inflammatory factors. It is well-established that total and LDL cholesterol reduction, control of hypertension, and cessation of smoking decrease the probability of clinical cardiovascular disease⁶. Most (>90%) patients with coronary heart disease have at least one of the major modifiable risk factors, dyslipidemia, hypertension, smoking, or diabetes. Reduced blood pressure in the ankle relative to the arm pressure indicates the presence of PAD, and is an independent risk factor for cardiovascular events⁷.

Definition of IC

“Exertional calf pain that does not begin at rest, causes the participant to stop walking, and resolves within 10 minutes of rest.”

Typical of patients with PAD are a small calf muscle area and poorer leg strength than those without, and it is associated with greater functional impairment. The individuals are primarily limited in walking endurance⁸.

Development and progression of IC

Although PAD is progressive in the pathological sense, its clinical course is surprisingly stable in most cases. Progression is identical whether or not the subject has symptoms in the leg, but development or not depends largely on the level of activity of the subject³.

Ankle-brachial index (ABI), a ratio of ankle systolic blood pressure to brachial systolic blood pressure is a routine clinical test for lower-extremity PAD. An ABI < 0.90 is a sensitive and specific measure of angiogram-positive PAD, low ABI values are related to clinical severity, and it is a sensitive predictor for coronary and cerebrovascular artery disease, indicating significant atherosclerosis in other vascular beds⁹.

Deterioration of PAD is best predicted by a progressively changing ABI, an ABI of < 0.50.

A number of studies have shown there is a strong correlation between ABI and mortality.

Edinburgh Artery Study also showed ABI to be a good predictor of non-fatal and fatal

cardiovascular events³. Resting and post-exercise ABI values are strong and independent

predictors of mortality. A reduction of post-exercise ABI over baseline readings can identify patients with normal ABI values at rest at increased risk of subsequent mortality¹⁰.

Besides, co morbidities, such as arthritis, low back pain, and heart, lung, and central-nervous system diseases have been shown to negatively predict physical functioning.

Management and treatment of IC

Generally there are four therapeutic strategies to improve functional status and QoL in PAD/IC: Conservative treatment (exercise), vasoactive drugs, PTA and bypass surgery. Patients with PAD/IC should be candidates for aggressive risk factor modification and a patient-specific exercise program¹¹.

Recommendations to risk-factor management are:³

- All patients who smoke should be advised to stop smoking.
- Patients who are overweight (BMI >25) should receive counselling for weight reduction and increased level of exercise.
- All symptomatic PAD patients would have their low-density lipoprotein (LDL)-cholesterol lowered to <2.59 mmol/L, and statins should be the primary agents to lower LDL cholesterol levels.
- All patients with hypertension should have their blood pressure controlled to <140/90 mm Hg
- Diabetic patients should have aggressive control of blood-glucose levels.
- All symptomatic patients with or without a history of other cardiovascular disease should be prescribed an antiplatelet drug long term to reduce the risk of morbidity and mortality.

An important issue in dealing with risk factors is the overall budgetary impact of enforcing compliance to published recommendations³.

For all cardiovascular risk factors, the most effective and cost-effective are the measures that combine a government-led action with individual preventions. A combination of laws that reduce the amount of added salt in processed foods and increased taxes on tobacco, which are the most the cost-effective measures would be better combined with individual prevention¹².

Conservative treatment: Exercise therapy

Exercise training is an efficacious therapy for IC, but is used very little in the clinical setting. It has proved significant improvement in community-based walking ability and QoL. Besides exercise has minimal associated morbidity, and is effective in almost all patients¹³.

A walking exercise programme for IC has been recommended since 1898¹⁴, 1966¹⁵, and current evidence suggests that it increases patients' metabolic efficiency of skeletal muscles and the blood flow to the leg. Besides training has a favourable effect on the lipid profile^{16;17}. In contrast to other claudication treatments, exercise is likely to improve the cardiovascular risk factor profile¹⁸.

Walking economy is yet another factor that may explain how exercise results in improved blood supply. Patients respond to their leg pain by adopting a walking pattern that favours gait stability at the expense of speed. The biomechanical alteration may have a secondary disadvantage of increasing the oxygen cost of walking, so that walking is performed at a higher percentage of maximal oxygen consumption capacity. After 4 months of exercise training, patients used less oxygen at a given workload¹⁹.

Clinicians should recommend supervised treadmill exercise to PAD patients, with or without classic symptoms of IC. Lower-extremity resistance training also improved MWD, QoL, knee-extension, plantar-flexion as well as stair climbing (WIQ)⁸.

Exercise in IC is a relatively inexpensive, low-risk option compared with other more invasive

therapies²⁰.

However, there are potential disadvantages to exercise therapy relative to revascularization, as 6 months for optimal results, 3 times a week of at least 30 minutes in duration are required.

Drug therapy

As recommended treatment with lifestyle modification and exercise programme often have been unsuccessful because of non-compliance, several drugs have been studied²¹, and meta-analyses are made comparing medication (pentoxifylline) and exercise²². Two drugs are FDA-approved in the USA; pentoxifylline has been used since 1984 with indifferent results, cilostazol have proved significantly more effective in improving walking distance. Little efficacy has been shown with other classes of drugs. At the moment, statins seem to be the most efficient drug²³.

Revascularization

Due to recommendations only selected claudicants undergo arterial reconstructive surgery or percutaneous transluminal angioplasty (PTA)^{3;24}. Revascularization by endovascular or surgical methods is an option considered on an individual basis depending on severity of the symptoms and disability in each patient¹¹.

Neither age nor co-morbidity burden adversely affected angioplasty-induced QoL improvements, so either should negatively influence the decision for PTA in PAD patients⁵.

New methods have been developed, and both surgery and PTA have been shown to improve limb hemodynamics (ABI), walking distances, and disease-specific aspect of QoL as well²⁵⁻²⁷. Vascular bypass grafts improve the exercise tolerance by increasing blood flow²⁵.

Health-related QoL has been shown to be better after surgical or PTA compared with exercise²⁵, therefore revascularization with stent placement should be strongly considered in addition to conservative treatment for moderate to severe claudication with aortoiliac obstruction²⁵.

However, revascularization of patients with IC remains controversial and a matter of debate.

Quality of life

Of particular interest is direct treatment to the improvement of QoL. QoL is of great importance rather than life-expectancy and the significance of QoL is embodied by the World Health Organization definition of health as a state of physical, social and mental well-being and not just an absence of infirmity.

Knowledge of health-related QoL has great importance as the increase in life-expectancy has resulted in a growing number of chronic and debilitating conditions, such as PAD.

Health-related QoL has been shown to be better after surgical or percutaneous revascularization or percutaneous revision compared with exercise therapy^{25;28}.

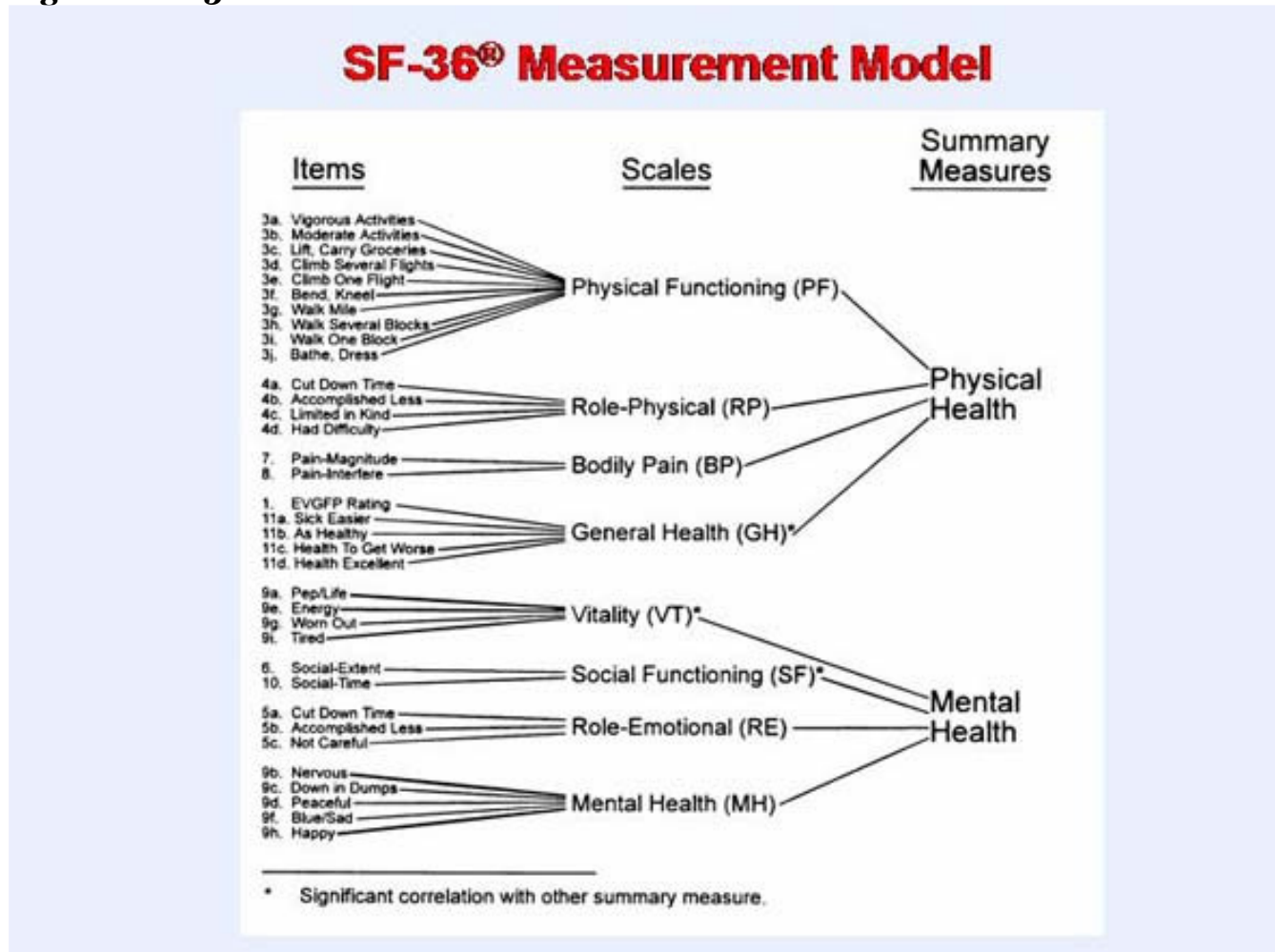
Studies have shown effectiveness of the strategy to include patients' perceived physical functioning into the process of clinical decision-making²⁹. Especially in older PAD patients objective measures of disease severity are correlated with a self-reported, disease-specific and generic QoL³⁰.

Short Form 36 Health Survey (SF-36) is a supposedly generic measure of health-related QoL, whereas Walking Impairment Questionnaire (WIQ) is disease-specific, although some argue

that WIQ is not a QoL instrument³¹. Both can be useful as a significant correlation in >80% comparisons between them has been shown³⁰.

The SF-36 is a multidimensional generic QoL questionnaire assessing change in health and eight health domains: physical and social functioning, physical and emotional role impairment, mental health, vitality, pain and general health experience (Figure 1).

Figure 1. SF-36 Measurement Model



The WIQ is a short disease specific questionnaire validated in patients with IC³²⁻³⁴. It contains three domains measuring important factors in symptomatic PAD patients: walking distance, speed and the ability to walk stairs.

The WIQ is the most specific questionnaire for documenting the qualitative deficits (the qualitative measure that best reflects actual ambulatory performance) of the PAD patients³⁵. WIQ correlates with ABI as a 10% increase in WIQ distance-score is associated with a 0.3 improvement in ABI.

Caffeine

History

Humans have consumed caffeine since the Stone Age; many cultures have legends that attribute the discovery of such plants a healing effect. That chewing the seeds, bark, or leaves had the effect of easing fatigue and stimulating awareness. In the ninth century, coffee beans were available only in their native habitat, Ethiopia. A legend traces its discovery to a goat herder, who experienced that goats had an energy boost after eating the fruit of the coffee tree. In the 17th century it was appreciated as a beverage in Europe, at first known as “Arabian wine”, and caffeine was first extracted from coffee in 1819 by Runge, a German chemist.

Caffeine is found in more than 60 plant species, where it acts as a natural pesticide. The most commonly used sources of caffeine are coffee, tea, cola and to a lesser extent cacao. It is the most widely consumed psychoactive substance in the world. More than 50 countries produce it and the consumption has been estimated to over 100.000 tons annually. About 80% of the caffeine intake is in the form of coffee in Scandinavia, where the intake per inhabitant is the greatest. In Denmark the caffeine intake per inhabitant is approximately 400 mg (4 cups of filtered coffee). Tea contains more caffeine, but a typical serving contains much less, only approximately half of that in coffee.

Pharmacology and metabolic effects

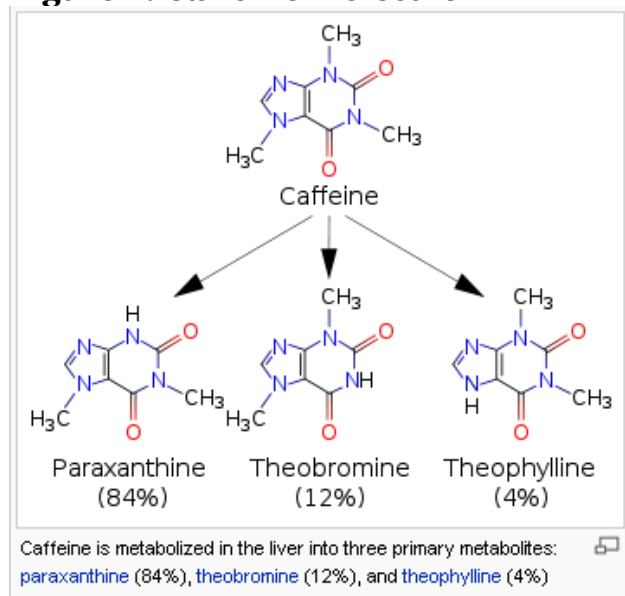
Caffeine is a white powder with a distinctly bitter taste and no odour. The caffeine molecule (1, 3, 7-trimethylxanthine) is structurally similar to adenosine, and its principal mode of action in the brain is bindings to adenosine receptors without activating them (an “antagonist” mechanism). Adenosine is found in every part of the body, it plays a role in the fundamental ATP-related energy metabolism.

Once inside the body, it has a complex chemistry. Caffeine is absorbed through the stomach and small intestine, and maximal plasma concentration is reached within 30-60 minutes³⁶. A variation of 15 to 120 minutes has been observed due to differences in the rate of stomach emptying, absorption of caffeine is increased in an empty stomach.

Caffeine can pass through the blood-brain-barrier and be distributed throughout all compartments of the body as it is soluble in both water and fat³⁶. Caffeine is primarily metabolized in the liver (figure 2) and excreted in the urine. The half-life is 3 to 6 hours with a variability of 2 to 12 hours due to individual differences and not to caffeine intake or caffeine concentration in the plasma.

Caffeine interacts with a number of other drugs. Smokers metabolize caffeine faster due to an enzymatic activity (cytochrome P-450 1A2) induced by hydrocarbons in the smoke, and former smokers’ level of caffeine is raised and therefore some describe that they are not capable of caffeine intake as well as before they stopped smoking.

Figure 2. Caffeine molecule



Side effects

Tolerance to caffeine develops within one to four days with regard to the cardiovascular and stimulating effects of epinephrine³⁷ and cortisol, but not to the effect on CNS and the muscular system. Withdrawal symptoms develop in almost 50% of caffeine users, who experience headache, tiredness, decreased alertness within 12 to 24 hours after the last caffeine intake

Higher doses can produce unpleasant feelings like restlessness, tension, irritability, and palpitation. High doses may lead to “caffeinism” with trembling, polyuria, dizziness, irregular heart rate and respiration, abdominal discomfort, and diarrhea^{38;39}

Physiological effects and clinical use

Several theories about the physiological effects of caffeine have been suggested. One theory is that caffeine’s effect is due to its increase of plasma epinephrine at rest and after work and thereby glycogen sparing^{40;41}. The stimulating effects are related to increased level of dopamine and adrenalin at rest and at work⁴¹. Some studies also show an increased level of free fatty acids before and under physical exercise, and of glycerol⁴². Caffeine also increases blood lactate during anaerobic exercise⁴³ and has an effect on blood glucose and insulin^{42;44}. At present the physiological effect of caffeine is primarily thought to be caused by antagonism to the adenosine receptor³⁶. Caffeine combines with the adenosine receptors on the cell surface thus blocking the effect of these receptors³⁶.

In summary most of caffeine’s effects are related to the methylxanthine and this mechanism³⁹. Caffeine has stimulating effects on the central nervous system (CNS), the cardiovascular and the muscular system.

CNS stimulation

In CNS caffeine improves alertness, decreases drowsiness, reduces the rate of perceived exertion, and decreases the need for sleep^{38;41;45}.

Caffeine has a cerebral vasoconstrictive effect whereas it has a vasodilative effect peripherally. In low to moderate concentrations (200-500 mg per day) caffeine leads to positive subjective effects such as elation, peacefulness, pleasantness, and improved performance.

Cardiovascular system stimulation

The cardiovascular effects of caffeine remain controversial. Earlier studies concluded that care should be taken because caffeine affects the cardiovascular system, causing blood pressure and pulse to rise and was associated with increased morbidity and mortality⁴⁶. However, Framingham and recent studies found no association between moderate coffee intake and cardiovascular events in post-myocardial infarction patients. Coffee consumption was not found to change the risk of coronary heart disease events, stroke, and sudden death⁴⁷, and new data even suggests that coffee consumption modestly reduces the risk of stroke⁴⁸.

Muscular system stimulation

Caffeine increases muscular endurance in situations with exhaustion within 30-60 minutes⁴⁹. It enhances performance and endurance in sub maximal long-term exercise. The endurance enhancing effect has also been shown at physical activity lasting 4-6 minutes⁴¹. However, caffeine has no effect on endurance when the physical effort exceeds a certain time limit, e.g. a 40-km march⁵⁰.

Caffeine increases the level of adrenalin, free fatty acids and glycerol, beta-endorphins and cortisol, and due to this substrate availability caffeine delay exhaustion during prolonged exercise⁵¹. Caffeine intake one hour before exercise reduced glycogenolysis by 55%, and the spared glycogen prolonged the time to exhaustion.

During short-term exercise caffeine is also shown to increase maximal anaerobic power⁴³. Maximal strength after caffeine intake is shown to improve 2% in a previous study⁵². A study of nine young men showed no significant effect on muscle strength with 300 mg caffeine⁵³, nor did a study with 200 mg, so the use of caffeine as an ergogenic aid in untrained to moderately trained individuals is questioned⁵⁴.

The experience of exhaustion - the rate of perceived effort (RPE) is reduced by caffeine, Norager showed a 11% reduction after 5 minutes of cycling in healthy citizens aged >70 years⁵².

The question is if the increased endurance is a physical or rather a psychological effect of caffeine that increases alertness and reduces tiredness. Caffeine could mask fatigue, thereby increasing work productivity³⁸. The increased release of beta-endorphins and hormones (plasma catecholamine) also helps reducing stress during and immediately after intake and hence also reduces the stress of exercise⁵⁵.

In summary caffeine is an active drug that elicits a number of effects including the increase in exercise endurance, and this may be clinically useful in relation to the growing number of IC patients who all should exercise. Caffeine's potent performance-enhancing effects might give patients possibilities of a more active lifestyle and QoL.

Aims of the studies

The main purposes of the PhD project were to study possibilities of treatment for the lifestyle limiting condition IC. Therapy is essential as improvement without intervention is rare⁵⁶. Management of IC is a complement of risk factor modification, pharmacotherapy, exercise and angiogenesis.

It is well-known that smoking and sedentary lifestyle affect IC. Aging itself may contribute to the progression, whereas only the lack of physical activity and nutritional deficiencies are potentially reversible⁵⁷.

The burden from demands on health-care resources has to be taken into account, so although care of patients has been revolutionized by endovascular and stenting technology only selected claudicants undergo surgery. From a medical and socioeconomic point of view, the IC complication rate and related treatment costs must be reduced to the lowest possible level.

Study I

The purpose of the first study was to select the robust RCTs that evaluate drugs used in the treatment of moderate IC and perform a pooled meta-analysis of drugs with similar mode of operation to get a valid estimate of the effect upon MWD of various classifications of drugs. The primary outcome measures were the MWD and PWD assessed by treadmill testing with either constant or graded load treadmill protocol. Secondary outcomes were health-related QoL and functional status.

Pharmacological management of IC remains to be defined precisely, as of yet there have been very few significant pharmacological breakthroughs in the treatment of IC.

With the aging population and the increasing prevalence of IC with age, there is a growing need for optimal medical management across all specialities treating patients with IC.

However, there is no widely accepted medication, as only pentoxifylline and cilostazol have received the US FDA approval, and no drug is recommended in Denmark to influence on claudication distance. Improvement of walking distance is considered as an important relief of impairment, which reduces the activities of daily living linked with a person's autonomy and QoL.

Study II

The second study's objectives were to evaluate the effect of caffeine. We investigated whether caffeine (6 mg/kg) improves physical performance in patients with IC.

The primary outcome measures were PWD and MWD on a treadmill.

Secondary outcomes were maximal isometric strength and sub maximal strength (endurance) of knee extension, postural stability (sway), reaction times, ABI and cognitive function measured by three tests.

If caffeine can be a useful tool for PAD patients, allowing them to extend their MWD and possibly improve their physical training, it would be a safe, tolerable and efficient drug to be used to augment walking distance in PAD patients^{47:58}.

Study III

The third study's primary aim was to evaluate and compare the effect of revascularization and conservative treatment on QoL, functional status and physical performance. Our hypothesis was that revascularization improves QoL, physical capacity and ABI more than conservative treatment.

Primary outcome measures were health-related QoL, measured by SF-36, functional status measured by WIQ, and pain-free and maximal walking distance (PWD, MWD) measured on a treadmill.

Secondary outcomes were maximal strength and sub maximal endurance of knee extension, and ABI.

The secondary aim was to achieve data for planning of robust randomised clinical studies in this area. The study analyses the consequences of a more liberal indication mainly based on the patient's choice if revascularization could be limited to above the knee.

Finally, we have earlier reported benefits in PWD and MWD by caffeine intake at baseline. Consequently, we aimed to study whether this benefit was sustained revascularization and conservative treatment.

Ethics and safety

The project was carried out in accordance with the Helsinki Declaration II and the regulations of Good Clinical Practice (GCP). The study was approved by the National Board of Health and the Regional Ethical Committee, and reported to the Danish Data Protection Agency. The project was monitored by the GCP Unit at the Aarhus University Hospital, Denmark and was registred in clinicaltrials.gov protocol registration system.

Adverse effects were recorded immediately and registered in the patients' CRF (Case Report Form). Serious side effects and events considered to have any causal relationship with the project or which were defined as serious side effects or events by the Danish Medicines Agency were reported to this.

Written informed consent was obtained from all participants prior to study entry.

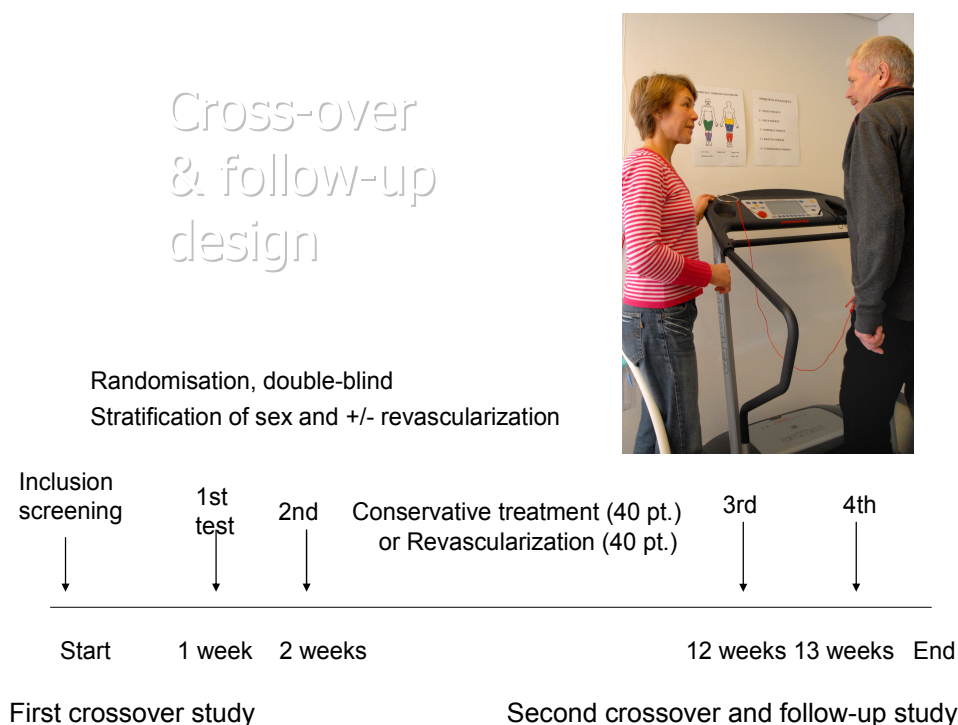
Part 2: Methods and material

The PhD-thesis is based on multicenter clinical studies carried out at the Surgical Research Unit, Department of Surgery, Regional Hospital Herning and Vascular Surgical Research Unit, Department of Vascular surgery, Regional Hospital Viborg, Denmark.

Study I was a review and meta-analysis based on literature searched from Medline and EMBASE and bibliographic searches.

Study II was designed as two randomized, double-blinded, placebo-controlled crossover studies, and study III was a non randomized, prospective clinical study with 3-month follow-up (Figure 3).

Figure 3. Design of the studies.



Materials used in the studies

Study I

The Medline (from 1966) and EMBASE (from 1974) were searched for all RCTs published until February 2009 with no language restrictions. In addition, bibliographic searches were carried out using reference lists from retrieved relevant reviews from the past five years. The websites www.vascularweb.org, www.tctmd.com, www.theheart.org, www.clinicaltrialresults.org were also searched.

Included studies were prospective, double-blinded, RCTs, parallel or cross-over trials, and meta-analyses involving participants with IC Fontaine-stage II (with the criteria explicitly described).

The search strategy used to search MEDLINE was based on following search terms:

#1 MeSH descriptor INTERMITTENT CLAUDICATION this term only

#2 MeSH descriptor RANDOMIZED CONTROLLED TRIAL this term only

#3 MeSH descriptor RANDOMIZED CONTROLLED TRIAL AS TOPIC this term only

#3 (#1 and #2)

Search "Intermittent Claudication"[Mesh] AND "Randomized Controlled Trial" [Publication Type]

#4 (#1 and #3)

Search "Randomized Controlled Trials as Topic"[Mesh] AND "Intermittent Claudication"[Mesh]

#5 (#3 or #4)

The search strategy we used to search EMBASE gave the following search history:

#1 "intermittent-claudication" / all SUBHEADINGS in DEM,DER,DRM,DRR

#2 "randomized-controlled-trial" / all SUBHEADINGS in DEM,DER,DRM,DRR

#3 ("randomized-controlled-trial" / all SUBHEADINGS in DEM,DER,DRM,DRR)

and ("intermittent-claudication" / all SUBHEADINGS in DEM,DER,DRM,DRR)

#4 ("randomized-controlled-trial" and "intermittent-claudication")

Study II

Participants were potentially all patients in the outpatient clinics in Regional Hospital Herning, Holstebro and Viborg. Screening for eligible patients was performed by the vascular surgeons in the outpatient clinics, and patients were offered participation if they met the following criteria: IC Fontaine II stage; verified ABI <0.9; no symptoms at rest; and age >40 years. Finally, the participants should be willing to avoid caffeine intake 48 hours before each test session.

Exclusion criteria were: dementia; diabetes; illness or other reason that made participation in the test program impossible; acute illness; reasons that contraindicated caffeine intake; intake of Teofyllamin and Trental; and bodyweight >100 kg.

Subject considered suitable for inclusion also counted those who had minor disabilities such as hypertension and were being treated with ACE-inhibitors or diuretics, and those who had well-treated asthma or slight osteoarthritis.

Study III

This combined non randomised, prospective clinical study and randomized, double-blinded, placebo-controlled crossover study was carried out at the Surgical Research Unit, Herning and Viborg Regional Hospital, Denmark. Screening for eligible patients was performed as a part of a randomized trial by the vascular surgeons in the outpatient clinics, who decided in consensus whether the treatment should be conservatively or by surgery⁵⁹. Patients were selected to be offered surgery after angiography, mainly based upon patient's choice if revascularization could be limited to above the knee, and after a careful discussion concerning risks and benefits. Patients underwent either an endovascular or open surgical procedures at the Vascular Surgery Unit, Viborg Regional Hospital. All patients were encouraged to stop smoking and exercise at home.

Patients were offered participation if they met the following criteria: IC Fontaine II stage; verified ABI <0.9; no symptoms at rest; and age >40 years.

Exclusion criteria were: dementia; diabetes; illness or other reason that made participation in the test impossible; acute illness; reasons that contraindicated caffeine intake or participation; intake of Teofyllamin and Trental; and bodyweight >100 kg. Subjects considered suitable for inclusion also counted those who had minor disabilities as hypertension and were being treated with ACE-inhibitors or diuretics, and those who had well-treated asthma or slight osteoarthritis.

Methods used in Study I

The review and meta-analysis is based on only robust and peer-reviewed RCTs in order to avoid the limitations of pooling small trials which may be heterogeneous with regards to outcome measures in meta-analyses. We have analyzed only primary outcome as it is widely accepted that the reliability of the findings of a meta-analysis is linked to the number of overall events accrued⁶⁰. We also followed the QUOROM statements standards and used well-known criteria when assessing the quality of trials⁶¹. Findings suggest that inclusion of report of low-quality RCTs in meta-analyses is likely to alter the summary measures of the intervention effect⁶¹.

Selection of studies

The review comprised prospective, robust, double-blinded, placebo-controlled, parallel or crossover RCTs, and meta-analyses studying patients with moderate IC (Fontaine stage II), and an ABI < 0.9. Only studies published in peer reviewed journals were included. Interventions were pharmacological agents compared with a placebo control group. Studies describe patients included gave informed consent and that Helsinki Declaration was followed.

Robust studies were identified by sample size due to the following power calculation using the formula: $N = (C_{2\alpha} + C_{\beta})^2 \times 2 \times CV^2 / \text{miredif}^2$ (unpaired data), where N=number of participants in each group, CV=coefficient of variation, miredif=the minimal relevant difference, $C_{2\alpha}$ is the alpha fractile in the t-distribution, and C_{β} is the beta fractile in the t-distribution. A power of 80% gives $C_{\beta}=0.84$ and $C_{2\alpha}=1.96$ at a 5% significance level. The coefficient of variation of repeated test of MWD reportedly varied from 16%^{62;63} to 21%⁶⁴. So, if miredif is set to 15% and CV 20%, we have: $N = (1.96 + 0.84)^2 \times 2 \times 20\%^2 / 15\%^2 = 28$ in each group. Consequently, studies < 56 patients were excluded.

Trials without primary outcome measures of either MWD or PWD were excluded, as were RCTs of phase II, single-blinded, non-blinded studies, and studies that compared different doses or agents without placebo. Trials evaluating surgical or physical training interventions were also eliminated.

Treadmill tests were used to evaluate PWD and MWD with protocols involving either constant or graded loads (most were 3 km/h).

Secondary outcomes were subjective assessment of health-related QoL and functional status.

Validity assessment

Two reviewers independently assessed each potentially relevant study for inclusion.

Interobserver agreement was established and consensus was reached before a trial was included in the review.

We sought information regarding blinding procedures at treatment and outcome assessment, quality of randomization, allocation concealment, description of drop-outs and withdrawals, and intention-to-treat analysis⁶⁵. In addition, we looked for the presence of a power calculation, and adequate description of statistical methods.

Data was double-checked by AM. Statistics was performed by AM and JL using Review Manager 4.2, (The Nordic Cochrane Centre, Copenhagen, Denmark).

Data extraction

AM reviewed each study and extracted information on: trial design, degree of blinding, details on patients characteristics, dosages and treatment periods, outcomes, details on treadmill

test, inclusion and exclusion criteria and additional quality items to assist in assessing heterogeneity between studies.

Quantitative data synthesis

Data on the MWD and PWD and secondary outcomes were recorded for patients receiving active drug compared to placebo at baseline to study end. We attempted to collect data from each trial on the means and standard deviations (SDs) for MWD and PWD; however, this proved difficult because there were numerous data-reporting inconsistencies.

In the meta-analysis, the weighted mean difference (WMD) in MWD was used to merge and compare results from the various trials. The data were pooled to obtain an overall estimate of the effectiveness of each drug dose as well as a total estimate of the effectiveness of each type of drug. These data are presented as a WMD of MWD with a 95% confidence interval (CI) and a relative improvement. ITT analysis was performed on all patients randomized to treatment. We evaluated between-trial heterogeneity using Chi-square test and the overall effect by Z-test.

Methods used in Study II

Randomisation

In a crossover design, participants were tested twice with a one-week interval and randomized to receive one dose caffeine and then placebo (group CP) or placebo and then caffeine (group PC). At 3-months follow-up the crossover study's test-procedures were repeated.

Randomization was stratified by gender and according to whether the person was scheduled for operation or conservative treatment (no operation). All participants undergo study drug administration prior to surgery. Computerized randomization was performed in blocks of four by the dispensary at Regional Hospital Herning. Patients were included consecutively until 88 patients were randomized.

The study was designed so that 56 evaluable participants would be sufficient to detect a 15% relative difference in walking distance with 80% certainty at the 5% level, assuming the standard deviation (SD) of the difference to be 10%. As we planned to reinvestigate these patients again 3 months later in a follow-up study, we included more patients than necessary to allow for drop outs.

Double-blinding

Glostrup Pharmacy, Denmark produced the medication (caffeine). Both the caffeine (containing 6 mg/kg caffeine) and placebo capsule (containing glucose monohydrate) were packed by the dispensary accordingly to the randomization. Participants and investigators were unaware of treatment allocation at all times. Code breaking sheets for emergency use were kept at the pharmacy department, but were never used.

At the end of the second test, participants were asked to consider if they had received caffeine or placebo or to state if they had detected any difference between the two tests. Data were entered and analyzed before treatment codes were broken.

Test procedure

Participants avoided caffeine-containing drinks and food for 48 hours and refrained from food intake and smoking two hours prior to each test. Figure 4 describes the flow of test sessions.

Figure 4. Flow of test sessions

First test: Written informed consent obtained Medical story obtained: <i>smoking, diseases, medication, NYHA class, activity level, years with IC</i> Weight, height, resting pulse Blood samples: <i>Cholesterol, triglycerides, Creatinine</i>
First two tests: Blood samples: <i>lactate</i>
All four tests: Blood pressures: <i>arms, ankles</i>
Test walk in treadmill: (3 km/h 0% incline)
Test medicine (<i>caffeine or placebo</i>) Break for 1 h 15 minutes, A light meal is served
Cognitive tests
Psychomotor test (reaction time)
Postural stability test (balance): with eyes open and closed
Pain score and localisation: <i>before walking</i> <i>at pain onset</i> <i>at stopping</i>
Walking test in treadmill: Pain-free distance and time Maximal distance and time
Blood pressures: <i>arms, ankles</i>
Maximal isometric strength: Knee extension <i>Rest for 15 minutes</i>
Sub maximal (50%) strength; Endurance of knee extension
First two test: Blood samples: <i>Lactate</i>

At the first session, a medical history was obtained, including registration of smoking, previous and current diseases, medication (type, dosage, and indication) and NYHA class (New York Heart Association class). Weight (kg) and height (cm) were measured and BMI was calculated. Blood samples were taken at the beginning of the first test with lactate also being taken at the end of both tests.

Arm and ankle blood pressure measurements (mmHg) were taken with the subject in the supine position after a 10-min rest period. Pressures in the brachial artery at both elbows were measured (A & D Medical UA-787, UK). The pressures in the posterior tibial artery and the dorsal artery of both feet were measured twice. A Doppler probe (Ultra Tec PD1, UK) and a sphygmomanometer cuff (Diester, Germany) were used to monitor the pulse while a sphygmomanometer cuff (Diester, Germany) was inflated above the artery (Figure 5). The cuff was slowly deflated, and the pressure at which the pulse returned was recorded⁶⁶. The ABI in both legs was calculated by dividing the systolic blood pressure in the ankle by the higher of the two systolic blood pressures in the arms. The blood pressure in the ankle was calculated as a mean of all pressures measurable in each leg⁶⁶.

Patients then had a test walk on the treadmill (Kettler, Marathon HS, Germany)(3 km/hour, no incline) to determine PWD and MWD prior to study medication.

After the above measurements had been performed, capsules with test medicine were taken with a glass of water and patients were served a light breakfast and rested for one hour and 15

minutes. We then measured: Walking distance, arm and ankle blood pressures, postural stability, reaction time, isometric knee extension strength, sub maximal knee extension endurance, and cognitive function.

Primary outcomes

Patients were asked if they felt any pain in either leg before they started to walk in the treadmill and to immediately report onset of pain in any area of either leg. This walking distance and time was registered as PWD. Pain was registered on a Verbal Rating Scale (0=none, 1=minor, 2=medium, 3=strong, 4=unbearable pain) illustrated with colours in 4 areas (calves, hamstrings, thighs, buttocks)⁶⁷.

Patients were encouraged to walk until the pain was unbearable. When they stopped, the score of pain, MWD and the time were registered. Immediately after, the blood pressure measurements were repeated.

Secondary outcomes

Postural stability (sway) was measured twice on a dynamometer platform (“Good Balance”, Metitur Oy, Jyväskylä, Finland). Patients were asked to stand upright on the platform with their feet slightly apart and parallel to each other and their arms hanging to their sides. Measurements were taken for 30 seconds alternately with eyes open (EO) and closed (EC). We registered velocity moment (mm²/s) calculated as the mean area covered by the movement of the centre pressure during each second of the test.

Reaction time (msec) was measured by a response unit (“Good Response”, Metitur Oy, Jyväskylä, Finland). The patient sat in front of the response unit with a finger from the dominant hand on a centre button. The reaction time was recorded as the time between seeing a light signal and lifting the finger from the centre button. Twelve measurements were taken electronically and the mean value (msec) was calculated. Patients familiarized themselves with the program once before the actual recording was made in the first test session.

Strength was measured as the maximum voluntary isometric knee extension (90° flexed position) in the most painful leg using a strain-gauge mounted on a dynamometer chair (“Good Strength”, Metitur Oy, Jyväskylä, Finland)⁶⁸. Patients were encouraged to do their best and the finest of three measurements was used. Figure 6 shows the test of strength.

Isometric endurance was measured with the patient in the same position as during the strength test. Patients were asked to hold a force of 50% of their maximal strength. The isometric knee extension was measured as the time until this force could no longer be held. Cognitive tests consisted of a Symbol Digit Modalities Test (SDMT) and a Trail Making Test (TMT) A and B⁶⁹. All tests are easily administered tests of visual conceptual and visomotor tracking. They measure attention, and scores can be suggestive of cerebral dysfunction. Lactate was determined in the beginning and at the end of each test session (ABL 800, Radiometer, DK). Blood samples of creatinine, triglyceride, cholesterol, HDL, and LDL were measured at baseline (Architect, Abbott, U.S.A.).

Data analysis

The primary variables for treatment evaluation were the relative changes in MWD and PWD from baseline.

Analyses were on an intent-to-treat basis according to a pre-established analysis plan, and $p < 0.05$ was regarded as being statistically significant.

Figure 5. Measurement of ABI



Figure 6. Measurement of strength



Data were log-transformed and the distribution was evaluated graphically and by Shapiro-Wilk's test for normality. If data were normally distributed, the two sample t-test for unpaired data was used and the mean with its standard deviation (SD) were presented; otherwise, the Mann-Whitney test for unpaired data was used and the median and its 95% CI were reported. Patients received placebo, then caffeine (group PC); or caffeine, then placebo (group CP).

To test for the presence of a treatment effect, the difference in response (period 1- period 2) was compared between groups PC and CP⁷⁰. The magnitude of the treatment effect was estimated as half the difference in response for group PC plus group CP thereby taking into account the different treatment order. To test for a possible treatment-period interaction, the means of both periods for the two groups were compared and the differences visually analyzed⁷¹. Analyses were carried out using STATA software version 11.0 (StataCorp 200X, College Station Texas, USA), and reported p-values were based on the two-sided alternative hypothesis.

Methods used in Study III

Randomisation

Patients were included consecutively until 88 patients were randomized⁵⁹. Randomization at baseline was stratified by gender and whether the person was scheduled for operation or conservative treatment (no operation)⁵⁹.

At follow-up participants were tested twice with a one week interval and received caffeine and then placebo or the opposite. The follow-up results are obtained when patients received placebo at baseline and 3 months afterwards with a minimum at one month after surgery⁷².

Test procedure

At baseline, a medical history was obtained, including registration of smoking, previous and current diseases, medication, and NYHA class. Weight (kg) and height (cm) were measured and BMI was calculated. Blood samples of creatinine, triglyceride and cholesterol were taken at baseline (Architect, Abbott, U.S.A.).

Arm and ankle blood pressure measurements (mmHg) were taken with the subject in the supine position after a 10-min rest period. Pressures in the brachial artery at both elbows were measured (A&D Medical UA-787, UK). The pressures in the posterior tibial artery and the dorsal artery of both feet were measured twice. A Doppler probe (Ultra Tec PD1, UK) and a sphygmomanometer cuff (Diester, Germany) were used to monitor the pulse. The cuff was inflated above the artery and slowly deflated (2mm/sec), and the pressure at which the pulse was first audible was recorded⁶⁶.

The ABI in both legs was calculated by dividing the systolic blood pressure in the ankle by the higher of the two systolic blood pressures in the arms. The blood pressure in the ankle was calculated as a mean of all pressures measurable in each leg.

Patients then had a test walk (PWD, MWD) on the treadmill (Kettler, Marathon HS, Germany)(3 km/h, no incline).

After the above measurements had been performed, test medicine was taken and patients were served a light breakfast and rested for one hour and 15 minutes. Meanwhile patients answered the SF-36 and WIQ with a research assistant present to explain the forms and answer questions.

We then measured: PWD, MWD, ABI, isometric knee extension strength and sub maximal knee extension endurance.

Primary endpoints

The SF-36 is a multidimensional generic QoL questionnaire assessing change in health and eight health domains: physical and social functioning, physical and emotional role impairment, mental health, vitality, pain and general health experience. The change in health is evaluated in a separate question with standardised response choices. For every domain the scores are summed up and transformed to a scale ranging from 0 to 100, a higher score means a better health condition.

The WIQ is a short disease specific questionnaire validated in patients with IC^{32;33}. It contains three domains measuring important factors in symptomatic PAD patients; walking distance, speed and the ability to walk stairs. For each domain separately, a sub score was calculated with a Likert scale. The total WIQ score was the mean of the three sub scores³⁴.

Patients were asked if they felt any pain in either leg before they started to walk on the treadmill and to immediately report onset of pain (PWD) in any area of either leg. Pain was registered on a Verbal Rating Scale (0=none, 1=minor, 2=medium, 3=strong, 4=unbearable pain) illustrated with colours in 4 areas (calves, hamstrings, thighs, buttocks)⁶⁷. Patients were encouraged to walk until the pain was unbearable. When they stopped the score of pain, MWD and the time was registered.

Secondary endpoints

Immediately after the walking test blood pressure measurements were repeated. The ABI in the more severely diseased leg was used in the analysis.

Strength was measured as the maximum voluntary isometric knee extension (90° flexed position) in the most painful leg using a strain-gauge mounted on a dynamometer chair (“Good Strength”, Metitur Oy, Jyväskylä, Finland). Patients were encouraged to do their best, and the finest of three measurements was used⁶⁸.

Isometric endurance was measured with the patient in the same position as during the strength test. Patients were asked to hold a force of 50% of their maximal strength. The isometric knee extension was measured as the time until this force could no longer be held.

Data analysis

The variables for treatment evaluation were the relative changes in scores from baseline to follow-up of: SF-36; WIQ; MWD; PWD; ABI; maximal strength; and endurance.

Analyzing was on an intent-to-treat basis according to a pre-established analysis plan, and $p < 0.05$ was regarded as being statistically significant.

Data were log-transformed and the distribution was evaluated graphically and by Shapiro-Wilk’s test for normality. If data were normally distributed, the two sample t-test for unpaired data was used and the mean with its standard deviation (SD) presented; otherwise the Mann-Whitney test for unpaired data was used and the median and its 95% CI were reported.

To test for a treatment effect of revascularization the difference in response was compared between the conservative group (C) and intervention group (I) and either two sample t-test for paired data or Wilcoxon signed-rank test was used⁷⁰. We also analyzed the physical and mental component summary score to be more specific and sensitive to the physical and mental components of QoL²⁵. Multiple regression analyses were made of the relative change in QoL, WIQ and walking distance. Unadjusted and adjusted ratios for treatment, age, smoking, ABI and BMI were compared between groups using a multivariate linear regression analysis.

The walking distance at follow-up relative to that at baseline was used to describe the impact in each group. Ratios were logarithmically transformed to ensure that the variation in the data followed a normal distribution. The results of the analysis were transformed back and expressed as ratios or relative change (ratio-1).

Patients received placebo then caffeine or caffeine then placebo and the difference in response was compared between groups. The magnitude of the treatment effect was estimated as half of the difference in response for the groups, consequently the different treatment order was taken into account

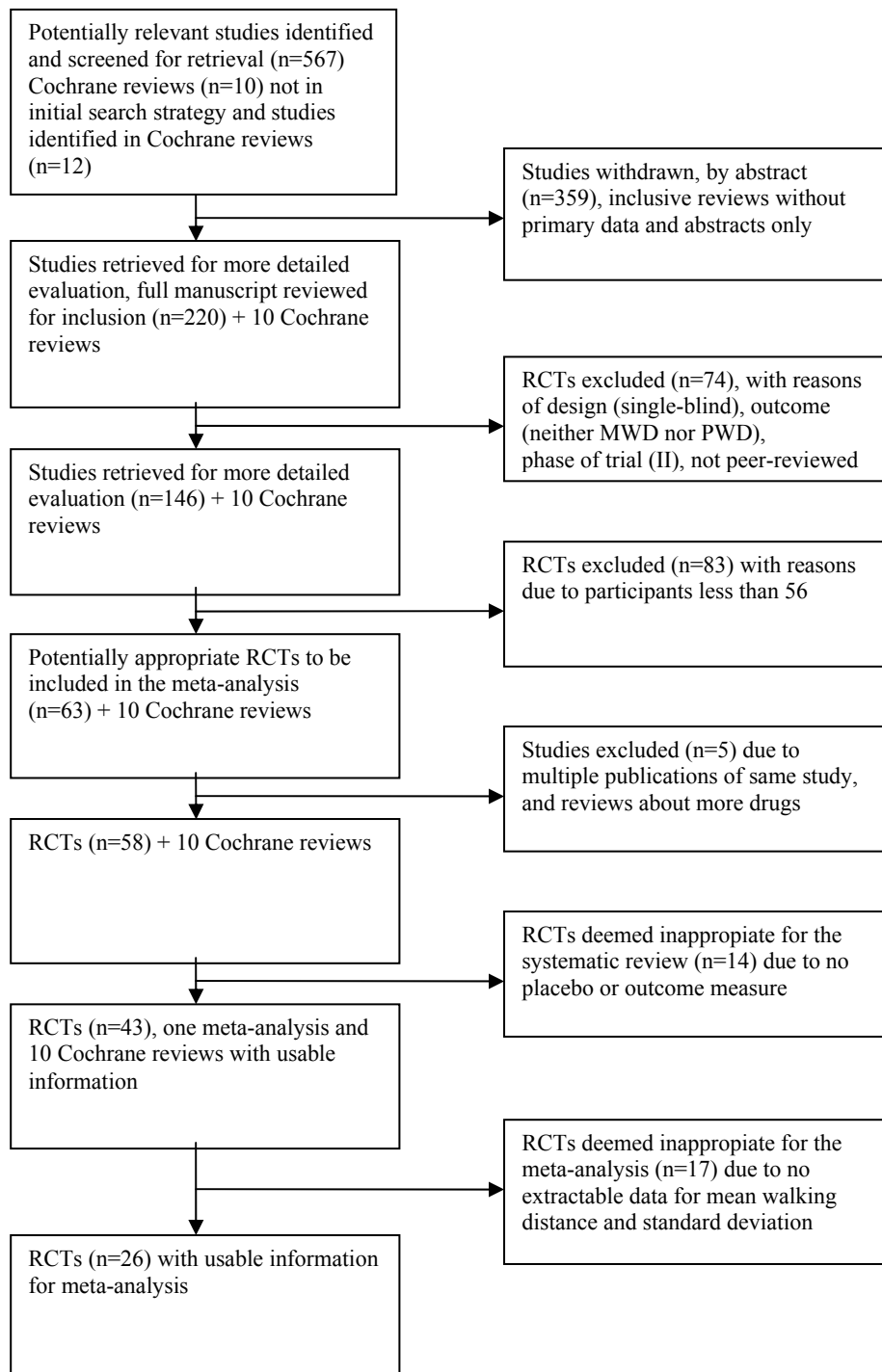
Analyses were carried out using STATA software version 11.0 (StataCorp 200X, College Station Texas, USA), and reported p-values were based on the two-sided alternative hypothesis.

Part 3: Results and discussion

Major findings in study I

The search identified 567 potentially relevant studies and 10 Cochrane reviews from which 12 studies were identified. Figure 7 show the trial flow.

Figure 7. Flow diagram of studies



However, only 220 of the studies were RCTs.

Of these, 74 were excluded due to the design, missing PWD or MWD, phase II study or not being peer reviewed publication, leaving 146 RCTs. Of these more than half had inappropriate sample sizes, other publications turned out to be duplicates and inappropriate information for the meta-analysis. This left only 43 robust studies testing different 23 drugs. Of these, only 26 reported data on mean walking distance with standard deviation suitable for data extraction for meta-analysis.

Previous Cochrane reviews have been performed concerning two vasodilators (bufloamedil and naftidrofuryl), two phosphodiesterase inhibitors (cilostazol and pentoxifylline), lipid lowering agents, prostaglandins, steroid sex hormones, diet supplementation with Omega-3-fatty acids, Vitamin E, and garlic as well as several meta-analyses with exercise. The Cochrane reviews identified the first 6 mentioned drugs with significant effect on walking distance (Table 2).

Table 2. Results from Cochrane reviews (CR) and meta-analyses on walking distance

Author	Drug (doses (mg))	Trials	N total	PWD, WMD* (95% CI)	MWD, WMD † (95% CI) ‡	Walking test Outcome
CR 2008, de Backer	Naftidrofuryl (200x3)	6	1083	48.44 (35.94, 60.95)		1.4 (1.19, 1.6) §
	(200x3)	6	968			
CR 2008, de Backer	Bufloamedil	2	127	76.92 (32.32, 121.52)	112.64 (27.73,197.54)	
CR 2007, Robless	Cilostazol (100x2)	8	1827	31.1 (21.4, 40.9)	49.7 (24.23, 75.18)	
	(50x2)	3	716	41.3 (7.1, 89.7)	31.9 (12.35, 51.53)	
	(150x2)	1	104	15.7 (-9.6, 41.0)	51.3 (-13.92,117.52)	
Meta-a.,1996, Hood	Pentoxifylline	11	612	29.4 (13, 45.9)		
CR 2007, Reiter	Prostanoids	5	438	21.34 (20.79, 21.89)	25.69 (25.16, 26.22)	
CR 2007, Aung	Lipid-lowering agents	7	317	89.76 (30.05, 149.47)	152 (32.1, 271.8)	
		3	95	7.16 (-25.47, 40.39)	23 (-69.14, 23.14)	
CR 2003, Lip	Anti-hypertensive drugs	2		8 (-30.66, 46.66)	-46 (-169.24, 77.24)	122 m vs. 53 m, MWD, n.s.
CR 2001, Cosmi	Anticoagulative drugs	3		66.6 (-2.3, 135.5)		¶
CR 2001, Price	Steroid sex hormones	3	109			¶
CR 1998, Kleijnen	Vitamin E	5	265			207 m vs. 203 m, PWD, n.s
CR 1997, Jepsen	Garlic	1	78			
Exercise						
Review 2007, Wind	Supervised exercise vs. standard care			81.29 (35.45, 127.14)	155.79 (80.84, 230.74)	
				143.81 (5.81, 281.81)	250.4 (192.35, 308.45)	
	All	15	761	94.65 (54.78, 134.52)	171.75(106.7, 236.8)	
CR 2008, Watson	Exercise/usual care	10	250	82.2 (71.7, 92.7)	113.2 (94.96, 131.43)	
CR 2007, Bendermacher	Supervised exercise vs. unsupervised exercise	8	319			PWD: 0.83 ** (0.44, 1.21) MWD: 0.89 (0.57, 1.21)

* PWD: pain-free walking distance (m), WMD: weighted mean difference (m)

† MWD: maximum walking distance (m), WMD: weighted mean difference (m)

‡ CI: confidence interval (m)

§ Relative improvement ratio

|| n.s.: difference not significant

¶ Different tests

** Overall effect size (6 months)

The characteristics of studies included in the systematic review are presented in table 3.

Table 3. Study characteristics

Author	Drug (doses)	N Drug	N Placebo	Follow up (months)	Treadmill test Protocol *	Walking test †	Quality of life ‡
Hiatt	Avasimibe (3)	337	105	12	3.2km/h,>2min:2%	n.s. §	n.s.
Wilson	L-arginine	66	67	6	Graded	n.s.	n.s.
Mohler	Atorvastatin (2)	240	114	12	Graded	n.s. MWD	n.s.
Antonicelli	ca-heparin	101	100	18	2.6km/h,>1min:4km/h	n.s. PWD	
Beebe	Cilostazol (2)	346	170	6	Graded	s.	s.
Dawson 98	Cilostazol	52	25	4	Graded	s.	s.
Dawson do	cil./pentoxifylline	227	239	6	Graded	s.	
Elam	Cilostazol	95	94	3	Graded	s.	
Money	Cilostazol	119	120	4	Graded	s.	
Strandness	cilostazol	265	129	6	Graded	s.	s.
Regensteiner	Cilostazol (2)	1061	740	6	3.2km/h,0%	s.	s.
Gresele	Cloricromene	81	78	6	3km/h,10%	n.s.	n.s.
Violi	Defibrotide	104	101	12		s.	
Guldager	EDTA	80	79	6		n.s.	n.s.
Hiatt	Hydroxytryptamine (3)	326	113	6	Graded	n.s.	n.s.
Messa	heparan sulfate	110	107	6	3km/h,10%	n.s.	s.
Creager	Iloprost/pentoxifylline	346	84	6	Graded	n.s.	n.s.
Tønnesen	Indobufen	154	148	6	3.2km/h,8%	s.	
Kiff	inositol nicotinate	40	40	3	var.speed,10%	n.s. MWD	
Nenci	Mesoglycan	120	122	5	3km/h,10%	n.s. PWD	
Clyne	Naftidrofuryl	48	45	6	3km/h,0%	n.s. <60 years	
Adhoue	Naftidrofuryl	64	54	6	3km/h,10%	s.	
Kieffer	Naftidrofuryl	89	92	6	3.2km/h,12,5%	s.	
Adhoue	Naftidrofuryl	52	42	6	3km/h,10%	s.	
Lindgärde	Pentoxifylline	76	74	6	3.2km/h,12,5%	s.	
Sanctis	Pentoxifylline	60	60	12	3km/h,12%	n.s. MWD	
Belcaro	Pentoxifylline	30	30	6	3km/h,12%	s.	
Cesarone	Pentoxifylline	100	100	9	3km/h,12%	s.	
Rudofsky	Pentoxifylline	88	88	3 weeks	3km/h,12,5%	s.	
Porter	Pentoxifylline	42	40	6	3.2km/h,7degrees	s.	
Brass	Phosphodiesterase (2)	256	130	6	Graded	s.	s.
Castano	Policosanol	27	29	1.5	3km/h,10%	s.	
Hiatt	propionyl-L-carnitine	82	73	6	Graded	s.	
Virgolini	Prostacyclin	54	54	1	2km/h,7.5degrees	s.	
Diehm	Prostaglandin	106	102	3	3km/h,12%	s.	
Lievre	Prostaglandin	42	41	3	3.2km/h,3,2%	n.s. MWD	
Mohler	Prostaglandin	385	377	0	3km/h,10%	n.s.	n.s.
Lièvre	prostaglandin	209	213	6	3km/h,10%	s.	s.
Mondillo	Simvastatin	43	43	6	3km/h12%	s.	
Aronow	Simvastatin	31	29	12	3km/h 12%	s.	
Mohler	Atorvastatin (2)	240	114	6	Graded	n.s. MWD	n.s.
Coccheri	Sulodexide	143	143	7	3km/h,10%	s.	s.
Arcan	Ticlopidine	83	86	6	3.2km/h,10%	s.	

* Graded: treadmill test at 3.2km/h, 0% followed by a 3.5% increase every 3 minutes

† PWD= pain-free walking distance, MWD= maximal walking distance

‡ Quality of life: measured by either Short form 36, Walking Impairment Questionnaire or both

§ n.s.: not significant

|| s. : statistically significant difference between drug and placebo, p<0.05

The tested drugs suitable for meta-analysis are shown in table 4.

The drugs were classified as:

antiplatelet agents (n=5), Calcium chelator (n=1), Serotonin receptor antagonist (n=1), lipid lowering agents (n=4), Phosphodiesterase inhibitors (n=4), prostaglandins (n=5), Proteoglycans (n=4), and vasodilators (n=2).

Table 4. Mean values of walking distances (PWD and MWD in m).

Author	Antiplatelets	N drug	PWD mean (SD)	MWD mean (SD)	N placebo	PWD mean (SD)	MWD mean (SD)	ΔMWD*
Arcan	Ticlopidine	83	194 (65)	236 (70)	86	123 (50)	170 (40)	39%
Gresele	Cloricromene	81	244 (122)	336 (182)	78	164.4 (116)	309 (145)	9%
Nenci	Mesoglycan	120	156 (124)	298 (234)	122	143 (120)	238 (202)	25%
Tönnesen	Indobufen	154	263 (140)	361 (242)	148	153 (87)	263 (140)	37%
Violi	Defibrotide	104		351 (171)	101		321 (141)	9%
Calcium Chelators								
Guldager	EDTA	80	97 (47)	180 (150)	79	119 (93)	194 (127)	-7%
CNS-stimulators								
Hiatt	Hydroxytryptamine	326	231 (136)	246 (136)	113	133 (83)	267 (149)	-8%
Lipid lowering agents								
Mohler	Atorvastatin 80mg	120	189 (31)	235 (36)	114	142 (11)	260 (22)	-10%
	Atorvastatin 10mg	120	187 (27)	316 (36)				22%
Hiatt	Avasimibe 750mg	110	187 (92)	325 (153)	105	165 (92)	288 (146)	13%
	Avasimibe 250mg	113	171 (85)	293 (146)				2%
	Avasimibe 50mg	114	203 (90)	341 (162)				19%
Castano	Policosanol	27	334 (29)	649 (54)	29	138 (22)	238 (28)	173%
Mondillo	Simvastatin	43	190 (38)	230 (45)	43	100 (34)	104 (29)	121%
Aronow	Simvastatin	31		267 (28)	29		184(30)	
Phosphodiesterase inhibitors								
Beebe	Cilostazol 100mg	175	138 (140)	259 (140)	170	96 (140)	175 (140)	48%
	Cilostazol 50mg	171	115 (139)	199 (139)		96 (140)	175 (140)	14%
Dawson 98	Cilostazol 100mg	52	113 (14)	232 (37)	25	85 (14)	152 (24)	52%
Dawson	Cilostazol 100mg	227	218 (149)	350 (209)	239	180 (115)	300 (180)	17%
	Pentoxifylline 400mg	232	202 (139)	308 (183)		180 (115)	300 (180)	3%
Elam	Cilostazol 100mg	95		335 (24)	94		304 (23)	10%
Money	Cilostazol 100mg	119		307 (19)	120		268 (19)	15%
Strandness	cilostazol 100mg	133		195	129		141	39%
	Cilostazol 50 mg	132		167			141	18%
Regensteiner	Cil. (meta-a.) 100mg	730	210 (143)	350 (214)	740	185 (135)	302 (189)	16%
	50mg	281	123 (125)	220 (296)		95 (70)	161 (129)	37%
Lindgärde	Pentoxifylline	76	139 (145)	198 (155)	74	126 (120)	200 (138)	-1%
Sanctis	Pentoxifylline	60		267 (38)	60		188 (19)	42%
Belcaro	Pentoxifylline	30	161 (21)	161 (21)	30	103 (22)	103 (22)	56%
Cesarone	Pentoxifylline	100	166 (220)	287 (340)	100	155 (440)	180 (120)	59%
Rudofsky	Pentoxifylline	88	217 (142)	360 (250)	88	162 (79)	287 (215)	25%
Porter	Pentoxifylline	42	195 (171)	268 (199)	40	180 (152)	250 (172)	7%
Brass	Phosphodiesterase 8	130	156 (82)	333 (111)	130	126 (64)	272 (103)	22%
	4 mg	126	149 (96)	298 (120)				9%
Prostaglandins								
Diehm	Prostaglandin	106	129 (206)	186 (206)	102	107 (212)	161 (192)	16%
Lievre -96	Prostaglandin	42	270 (280)	428 (461)	41	190 (216)	267 (237)	60%
Mohler	Prostaglandin	385	455 (645)	751 (780)	377	487 (695)	795 (847)	-6%
Lièvre	prostaglandin	209	280 (65)	467 (229)	213	245 (71)	378 (240)	24%
Creager	Iloprost	266	170 (88)	321 (171)	84	144 (88)	302 (161)	6%

Proteoglycans								
Messa	heparan sulfate	110	268 (175)	380 (308)	107		352 (294)	8%
Antonicelli	ca-heparin	101	268 (15)	361 (19)	100	237 (15)	321 (19)	12%
Coccheri	Sulodexide	143	224 (9)	344 (16)	143	181 (6)	258 (8)	33%
Wilson	L-arginine	66	110 (11)	314 (25)	67	146 (12)	392 (28)	-20%
Vasodilators								
Clyne	Naftidrofuryl	48	142 (96)		45	137 (79)		
Adhoute	Naftidrofuryl	64	416 (274)		54	313 (170)		
Kieffer	Naftidrofuryl	89	331 (64)	351 (62)	92	208 (63)	231 (63)	52%
Adhoute -90	Naftidrofuryl	52	351 (155)	469 (182)	42	287 (137)	337 (171)	39%
Kieffer	inositol nicotinate	40		197 (126)	40		221 (154)	-11%

* Δ MWD: improvement drug vs. placebo

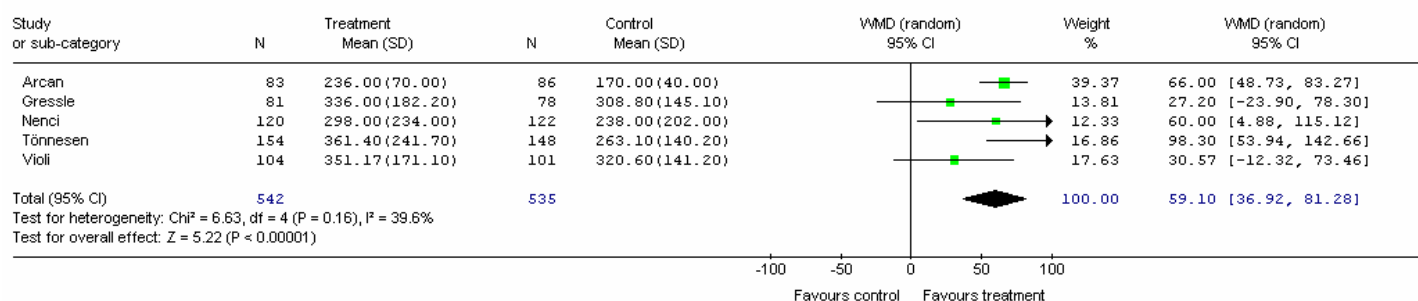
Antiplatelet agents

The meta-analysis included 5 different drugs: ticlopidine, cloricromene, mesoglycan, indobufen, and defibrotide (figure 8). The effect estimate was positive though not statistically significant in all studies. The overall pooled estimate was in favour of treatment, but with a modest increase in MWD of 59 m (95% C.I.: 37 to 81 m).

The most promising on the individual drugs was indobufen with an estimated increase in WMD of 98 m (n=302)⁷³.

Figure 8 Meta-analysis of antiplatelet agents

Review: Medical treatment of IC
 Comparison: 01 Antiplatelets
 Outcome: 01 MWD



Calcium chelator and serotonin receptor antagonist

EDTA chelation therapy for atherosclerosis was studied in one RCT (n=153). The placebo group's improvement was found 1.1-fold better with regard to both PWD and MWD than that of the EDTA treated group⁷⁴.

One study evaluated AT-1015, a serotonin receptor antagonist⁷⁵. The study arm with highest drug dose was prematurely closed due to an excess number of non-fatal myocardial infarctions. In addition, the authors concluded that selective serotonin receptor blockade did not improve exercise tolerance or QoL⁷⁵.

Lipid lowering agents

The studies of lipid lowering agents included 4 different drugs: atorvastatin, simvastatin, policosanol and avasimibe.

Statins

Mohler studied 10 mg and 80 mg of atorvastatin, but failed successful randomization of patients receiving the highest dose of 80 mg because the intervention group had significantly lower walking distance at baseline compared to the controls, so we excluded this group in the meta-analysis. Using 10 mg, the increase in MWD was 56 m (95% C.I.: 52-59) ⁷⁶.

In two studies testing simvastatin (doses of 750, 250, 50 mg) the MWD increased significantly (104 m (95% C.I.:62-147). Aronow showed a 42% increased exercise time after 1 year treatment, and in Mondillo's study an increase was already seen at 3 months and even greater at 6 months with 90 m more PWD and 126 m more MWD in the simvastatin group ^{77;78}.

Policosanol

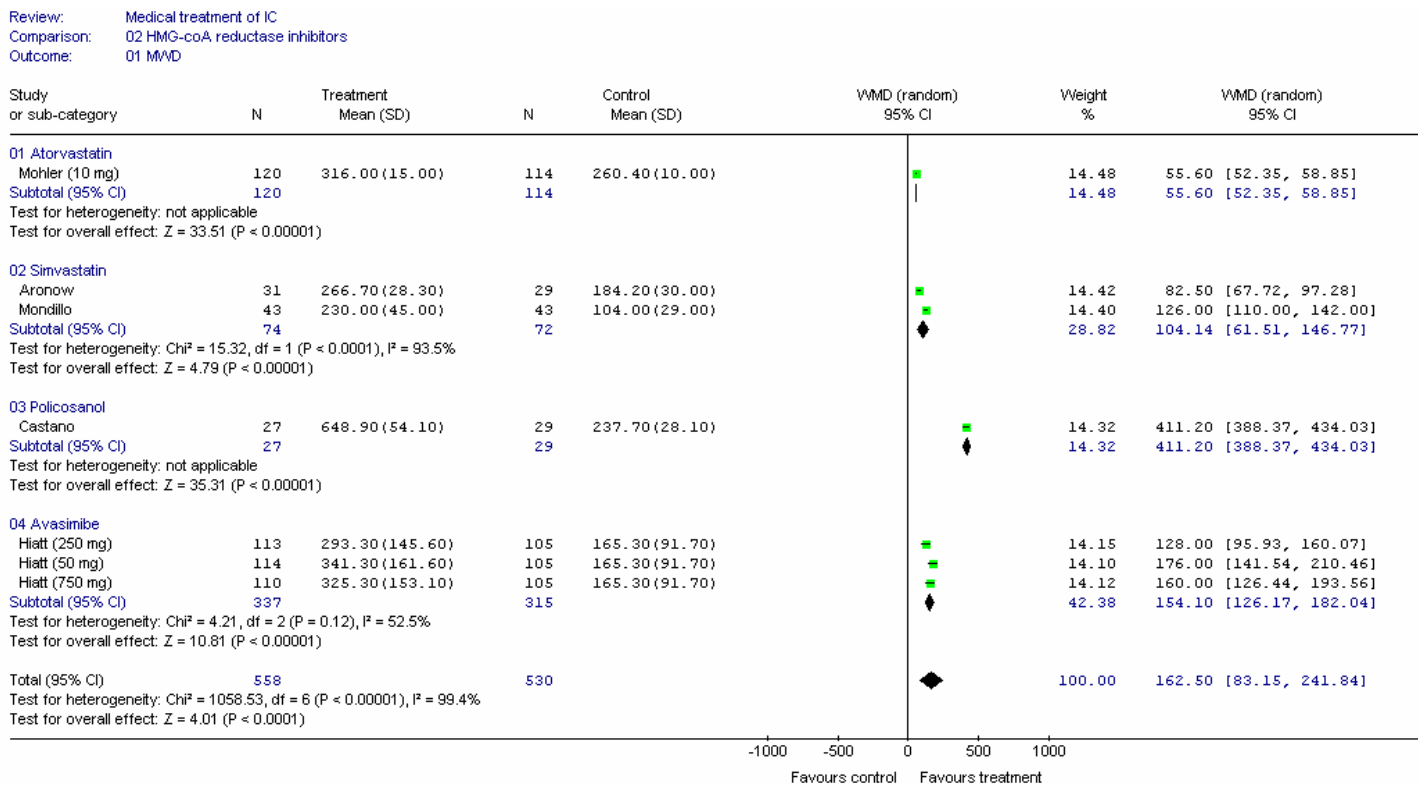
In a 2 year follow up study, policosanol showed significant results of PWD, MWD, ABI and subjective assessments. Intervention PWD increased 100 m and MWD 314 m compared to the placebo group ⁷⁹.

Avasimibe

A study testing the inhibitor of acyl coenzyme A-cholesterol acyltransferase, Avasimibe, showed a significant effect upon MWD of 154 m (95% C.I.: 126-182) in the corresponding meta-analysis. The effect estimates of the three individual doses (750, 250, 50 mg) suggest that the lower is the most effective.

The effect estimates favoured lipid lowering agents in all studies and was statistically significant in all but one study. The pooled effect estimate in the present meta-analysis was in favour of intervention with a clinically relevant increase in MWD of 163 m (95 % C.I.: 83-242 m) (Figure 9. Note: The WMD scales are different)

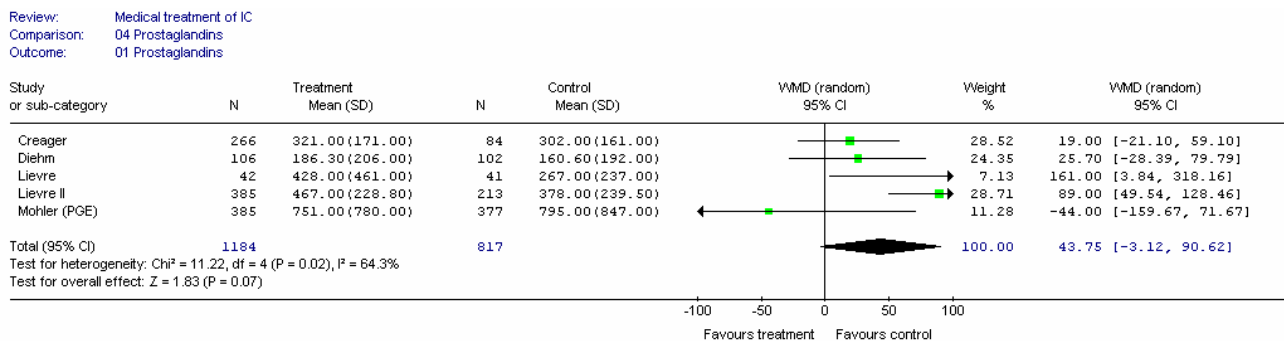
Figure 9. Meta-analysis of lipid-lowering agents.



Prostaglandins

Of 5 studies of prostaglandins 4 were included in the meta-analysis (Figure 10). The pooled estimate was in favour of treatment with a modest increase in MWD of 66 m (95% C.I.: 5-128 m) with a marked signs of heterogeneity between studies.

Figure 10. Meta-analysis of prostaglandins



Phosphodiesterase inhibitors

The studies of phosphodiesterase inhibitors included 3 different drugs: cilostazol, pentoxifylline and phosphodiesterase inhibitor NM-702.

Cilostazol

Studies with cilostazol all showed a significant effect on walking distance. Doses of 50 mg and 100 mg have been examined. MWD increased 36 m (30-41) with 50 mg, but almost twice that, 70 m (47-93), with the 100 mg dose.

The first study to focus on community-based measures of functional status using the Walking Impairment Questionnaire (WIQ) was Regensteiner's, who showed a significant increase in both WIQ, SF-36, and MWD (95 vs. 50 m, 76% vs. 20%) compared to placebo⁸⁰.

Strandness's study, which was not suitable for the meta-analysis, showed only significance with the 100 mg dose (MWD increased 76 m)⁸¹.

Pentoxifyllin

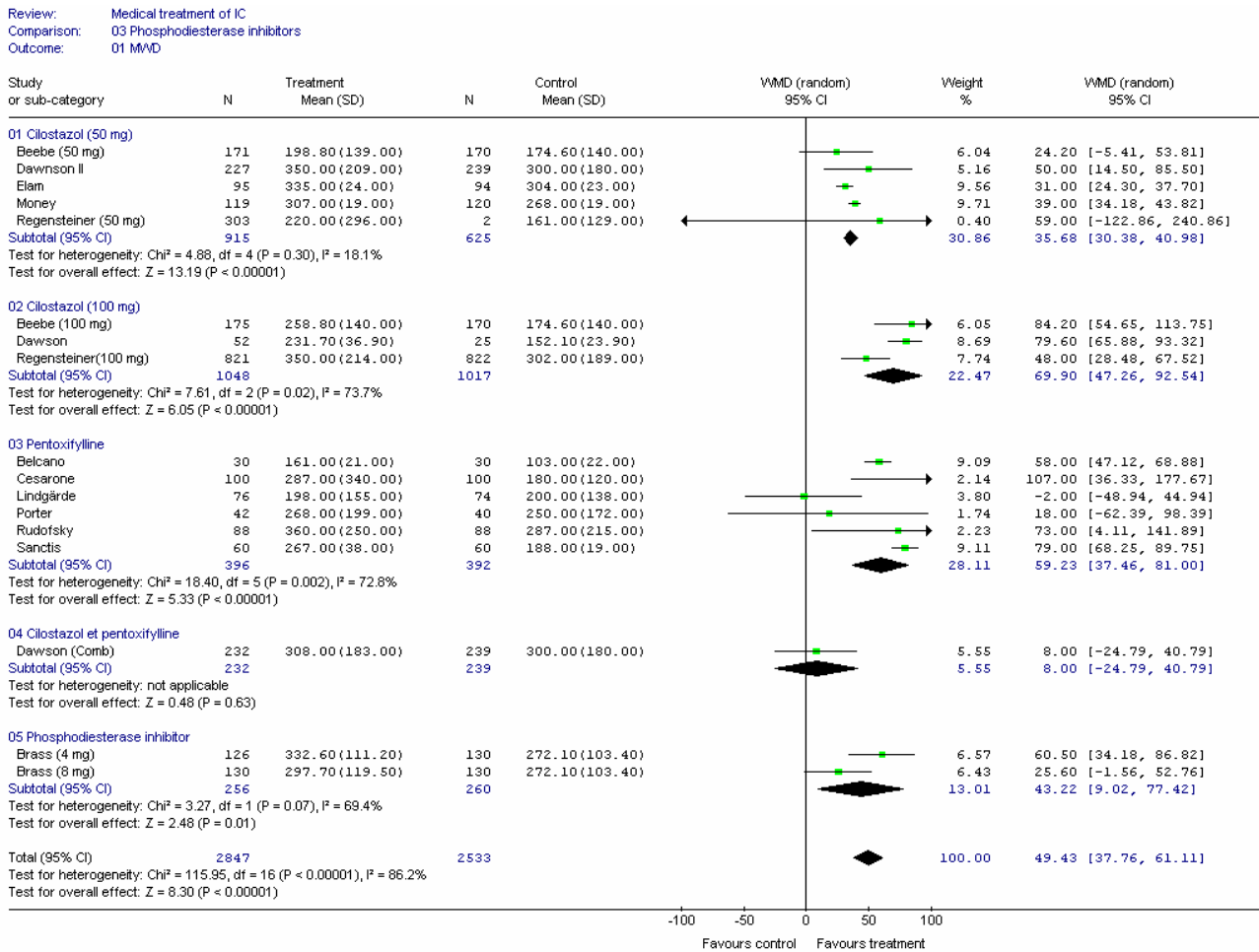
Our meta-analysis of robust studies included 6 studies totalling 788 patients and found a significant increase in MWD for pentoxifyllin in WMD of 59 m (95% C.I.:37-81). The estimated effect varied between -2 to 107 m in the individual studies like doses did (300 to 1600 mg).

Phosphodiesterase inhibitor NM-702

The Phosphodiesterase inhibitor NM-702 has been tested with the doses 4 mg and 8 mg. With 4 mg MWD increased 61 m (34- 87), but only 26 m (-2 - 53) with the 8 mg dose.

The pooled estimate of all robust phosphodiesterase inhibitors trials in the meta-analysis was in favour of treatment with a modest increase in MWD of 49 m (95% C.I.:37-61). (Figure 11)

Figure 11. Meta-analysis of phosphodiesterase inhibitors



Proteoglycans

The studies included 3 different drugs: heparin sulphate, calcium-heparin and sulodexide. The effect estimate was positive in all studies though not statistically significant in all the individual studies. The pooled estimate was in favour of treatment with a modest increase in MWD of 57 m (95% C.I.: 16-97 m). Of the individual drugs the effect estimate pointed to Sulodexide as the most effective with an increase in MWD by 86 m (83-89). (Figure 12).

Vasodilators

Naftidrofuryl

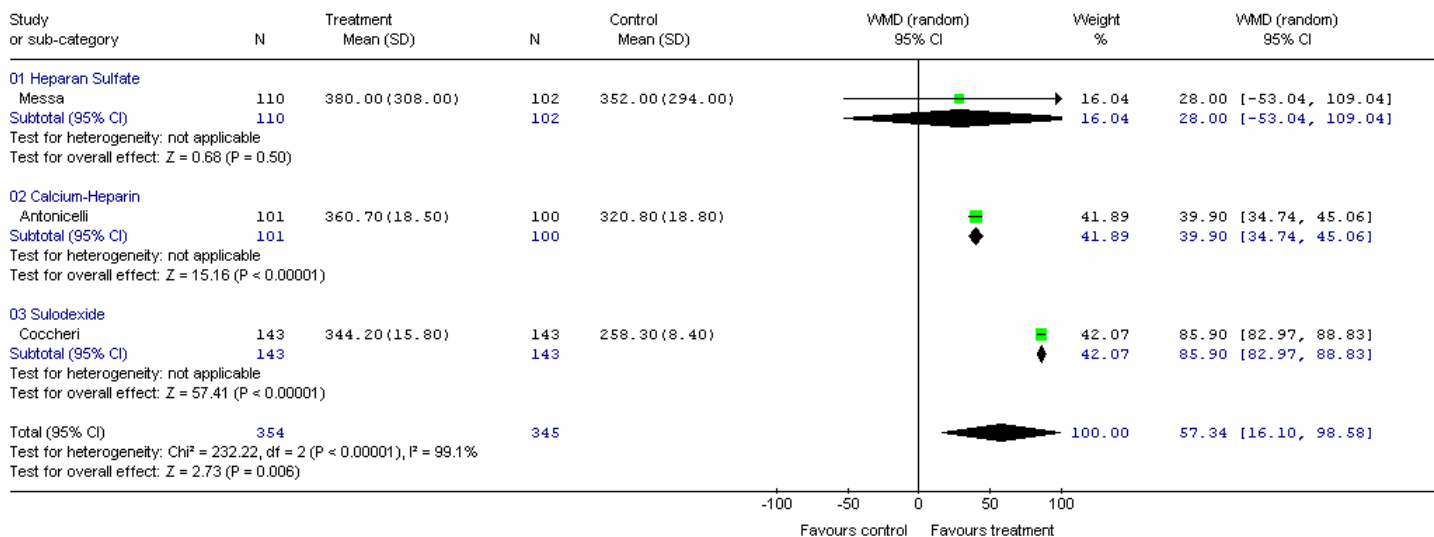
The effect estimate was positive and statistically significant in 3 of 4 studies with naftidrofuryl with effect estimates of 103 to 133 m in the 3 positive studies compared to only 5 m in the non significant study of Clyne. The pooled subtotal effect estimate showed an increase in MWD of 90 m (95% C.I.: 14-166 m) (Figure 12).

Inositol

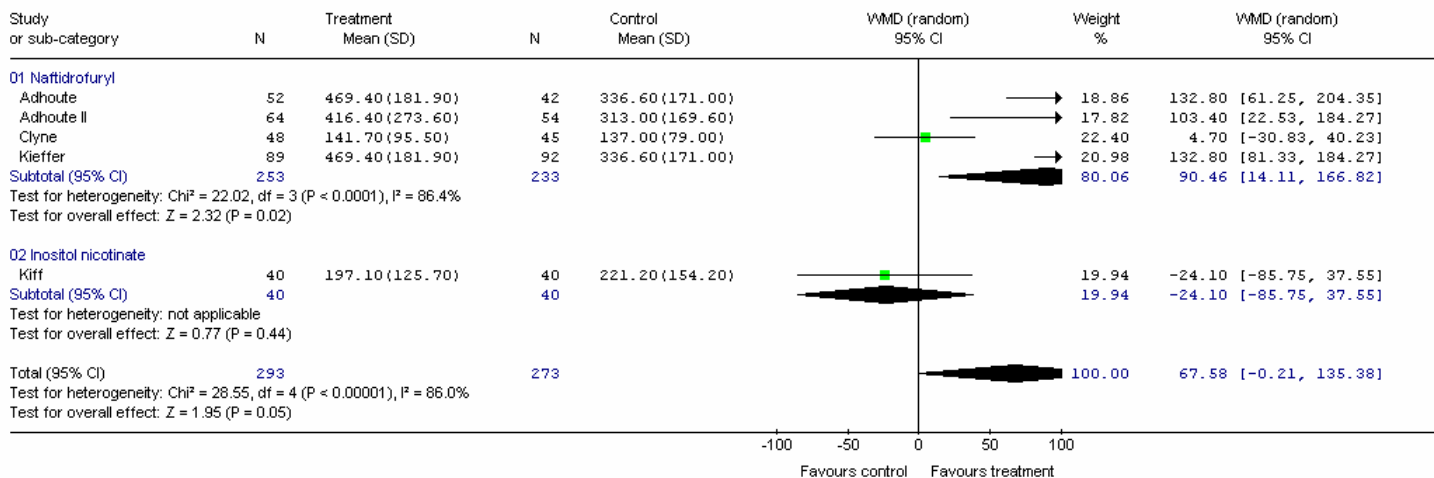
Only one study (n=80) examined 3 months of intervention with Inositol nicotinate and found that the change in MWD was -24 m (-86 – 38). The pooled effect estimate in the present meta-analysis was in favour of vasodilator treatment, but with a modest increase in MWD of 59 m (95 C.I.: 37-81 m).

Figure 12. Meta-analysis of Proteoglycans and vasodilators

Review: Medical treatment of IC
 Comparison: 05 Proteoglycans
 Outcome: 01 MWD



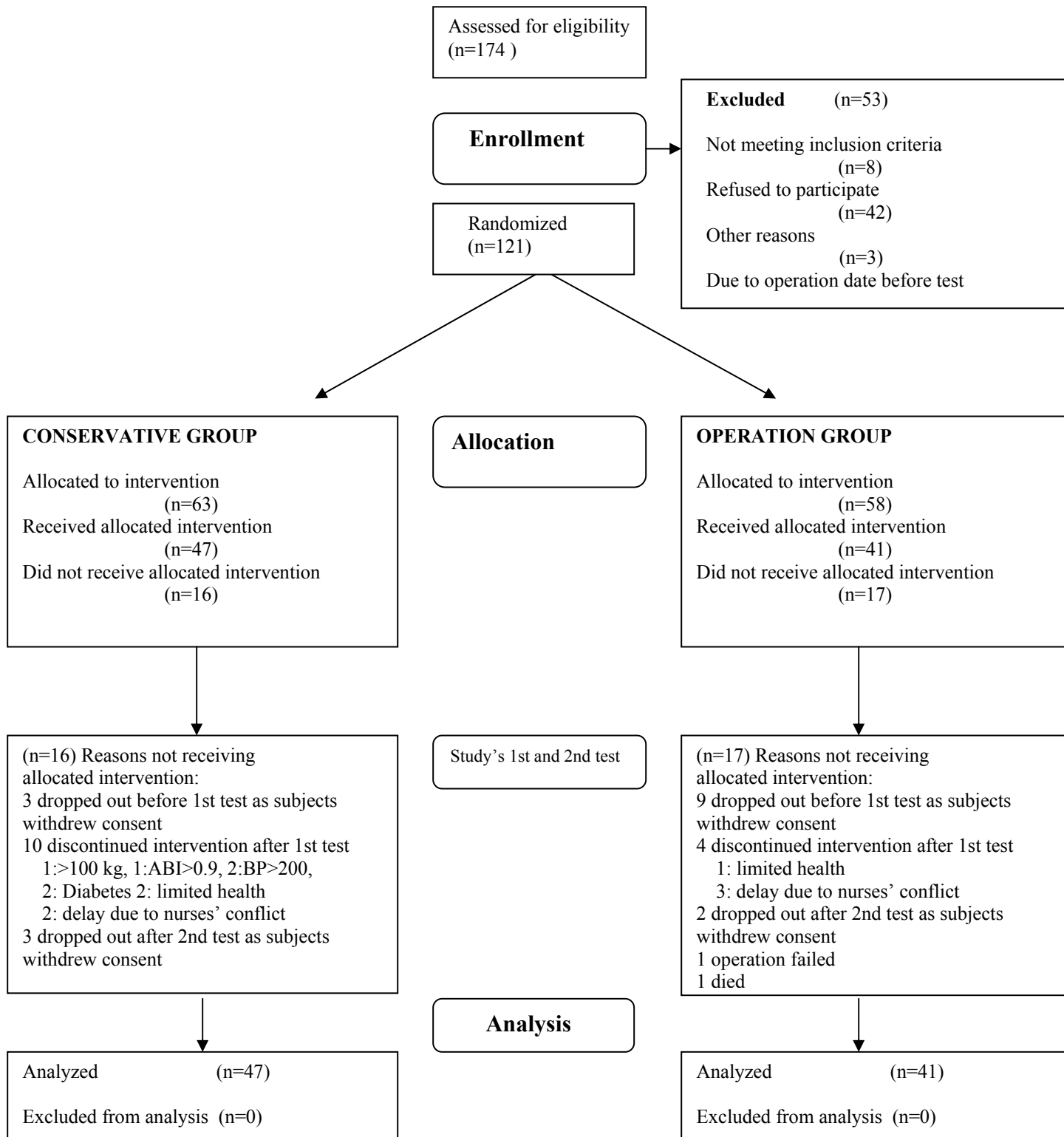
Review: Medical treatment of IC
 Comparison: 06 Vasodilators
 Outcome: 01 MWD



Major findings in study II

Among 174 participants initially assessed for eligibility, 42 declined to participate, 11 were excluded before randomization, and 88 completed first crossover study of whom 47 were conservatively treated and 41 were planned for surgery. Figure 13 describes the flow⁷².

Figure 13. Flow diagram of subjects



Baseline values of all patients are summarized in Table 5. No gender-based or ethnic-based differences were present.

Only three patients had never smoked, 49% were former smokers, and the rest (48%) were still smoking 1–20 cigarettes daily. All but two patients had a daily intake of medicine. Anti-coagulant agents, mainly low dose aspirin were taken by 81 of 88 patients, and 74 received statins.

Caffeine consumption showed a wide variation from no coffee or tea (1) to 25 cups daily. The mean daily intake was 6.5 cups of coffee, corresponding to approximately 650 mg caffeine. The number of years patients had had symptoms of IC varied from 1 to 20 years.

There was no difference between the groups' physical activity. Blood sample analysis showed wide variations, but no significant between-group differences were observed. There was no difference in lactate concentration between the groups (mean:1.09/1.02 mol/l, $p=0.12$) at baseline, but after intervention lactate increased in both groups with a significant difference between the groups (C): mean 1.72 mol/l; (P):1.29 mol/l, $p<0.05$).

Baseline values of PWD and MWD were not different between the two groups ($p>0.05$). Test-retest of walking distances before medication in both tests showed no significant difference (PWD: $p=0.92$; MWD: $p=0.16$).

Table 5. Baseline Characteristics of patients in study II

Variable	All patients N=88	Group CP vs. PC p-value
Mean age, (years)	67.5 (6.9)	0.45
Female/Male (n)	38/50	0.6
Body Mass Index	25.6 (3.7)	0.006
Years with IC	4.8 (4.3)	0.6
Physical activity*	2.5 (0.7)	0.87
Smoking	2.8 (1.2)	0.6
Coffee (cups/day)	6.4 (3.8)	0.52
Brachial pressure	151 (19)	0.45
ABI at rest:	0.53 (0.16)	0.06
Triglycerides †	1.51 (0.84)	0.18
Cholesterol	4.65 (1.06)	0.56
HDL	1.49 (0.43)	0.60
LDL	2.49 (0.98)	0.54

Values are presented as mean (+/- SD)

* Physical activity: 1=<2h/week, 2=2-4h/week, 3=4 h/week, 4>4h/week

† Plasma concentrations of triglycerides, total cholesterol, high density lipoprotein and low density lipoprotein (mmol/l)

Table 6 shows the results after the first crossover study (test 1 and 2).

Primary outcomes

Caffeine increased MWD in the CP group by 4.6% and in the PC group by 53.3%, the difference between the groups was statistically significant ($p=0.0042$). When taking the order of treatment into account (CP and PC), the overall effect estimate was that caffeine increased MWD by 26.7% (95% CI: 12.1 to 43.1) ($p=0.0002$). There was no treatment-period interaction in MWD ($p=0.42$).

No participants had pain before walking the treadmill. Eighty-four percent stopped walking due to strong or unbearable pain (22% score at 4), and 16% stopped due to tiredness.

Caffeine increased PWD by 1.6% for the CP group and by 18.1% in the PC group; a statistically significant difference between the two groups ($p=0.0229$). The overall effect estimate was

20.0% (95%CI: 3.7 to 38.8, p=0.0014). There was no indication of a period-treatment interaction for PWD (p=0.32). Three patients had no onset of pain and the PWD was equal to the MWD.

Secondary outcomes

Compared with placebo, caffeine also significantly increased isometric strength, which rose by 10% (p=0.0049), and sub maximal strength, which rose by 21% (p=0.0036). No indication of period effect (p=0.87, p=0.7) or treatment-period interaction (p=0.4, p=0.97) for strength and endurance measurements were observed.

Postural stability was significantly impaired by caffeine with an overall effect estimate of 22% (p=0.0001) with eyes open and 22% (p=0.0043) with closed eyes. There was no indication of either a period effect (p=0.29) or a treatment-period interaction effect (p=0.47) in the balance tests.

There was no significant effect on psychomotor function (reaction time, p=0.8). None of the three cognitive tests showed significant between-group difference: SDMT, p=0.38; TMT A, p=0.09; and TMT B, p=0.34).

ABI dropped significantly from before to after exercise (mean difference 0.07) with no difference between the treatment groups in either test (p=0.6; p=0.5), respectively.

Table 6. Main results

Outcome	Caffeine Median 95% CI	Placebo Median 95% CI	Mean difference 95% CI	Per cent difference* 95% CI	Caffeine vs. placebo p-value
Maximal walking distance (m)	320 218-465	220 180-230	140 44-236	26.6 12.1-43.0	0.0001
Pain free walking distance (m) †	90 80-120	80 70-101	94.5 29.5-159.5	20.0 3.7-38.8	0.0062
Maximal isometric muscular strength (N)	291.9 267-318	274 243-304	63.4 -23-150	9.8 3.0-17.0	0.0002
Isometric sub maximal strength (s)	34.8 26-40	27.3 22-30	5.68 2.3-9	21.4 1.2-45.7	0.0002
Postural sway ‡					
Velocity moment eyes open (mm ² /sec)	12.5 10-14.4	9.15 7.7-11	3.15 1.06-5.24	22.1 11.7-33.4	0.0007
Velocity moment eyes closed (mm ² /sec)	23 18-30.8	20.6 15.5-20.1		21.8 7.6-37.8	0.0043
Reaction time (ms)	0.53	0.56	-0.01 0.019-0.696		0.16
Cognitive function					
SDMT (s)	320 219-466	220 180-330	140.4 44-236		0.38
Trail A (s)	0.47 0.43-0.49	0.46 0.44-0.51	0.03 -0.2-0.09		0.4
Trail B (s)	1.51 1.4-2.03	1.54 1.4-2.14	-0.07 -0.2-0.04		0.14

* The mean difference calculated from the log transformed data and expressed as per cent difference between caffeine and placebo treatment.

† Three patients had no onset of pain so PWD was equal to MWD

‡ A positive result indicates an enhanced postural sway and thereby a reduced postural stability.

The baseline lactate level was similar prior to both treatments (mean: 1.09/1.02mol/l, p=0.12).

After the treadmill test, the lactate concentration increased, but significantly more during caffeine treatment than during placebo treatment (mean 1.72 mol/l and 1.29 mol/l, respectively, p<0.05).

After 48 hours of caffeine withdrawal, 28% of the patients reported withdrawal symptoms, mainly headache (20%) and tiredness (9%) in at least one of the tests. During treatment, the percentage of patients who had side effects varied from 5% (test 1) to 18% (test 2), but there was no significant between-group difference (p=0.26).

Major findings in study III

Figure 14 describes the flow of patients⁷². Forty-two patients declined to participate, with a mean age (I: 66.8; C: 68.4), ABI at rest (I: 0.53; C: 0.75), part of males (I: 40%; C: 30%).

Eighty-eight patients were included: 47 in C and 41 planned for surgery. After angiography 5 patients were excluded in I leaving 36 in the analysis.

Baseline values are summarized in Table 7 and show no significant between-group differences in physical performance, but in ABI at rest.

Table 7. Baseline characteristics of patients

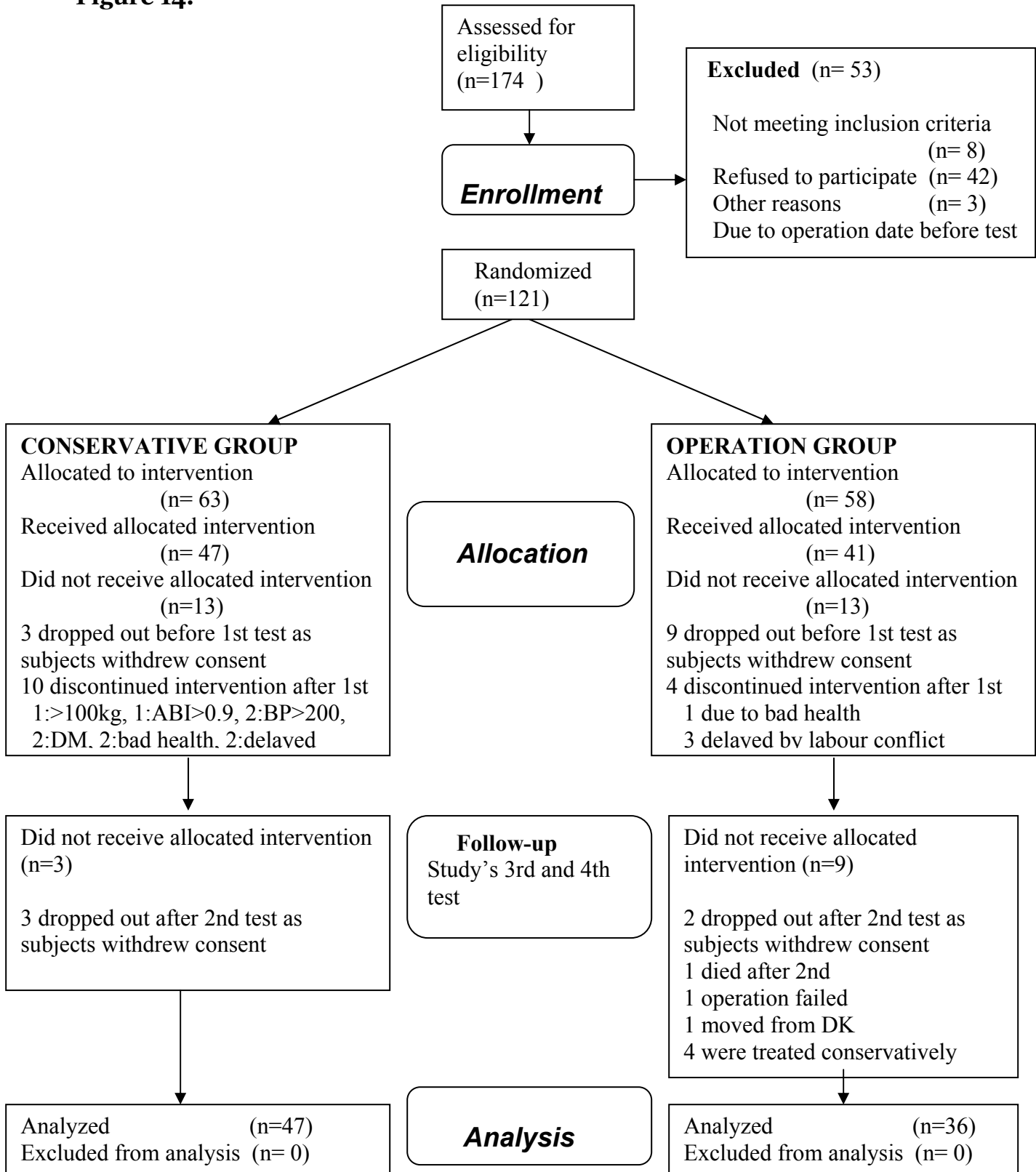
Variable	Conservative N=47	Intervention N=41	p-value
Age (years)	68.0 (6.9)	66.7 (6.9)	0.36
Men (%)	57	56	0.9
BMI	25.2 (3.7)	26.0 (3.6)	0.27
Physical activity (h/week)	2.49 (0.7)	2.47 (0.7)	0.88
Smoking %	49	49	0.87
Former %	51	46	
ABI: at rest	0.58 (0.16)	0.49 (0.15)	0.009
ABI: after exercise	0.48 (0.19)	0.42 (0.16)	0.155
Pulse at rest	70.2 (11.6)	73.0 (13.7)	0.3
Creatinine (umol/l)	75.5 (17.9)	73.7 (23.4)	0.22
Triglycerides *	1.31 (0.53)	1.72 (1.05)	0.15
Cholesterol *	4.65 (1.09)	4.64 (1.03)	0.63
HDL *	1.58 (0.44)	1.38 (0.39)	0.03
LDL *	2.5 (0.97)	2.5 (1.00)	0.95
Years with IC	4.7 (4.3)	4.9 (4.3)	0.8
Pain in leg (%) †	51	63	0.24
Pain in chest (%) †	6	2	0.38
Breathless (%)	45	46	0.88
MWD (m)	316 (3.2)	227 (2.1)	0.12
PWD (m)	126 (3.2)	86 (2.3)	0.09
Max. strength (N)	253 (1.5)	281 (1.5)	0.27
Endurance (sec.)	27 (1.8)	24 (1.8)	0.93

Data are presented in mean +/- (SD)

PWD: pain-free walking distance, MWD: maximal walking distance

* mmol/l, † Pain while perceiving exertion (Yes %)

Figure 14.



Primary outcomes

Mean age was 67 (52-81 years), BMI varied from 17-35, and the physical activity was equally low. Only three patients (I) had never smoked, 53% were former smokers (47% in I).

Anti-coagulant agents were taken by 81 of 88 patients, and 74 received statins. Patients had had symptoms of IC from 1 to 20 years.

After revascularization SF-36' physical function, restriction, and pain increased (52%, 69%, 52%), respectively. Physical component increased 29%, and the overall change in health (12%) was significant. Table 8 show the averaged scores for each dimension of SF-36 and WIQ.

Table 8. Dimensions of SF-36 and WIQ compared pre- and postintervential within and between the two groups.

Questionnaire scores	Conservative	p-value for change*	Intervention	p-value for change* (%)**	C vs. I p-value Baseline Follow-up
	Baseline (SD) Follow-up (SD)		Baseline (SD) Follow-up (SD)		
SF-36 Dimension					
Physical component	41.9 (7.2)	0.41	35.0 (7.6)	0.000	0.000
	43.2 (7.3)		45.3 (7.5)	(29.4)	0.222
Physical function	63.3 (19.2)	0.97	48.5 (17.3)	0.000	0.085
	63.3 (19.2)		73.6 (18.9)	(51.7)	0.332
Physical restriction	61.2 (39.6)	0.15	40.3 (36.5)	0.003	0.169
	72.3 (35.1)		68.1 (38.6)	(68.9)	0.25
Bodily pain	64.6 (19.8)	0.04	49.9 (19.3)	0.000	0.001
	73.4 (21.8)		75.8 (26.7)	(51.9)	0.345
General health	67.9 (18.2)	0.29	63.2 (15.1)	0.114	0.01
	64.2 (16.3)		68.9 (16.4)	(9.0)	0.59
Mental component	54.7 (10.6)	0.70	55.9 (10.3)	0.82	0.75
	55.4 (8.3)		56.4 (8.3)	(0.9)	0.65
Vitality	64.1 (22.2)	0.71	63.7 (18.8)	0.104	0.73
	65.7 (18.4)		71.7 (23.9)	(12.5)	0.69
Social functioning	91.7 (19.9)	0.83	88.4 (18.6)	0.48	0.34
	90.9 (17.6)		91.2 (16.8)	(3.2)	0.42
Emotional restriction	68.1 (47.1)	0.36	63.4 (48.8)	0.27	0.64
	76.6 (42.8)		75.0 (43.9)	(18.2)	0.86
Mental health	81.2 (19.7)	0.69	79.2 (20.1)	0.040	0.56
	82.6 (14.7)		87.5 (13.3)	(10.4)	0.08
Health transition	2.9 (0.15)	0.56	3.05 (0.23)	0.009	0.069
Overall change	2.9 (0.48)		2.69 (0.58)	(11.8)	0.012
WIQ Dimension					
Distance score	53.8 (32.6)	0.08	29.0 (26)	0.0004	0.0002
	57.5 (33)		70.6 (39)	(143.4)	0.09
Speed score	69.1 (43)	0.67	42.8 (42)	0.0004	0.0048
	62.5 (42)		72.9 (42)	(70.3)	0.251
Stair-climbing Score	81.3 (42)	0.388	60.2 (42)	0.017	0.02
	89.6 (48)		73.5 (40)	(22.0)	0.09
Total score	0.68 (0.31)	0.66	0.44 (0.30)	0.0002	0.0002
	0.69 (0.31)		0.72 (0.38)	(63.6)	0.44

Data are presented in mean +/- (SD), * Change from baseline to follow-up, p-value within-group,

** Significant change in percent after revascularization

Only the mental health domain increased in I (p=0.04).

As seen in table 9 the changes in QoL remained highly significant after adjustment for treatment, age, ABI, BMI and smoking as independent variables.

All WIQ dimensions increased in revascularized patients and the between-group differences became non-significant. The distance-score increased 143%, the speed-score 70%, the stair-climbing 22%, and total WIQ 64%.

Table 9. Independent predictors of primary outcomes using multiple regression analysis

	Relative change	95% CI	p-value	Relative change **	95% CI	p-value
	SF-36 physical component			Pain-free walking		
Revascularization	0.305	0.16-0.46	0.000	2.64	1.79-3.78	0.000
Age*	-0.005	-0.015-0.005	0.328	0.98	0.95-1.00	0.026
Smoking*	-0.01	-0.16-0.13	0.85	0.90	0.62-1.28	0.54
ABI	0.318	-0.09-0.73	0.12	4.31	1.57-12.18	0.007
BMI	-0.003	-0.02-0.017	0.77	0.99	0.94-1.04	0.70
	WIQ total score			Maximal walking		
Revascularization	2.09	0.90-3.29	0.001	1.73	1.22-2.44	0.003
Age*	-0.014	-0.09-0.06	0.71	1.00	0.97-1.02	0.84
Smoking*	-0.609	-1.77-0.55	0.29	1.10	0.78-1.52	0.57
ABI	0.746	-2.5-3.9	0.65	4.48	1.75-11.24	0.002
BMI	-0.146	-0.309-0.016	0.07	0.97	0.79-1.52	0.227

ABI: Ankle-brachial index; BMI: Body Mass index; CI: confidence interval

*Age and smoking were entered as continuous variables

** The relative change calculated from the log transformed data

Before walking no participants had pain, 42% stopped walking due to strong or unbearable pain and 23% due to tiredness. The rate of improvement (pain-free on walking test) was 50% compared to 21% (C).

Revascularization significantly increased PWD by 313% (C: 26%), and MWD by 135% (C: 18%). Results of physical performance are shown in table 10.

Results of the multiple regression analysis of the ratio of PWD and MWD showed that the increase in both PWD and MWD associated with revascularization remained highly significant after adjustment for age, ABI, BMI and smoking (Table 9). The ratio for PWD was a factor 2.6 (CI: 1.8-3.8, p=0.000) larger in the revascularized group, and for MWD a factor 1.7 (CI: 1.2-2.4, p=0.001).

A higher baseline ABI was a strong predictor for improvement in both distances with a factor 4.4 (p=0.026; p=0.002). Figure 15 shows that age was also related to PWD with a factor 0.97 for each year (p=0.026).

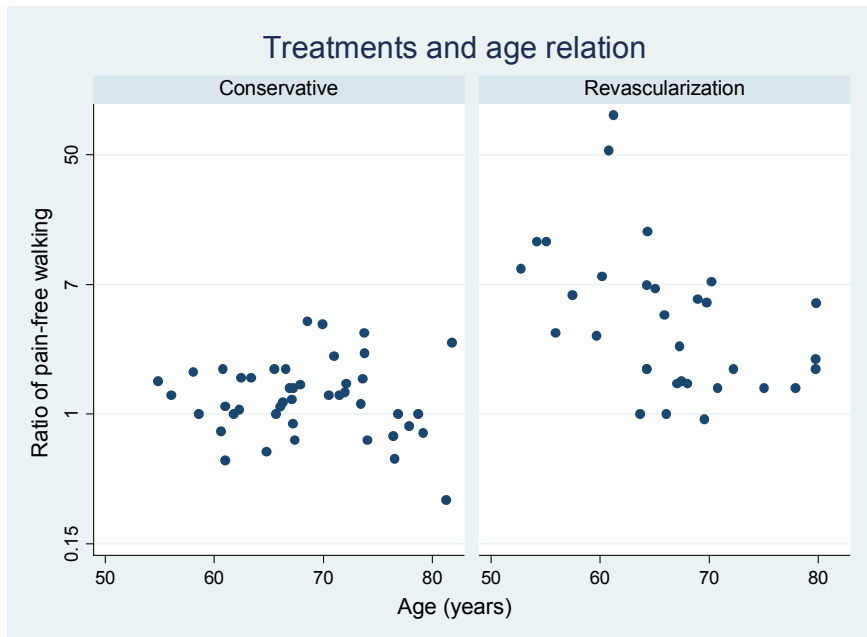
Table 10. Results of primary and secondary objective outcomes in Study III

Variable	Conservative	Difference	Intervention	Difference	C vs. I p-value
	Baseline (SD) Follow-up (SD)	%* (p-value)	Baseline (SD) Follow-up (SD)	%* (p-value)	
MWD (m)	316 (3.18) 380 (3.19)	18 (0.07)	227 (2.08) 533 (2.64)	135 (0.000)	0.0002
PWD (m)	126 (3.16) 152 (3.41)	26 (0.009)	86 (2.34) 343 (3.30)	313 (0.000)	0.000
Maximal isometric muscular strength (N)	253 (1.53) 299 (1.64)	18 (0.0009)	280 (1.54) 298 (1.52)	8 (0.034)	0.17
Isometric sub maximal Strength (s)	27 (1.83) 24 (1.76)	2 (0.77)	24 (1.75) 30.5 (1.57)	28 (0.16)	0.25
ABI at rest	0.575 (0.161) 0.559 (0.151)	† 0.016 (0.000)	0.485 (0.153) 0.680 (0.212)	†-0.175 (0.000)	0.005
ABI after exercise, 3-months	0.475 (0.191) 0.544 (0.168)	†-0.064 (0.0016)	0.420 (0.162) 0.649 (0.239)	†-0.234 (0.0016)	0.032

Continuous variables are given as mean and (SD)

* The mean difference calculated from the log transformed data and expressed as per cent difference between intervention and conservative treatment, p-value within-group

† Indicates the difference before and after intervention, p-value between groups

Figure 15. Relation of pain-free walking distance with treatment and age

Secondary outcomes

Maximal knee extension strength significantly increased in both groups (C: 18%, $p=0.0009$; I: 8%, $p=0.03$), with no between-group difference, and sub maximal endurance showed no significant difference (Table 10).

Revascularization significantly increased ABI at rest (I: 0.68, C: 0.56; $p=0.005$), and after exercise (I: 0.65, C: 0.54; $p=0.027$). In both groups ABI dropped significantly from rest to after exercise.

In the crossover randomized controlled trial, Caffeine treatment significantly increased PWD (31%, p= 0.009) and MWD (21%, p= 0.0045) in the C-group, while the benefit disappeared among those who underwent reconstruction (Table 11).

The level of physical activity was not increased in either group (C: p=0.44; I: p=0.07).

Table 11. Changes in physical performance after caffeine treatment and revascularization (Intervention) and conservative treatment (Conservative)

Variable	Caffeine Mean (SD)	Placebo Mean (SD)	Caffeine vs. placebo p-value	Per cent difference *	Caffeine effect-estimate p-value
Intervention					
MWD (m)	860 (997)	857 (950)	0.65	0.8	0.86
PWD (m)	634 (729)	651 (797)	0.46	0.1	0.97
Conservative					
MWD (m)	784 (855)	664 (831)	0.0046	20.6	0.0045
PWD (m)	425 (657)	374 (748)	0.013	30.9	0.009

* The mean difference calculated from the log transformed data and expressed as per cent difference between caffeine and placebo treatment

Discussion

Discussion of major findings in study I

The meta-analysis is based on only robust and peer-reviewed RCTs in order to avoid the limitations of pooling small trials which may be heterogeneous with regards to outcome measures in meta-analyses and publication biased⁶⁰. We have analysed only primary outcome as the reliability of the findings of a meta-analysis is linked to the number of overall events accrued⁶⁰. We followed the QUOROM recommendations and used well known criteria when assessing the quality of trials. Findings suggest that inclusion of reports of low-quality RCTs in meta-analyses is likely to alter the summary measures of the intervention effect⁸². In addition, the European methodology guidelines for design on clinical investigation of medicinal products for PAD are to be followed⁸³.

Only 43 out of 214 trials fulfilled the criteria for robust quality trials.

Robust significant findings

To improve walking distance phosphodiesterase inhibitors (pentoxifyllin, cilostazol), vasodilator agents (naftidrofuryl, buflomedil), and lipid-lowering agents show robust significant results compared to placebo, but the changes in walking distance are relatively modest. The highest benefit was seen among patients allocated to lipid lowering agents; for the most commonly used agent, Simvastatin, MWD improved with approximately 100 m. Simvastatin and atorvastatin are well established drugs, while avasimibe was suddenly withdrawn by Pfizer in 2003^{77;84}. The clinical improvement comes slowly and patients should expect improvement after months rather than weeks of treatment⁸⁵. Besides statins are advocated to reduce risk of cardiovascular events. These dual benefits of statins re-enforce their importance for patients with PAD.

Policosanol works by inhibiting cholesterol formation in the liver, as well as statin drugs it has been touted as a dietary supplement. However, most studies (>80) are conducted by a single Cuban research group that owns the sugarcane policosanol patent. An independent study published in the Journal of the American Medical Association 2006, found no benefit on cholesterol profile and questions the reliability of the Cuban research group⁸⁶.

Apart from the statins, only two of the drugs (pentoxifylline and cilostazol) have received the US FDA approval⁸⁷. The estimated effect of Pentoxifylline on PWD was only in the order of 60 m. The effect upon QoL has not been evaluated and in all it is difficult to support its widespread use⁸⁷.

Cilostazol received FDA approval in 1999 and has significant antiplatelet, vasodilatory capacity and vascular antiproliferative properties. The estimated effect of 50 mg was 36 m and of 100 mg 70 m. It has a significant positive effect on health-related QoL and lipid-profile, but may have side effects in patients with heart failure^{87;88}.

Vasodilators such as naftidrofuryl and buflomedil were the first class of agents used to treat IC. Naftidrofuryl is a serotonin antagonist and has been available in Europe since the 1980s, but not in the US. The improvement of walking distance is approximately 90 m and in three recent RCTs (n=709) 600 mg Naftidrofuryl daily significantly improved aspects of health-related QoL⁸³.

Buflomedil is also only available in Europe and has small but significant improvement in PWD and MWD⁸⁹. The two studies in the Cochrane review showed significant WMD (77 m,

113 m), but these results are considered to be undermined by publication bias due to other inconclusive and unpublished studies⁸⁹.

In 2000, De-Backer evaluated the role of orally administered vasoactive medication in the management of IC in a meta-analysis of 26 trials with buflomedil, naftidrofuryl and pentoxifylline, and concluded that none of the products had more than marginally positive effect versus placebo⁹⁰. A large international multicenter RCT (n=2078) with mean treatment 33 months investigated buflomedil's contribution to reduction of symptomatic cardiovascular events in patients with PAD, and showed a 26% decrease. They conclude buflomedil should be considered in addition to an antiplatelet agent in PAD patients⁹¹. Our meta-analysis show only a modest increase in MWD, and the Cochrane review about buflomedil concluded it has only a narrow therapeutic range.

Prostaglandins cause vasodilatation and inhibition of platelets aggregation by increasing cAMP. However, daily intravenous administration is not practical for most patients, so it is not recommended. Oral prostacyclin analogues exist, however, beraprost has shown inconsistent results, and iloprost was recently studied in a multicenter RCT with insignificant differences in PWD, MWD, and QoL compared to placebo⁹².

A meta-analysis showed that 9 studies with PGE1 (n=344) increased PWD (107%) and MWD (97%) significantly ($p < 0.01$), and therefore proved the most effective and best tolerated of all prostaglandins evaluated⁹³. Our meta-analysis showed marked signs of heterogeneity, but in two studies by Lievre WMD was increased by 161 m (n=83) and 89 m (n=598) respectively.

Antiplatelet treatment is beneficial in patients with IC for prevention of future cardiovascular events but has not been shown to influence claudication distance^{94;95}. Neither of the antiplatelets we included is commonly used for cardiovascular prevention in PAD patients, whereas clopidogrel is approved by the FDA for the secondary prevention and should always be considered. Clopidogrel which is more costly or low dose aspirin are the preferred first-line therapies⁹⁵.

Limitations

Most studies have MWD and/or PWD as primary outcomes. In the meta-analysis we look at both. Historically, data on PWD are more readily available. In previously published trials often a significant difference was found in PWD but not in MWD. European and/or Trans-Atlantic guidelines on clinical trial methodology in PAD recommend that the change in both distances be assessed because improvement of functional capacity for a patient is assessed by measuring the improvement of walking distance. Our decision to include both is supported by the fact that daily activities are typically governed by the onset of pain and not maximally tolerated discomfort, so findings of improvement in PWD is also important.

Treadmill testing is notoriously associated with wide intra- and inter-individual variation, and the protocols included were either graded or constant, with no or varying slope. It is likely that such heterogeneous ways of testing imply that walking distances are not fully comparable. If the study focuses on longer walking distance (>100m as suggested by the EU agency for IC trials) both test protocols can be used with comparable reliability⁹⁶.

This meta-analysis and all reviews of class Co4A drugs except the Cochrane review concerning naftidrofuryl, were based on published aggregate data, which is the dominant method and a valuable approach for synthesizing efficacy, but it has several drawbacks. We found insufficient information such as missing standard deviation, and confidence interval may be

provided for baseline and final values, but not for the mean change. In all, in spite of attempts to achieve these missing informations from the authors, only 26 of the 43 relevant studies could be included in the meta-analysis.

The overall pooling of data in various drug classifications was performed in order to analyse the value of the physiological target of the drug. However, this strategy risk that a specific drug with benefit are judged without benefit, and vice versa. Consequently, subgroup analyses were performed concerning the specific drug.

Improved MWD is found to correlate with improvement in quality of life instruments like WIQ and SF-36⁸⁰. Unfortunately assessment of QoL is reported in only 23 of 42 trials, but there is correlation with increase in walking distance in all these reports. Cochrane reviews do not report QoL.

Significant placebo-effect is a common feature and can be explained partly by exercise itself or habituation to treadmill testing⁹⁷.

Other potential bias as medications not assessed and can play an important role. Typically IC patients have a daily intake of a range of cardiovascular drugs, anti-hypertensive and lipid-lowering agents. IC patients are at risk as 30-50% has sign of prior stroke on brain imaging. Another limitation is that little attention was paid to baseline risk factors, although it is known that IC is strongly affected by sedentary lifestyle and smoking. All but one study have not taken into account the level of physical activity of the patients recruited, and only four studies evaluated the motivational aspects of exercising. Smoking status and physical activity are therefore not included in the review.

Clinical relevance

Reduction of walking distance reduces the activities of daily living linked with a person's autonomy, influences social life and quality of life. European guidelines suggest at least 30% increase from baseline in both PWD and MWD. In patients with a baseline MWD at 200 m, an improvement of 100 m (+ 50 %) is considered clinically meaningful to help maintain essential activities of daily living⁸⁹. The ability to walk about 70 m without pain enables patients to work in a non-physical job, participate in most social activities and be fairly self-sufficient⁹⁸. The improvements in MWD for the clinically most important drugs in our meta-analysis was for simvastatin (+104 m), atorvastatin (+56 m), cilostazol (+69 m), indobufen (+98 m), and naftidrofuryl (+90 m). Besides their effect upon MWD statins are important in relation to reducing the risk of cardiovascular morbidity and mortality.

Clinical relevance in relation to QoL, is particularly focused on pain and limitations in activities of daily living⁸³, whereas an increase in walking distance may not be subjectively appreciated by the patient.

Discussion of major findings in Study II

This study showed that caffeine improved the physical capacity in patients with moderate IC, as an intake of 6 mg/kg significantly increased MWD 27% and PWD 20%. The maximal strength was increased 10% and knee extension endurance by 21%. Caffeine treatment also impaired the postural stability by 22% both with eyes open and closed, but had no significant effect on reaction times or cognitive test.

The study was adequately powered to demonstrate a clinical relevant difference in physical performance in PAD patients, it followed the good clinical practice rules, was randomized and double-blinded.

Walking

The increase in MWD at 27% and PWD at 20% is like the highest benefit found in a review of robust randomized clinical trials²³; lipid-lowering agents compared to placebo have shown a significant gain in MWD at 130 m while the other agents only improved MWD about 50 m⁹⁹. Studies with vasoactive agents (buflomedil, naftidrofuryl, pentoxifylline) have shown significant results compared to placebo, but moderate improvement of walking distance^{89;90;100}.

The EU-guidelines are >30% increase from baseline in both PWD and MWD. We tested both distances as recommended³. Daily activities are typically governed by the onset of pain but MWD is reportedly best predictor for functional status and quality of life. However, it can be discussed what improvement is needed, a 50% improvement is based on the rationale that above a baseline at 200 m, a value of 50% is at least 100 m, and 300 m is considered as clinically meaningful to help maintain essential activity of daily living¹⁰¹.

The ability to walk about 70 m without pain enables patients to work in a non-physical job, participate in most social activities and be fairly self-sufficient⁹⁸.

Strength

In contrast to our previous study of healthy elderly⁵² we found that maximal knee extension was improved by 10% in the present study, and a similar improvement was reported in a recent study of young people⁵³. A review of 21 studies concludes that caffeine ingestion can be an effective ergogenic aid for endurance athletes when taken before and/or during exercise (>5 minutes performance) in moderate quantities (3-6mg/kg)¹⁰².

In a study 9 young men reported increased alertness and enhanced mood, but no significant effect on muscle strength (bench press), endurance or peak anaerobic power was found with 300 mg caffeine¹⁰³.

The use of caffeine as an ergogenic aid in untrained to moderately trained individuals is questioned¹⁰⁴.

Maybe the acute effects of caffeine are affected by differences in training status and/or the relative intensity of the exercise task? The dose we used was higher (6 mg/kg) and the task in our study was only a short performance and one leg knee extension, and generally patients were untrained. It was performed without the pain, which most patients experience when exercising, and therefore was mostly a positive experience. A study with young subject support our findings, they also used 6mg/kg and knee extension and showed a 10.4% increase in maximal voluntary isometric contraction ($p < 0.01$), and this was attributed to an increase in muscle activation (6.2%, $p = 0.01$)⁵³. The direct effects on single events like involving strength and power is unclear and individual responses also need to be considered.

Endurance

The effects of caffeine found in this study are generally in accordance with reports of the effect of caffeine in both young healthy athletes^{49;53;54} and our own findings in healthy 75 year old citizens¹⁰⁵ where a similar caffeine dose increased the endurance on a bike with 25 %, the ability to hold a sub maximal arm flexion force by 54 % and impaired postural stability. In most studies exercise duration is about 1 h long. In this study the endurance test was of another character, as the sub maximal contraction of knee extension was not a full body performance and did not involve capacity of oxygen consumption for more than a few minutes. The question is, if the increased endurance is due to a physical or rather a psychological effect of caffeine as to increased alertness and reduced tiredness?

Balance

Caffeine treatment also impaired the postural stability with eyes opened and closed, which is in accordance with previous studies in healthy elderly⁵² and healthy students after intake of caffeine¹⁰⁶. The postural sway increase is not a limiting factor; however performance of balance needs attention during treadmill exercise in the elderly. The mechanism is most likely by antagonism of adenosine receptors in the CNS as blockade of these receptors leads to removal of adenosine's inhibitory effect. Thereby neurotransmitters as dopamine are released with an important role in controlling the loco motor function¹⁰⁷. Caffeine increases the tension developed in the muscle at rest which is the case in the standing test of postural stability³⁸.

Reaction time

Caffeine is shown to improve performances such as visual perception, speed of reaction to road signs driving a car³⁸, but this was not seen in the test of reaction time in our study. Maybe the measured test of reaction was more complex, as it combined visual and tactile exercise and therefore caffeine showed no effect, like reported by some authors³⁸.

Caffeine's effects

The selection of 6 mg caffeine/kg bodyweight was hypothesized to have maximum effect in human, and reportedly is was below the former International Olympic Committee's limitation^{41;55}. The hypothesis was based on caffeine's stimulation of lipolysis which spares stored glycogen utilization during moderate intensity exercise and delays fatigue, because the glycogen saved becomes an available energy source for the following phases of exercise. Caffeine also stimulates release of beta-endorphins and hormones (plasma catecholamines) which help during and immediately after to reduce the stress of exercise⁵⁵. The mechanism by which caffeine increases the muscular endurance is not fully understood. A study indicated that coffee contained components that block the endurance effect of caffeine¹⁰⁸. It has also been shown that effects are less pronounced in smokers, by whom half-life of caffeine is 55% shorter³⁸. Besides elderly seem more sensitive to the objective effects of caffeine than the young people. Tolerance to caffeine develop but not to the muscular endurance enhancing effect and the effect on CNS. Therefore caffeine can be useful to improve physical training.

Where exhaustion is reached in the range of a few minutes to two hours, caffeine elevates the muscular endurance³⁶. During 15 minutes exercise 55% of muscle glycogen was saved and onset of fatigue delayed^{49;55}. Sparing of glycogen is possibly not the only way by which caffeine induces this effect. The most supported theory is that caffeine acts by antagonism of the adenosine receptor, and acting this way can lead to elevation of free fatty acids before and during exercise⁴⁹. In the active muscle glycogen sparing does occur though in the first few minutes, where caffeine is associated with elevated plasma epinephrine.

By untrained the resting metabolic rate increase, which can be an extra benefit for those with high BMI, whereas it was discussed whether only well-trained athletes can benefit from the use^{38;55}.

Limitations

Significant placebo-effect is a common feature in IC trials, but the crossover design eliminates it. Baseline characteristics show our study is a typical case-mix of IC patients: mostly male, >60 years, BMI about 25, smoking or former smokers, daily medicine intake and low physical activity.

Our study had an almost equal number of men and women; PAD has traditionally been registered more prevalent in men. A study of gender differences in the risk factor profile showed that the prevalence of PAD did not vary by gender¹⁰⁹. An epidemiologic investigation of 20.000 Norwegians 40-69 year old showed the prevalence increased gradually by age. However, in contrast to previous reports with no difference by sex¹¹⁰. This will be comparable with a Danish population.

McDermott reports in 2003 that women are at a greater risk for a compromise in daily function and quality of life, and therefore prevention is needed particularly for women¹¹¹.

It is well-known that patients with PAD should be candidates for aggressive secondary prevention strategies including antiplatelet, lipid lowering agents and antihypertensive treatment. The aim of this study was not to judge the patients treatment, but we found they generally used a range of other cardiovascular drugs.

The blinding of tester ensures that bias in the conduct of the tests was minimized. The patient was in two following tests in most cases treated by the same tester and standard procedures were ensured.

The blinding could also be compromised due to an increased number of side effects reported with caffeine compared to placebo. This was not the case in the first test. But there was 3-4 fold more patients treated with caffeine than placebo who reported side effects.

During treatment with caffeine there were more participants in both groups noticing side effect in test 2 than in test 1, a 4 fold increase in the caffeine treated group. Why that is could maybe be due to more awareness about signs during the study.

High doses of caffeine can lead to "caffeinism" with polyuria, trembling, dizziness, irregular pulse and ventilation, abdominal discomfort and diarrhoea³⁸. Caffeine seems to induce arm and hand tremors which interfere with performance, and has been described after a single cup of coffee or 300-900 mg of caffeine³⁸. The cognitive test with use of writing with a pencil showed this side effect in some patients.

Withdrawal symptoms reported before both test were mainly headache, and our findings are well-known, as 50% of moderate caffeine users (250-500 mg/day) develop symptoms. Generally symptoms began 12-24 hours after coffee consumption had ceased and reach a peak after 20-48 hours. Withdrawal symptoms were without influence on the measurements of physical capacity.

Other bias

Treadmill, test-retest showed a large intra-subject variability in both groups. Treadmill testing is notoriously associated with wide within-subject and between-subject variation, commonly >50% of patients show >25% deviation in both PWD and MWD.

Between-subject coefficient of variance is reported up to 72%. Spontaneous fluctuation in the distances of at most 25% is regarded as the limit for stable walking distances¹¹². Patients were

only tested once after test medicine. Optimal assessment of baseline MWD was shown to be the graded treadmill test using only one test ¹¹³. However, we used a constant load protocol and no incline to ensure that possibly frail patients to participate. The reliability of graded and constant protocol is reportedly comparable in the entire study population, whereas the graded test is preferable in low PWD and MWD ⁹⁶. As this study focused on longer walking distance (>100 m as suggested by the EU agency for IC trials) we chose the constant load, as both test protocols can be used with comparable reliability ⁹⁶.

Some most usual treadmill test failures are avoided; Hiatt has reported lack of familiarization, poor timing of the test and not pushing the patients to their maximal claudication-limited performance as primary problems seen in clinical trials ¹¹⁴. Patients in this study tried to walk in the treadmill before intervention, the testers trained with a mock treadmill test, we followed a standardised procedure and most patients were tested by the same tester. Whether patients actually walked to their maximum was tried assured by score of pain, but some patients stopped before unbearable pain.

However, whether treadmill testing reflects functional performance is unclear, but in this study a highly controlled although artificial measure compared to usual walking was useful ¹¹⁵. Treadmill walking with a constant speed and load is reportedly the most natural way of walking. However, distances walked in a treadmill can be multiplied by a factor of 3.

ABI was measured and like in other studies we found a significant decrease after exercise with no difference between treatments. A cohort study measured ABI at rest 0.65 and ABI after exercise at 0.45, with 14% of patients (younger, with lower prevalence of smoking and hypertension) having a higher post exercise ABI ¹⁰.

Some studies assessed ABI with the measure of highest systolic pressure in the ankle¹¹⁶.

We used the method based on a previous study, which indicated that the association between ABI and lower-extremity function was strongest when ABI was calculated by averaging the values from both the dorsalis pedis and posterior tibial arteries ⁶⁶. There is not consensus as the higher of the dorsalis pedis and posterior tibial artery pressures is reported used, when a discrepancy was measured ¹⁰. Studies show that the ABI is independently associated with seven diverse, objective measures of lower-extremity function in PAD patients (shorter distance, greater likelihood of stopping in the 6-minute walk test, slower velocity, lower level of physical activity, poorer standing balance, lower summary performance scores ⁶⁶.

Measurement of ABI below 0.9 is related to vascular risk and can be used in a selected population as a simple predictive measure. Prognostic information in PAD may provide the basis for optimal management strategies at an early stage ¹¹⁷. Resting and post exercise ABI values are strong and independent predictors of mortality.

Clinical relevance

Participants had to abstain from caffeine for 48 hours to avoid the influence from their usual caffeine intake. Whether the effect should be the same following a shorter interval without their usual intake of coffee and tea we do not know, and the literature is indeterminate in this respect. If it is necessary to abstain from coffee for a long period this might limit the clinical usefulness of the study as almost all of the participants were regular coffee users and 50% reported abstinence symptoms, as well-known from the literature of moderate caffeine users (250-500 mg/day). Abstaining from caffeine at least 7 days before use will give the greatest chance of optimizing the ergogenic effect¹⁰², other studies recommend 4 days³⁸.

Discussion of major findings in Study III

This study showed revascularization significantly improved QoL, functional status and physical performance. SF-36's physical component score increased by 29% and total WIQ score by 64%. Finally, PWD increased 313%, and MWD 135%, respectively.

The improvements in QoL are described in other studies after PTA, arterial reconstruction or stenting to increase even more compared with exercise^{25;26;28}. Although short-term results favor angioplasty, exercise program patients can have durable comparable benefits if their program was maintained^{11;118}.

Studies with exercise by Regensteiner show increased functional status and QoL comparable to our findings (speed-score by 65%, distance-score by 44%, SF-36' physical function by 67%)¹¹⁹. However, we found no deterioration in QoL in C in contrast to other studies²⁶.

Walking

Our results indicate better improvement in walking after revascularization (PWD 313%, MWD 135%), and clinically relevant, as EU guidelines are >30% increase from baseline in both PWD and MWD³.

Walking distance has been shown to increase with exercise training (PWD 44%-300%, MWD 25% to 440%)¹²⁰, and Cochrane review of exercise concludes that it is a relative inexpensive, low-risk option in IC. However, trials included are small (N: 20-49), and robust cost effectiveness analyses are missing²⁰.

Clearly IC patients should exercise, but there are potential disadvantages like the commitment, the time involved and the cost of supervised therapy.

However the rate of improvement was less than in another study²⁷, some patients (I: 50%, C: 21%) became pain-free in walking testing. Such opportunity to perform more exercise possibly gives a better survival rate after revascularization²⁷.

Strength and weaknesses

The study was adequately powered to demonstrate a clinical relevant difference in physical performance, it followed the good clinical practice rules, and we tested both PWD and MWD as recommended³.

Baseline characteristics of patients recruited are a typical case-mix of IC patients and there were no differences in terms of age and sex. Surveillance bias was eliminated as all were investigated identically.

Although we did not randomize between operation and conservative treatment, the improvement in QoL and functional status suggests that revascularization was efficacious.

However, groups may not be matched, a randomized clinical trial would be needed to properly assess treatments, and we achieved useful outcomes to design such ones.

The participants who declined to attend could reduce the generalizability of our findings.

However, their mean age and ABI at rest were similar to participants, whereas the number of men was less.

This study has several limitations:

First, we were not differing between PTA and open surgical reconstruction. However, they might differ in terms of disease severity. Second, participants were all asked to stop smoking and start exercising, but we only recorded smoking at baseline. Third, five in the I-group were excluded due to postponing of the operation, whereas there was no loss to follow-up in the C-group.

Fourth, a longer-term study would be required to demonstrate whether the beneficial effects are maintained, and to which extent it depends on patency years of the intervention.

Discussion of methods

When participants answered questionnaires the tester was available if needed to avoid mistakes.

SF-36 is a supposedly generic measure of health-related QoL, whereas WIQ is disease-specific, although some argue that WIQ is not a QoL instrument¹²¹. The significant correlation in >80% comparisons between them shows that both can be useful³⁰. WIQ best describes the ambulatory limitation of claudicants which closely relate to QoL, and WIQ more appropriately describes problems caused by flow limitations than does the SF-36¹²².

The treadmill protocol we used with no incline can be performed by a wider spectrum of claudicants, and it was believed to have a better ability to describe true differences in walking^{25;114;114}, whereas a constant load test showed to be more variable⁹⁶. Laboratory test does not necessarily reflect walking ability during daily activities, whereas the WIQ estimates the degree of physical functioning in social life, and the distance-score correlates well with peak walking time¹²³.

Although we found a significant increase after revascularization, ABI is less predictive of leg function in claudicants, and distances are more related with QoL^{18;30;30;35}, except at extremes¹¹.

Implications for clinicians or policymakers

Initially patients must understand that interventions do not cure PAD, and first choice of treatment should be risk-factor management and a patient-specific exercise program¹¹. However, like another study with stent placement in aortoiliac obstruction²⁵, we found revascularization of lesions above the knee significantly improve QoL and functional status. Thereby the patient's possibility to exercise improves and progression can be prevented by reducing overall risk factors.

Patients with poor self-reported physical functioning and a younger age are more likely to be treated invasively¹²⁴. This study found no difference in age but in self-reported QoL between the groups. Clinical decision-making might well include patients' perceived QoL and physical functioning²⁹. Objective and subjective measures of functioning are complementary and combining these direct treatment in a way that meets patients' needs. Our study emphasizes the importance of patient-tailored decision making.

Patients' age is associated with IC and the results showed an association between the effects of revascularization on walking distances. However, a study has shown that neither age nor co morbidity should negatively influence the decision for revascularization⁵.

Part 4: Summary and conclusions

Conclusions

Conclusion study I

This systematic review and meta-analysis of robust RCTs shows that pharmacological management of IC remains to be defined precisely, as of yet there have been very few significant pharmacological breakthroughs in the treatment. Pooled effect estimates revealed modest improvements of walking distance for antiplatelets, vasodilator agents as naftidrofuryl, phosphodiesterase inhibitors as cilostazol and pentoxifylline, prostaglandins and proteoglycans. However, their role remains controversial.

Statins showed the highest benefit in walking and in addition it reduces the risk of cardiovascular morbidity and mortality. However, statins do not cure claudication, and as improvement of walking distance is associated with improved quality of life, consequently, additional trials to develop therapies are needed.

Conclusion study II

This study examined the clinical usefulness of caffeine in patients with IC who abstained from caffeine 48 hours before each session and found an increased physical capacity. Patients with moderate IC significantly increased their walking distance, knee extension strength and endurance.

Conclusion study III

This study showed that in contrast to conservatively treated patients, revascularization in moderate IC improved health-related QoL, functional status and walking distance clinically significantly, and thereby patients' possibility to exercise and prevent progression. Caffeine only increased walking distance in the C-group but clinically significant.

Perspectives

From a medical and socioeconomic point of view, the PAD complication rate and related treatment costs must be reduced to the lowest possible level. PAD is largely unrecognized in medical practice. However, lower-extremity function is an important predictor of future disability, mobility loss, and nursing home placement⁶⁶.

With the aging population and the increasing prevalence with age, there is a growing need for optimal medical management across all specialities treating patients with PAD. Structured regular exercise and smoking cessation is the most important non-pharmacological way to prevent cardiovascular events, improve the walking distance, and quality of life, and has to be complemented with statins and antiplatelet medication.

Although exercise therapy is considered to be of significant benefit to people with IC, almost half of those affected do not undertake any exercise therapy²⁰. In addition, compliance with supervised exercise is poor, and in practice, compliance with smoking cessation and medical treatment is also poor and most people remain symptomatic with consequently impaired quality of life⁹⁴.

Therefore, development of additional therapies are needed, and strict trials should also examine issues of cost and QoL¹²⁵.

A national consensus conference, based on a recent Cochrane review, concluded that health resources should be allocated to prevention, rehabilitation and physical exercise rather than to reimbursement of these products with doubtful efficacy^{100;126}.

So the key questions remain, if particular drugs have synergistic interactions with physical exercise and smoking cessation, and how to educate the patients to take responsibility in their own smoking cessation and rehabilitation with exercise.

We found that caffeine can be a useful mean for PAD patients, allowing them to extend their walking distance and possibly improve their physical training and thereby health-related QoL. The question remains how the benefit of caffeine can be implemented in practice.

Future trials should address the possible benefit of combining training and caffeine and should include cost and quality of life. Identifying therapies that improve functional performance would be of benefit to the growing number of patients with PAD¹¹⁵.

Interventions specifically targeted to physical activity behavior may be necessary to increase daily physical activity in persons with PAD⁸.

A study (N=150) found that revascularization costs more than the generally accepted threshold willingness-to-pay value, which favor supervised exercise¹²⁷, as it is a relative inexpensive, low-risk option¹⁸. But in clinical practice some patients may be good candidates for revascularization and poor candidates for exercise therapy and vice versa¹²⁷. The patency for reconstructions improves due to better materials¹²⁸ and general cardiovascular prevention (statin and patency), and increased preventive attention will improve such patients' survival in the future.

However, long term observation is obviously needed and future topics is to conduct RCTs comparing treatments including costs and quality adjusted living years gained - probably stratified or separated concerning endovascular or open reconstruction. Besides research is needed to recognize how to motivate patients to take responsibility in their own rehabilitation with exercise.

Summary

This thesis originates from the Surgical Research Unit, Regional Hospital Herning and Department of Vascular surgery, Regional Hospital Viborg. The thesis is based on an overview and three papers.

Background for the thesis

Atherosclerosis-related complications account for the largest group of deaths in the Western world, and atherosclerosis in the arteries of the leg, *Peripheral Arterial Disease* (PAD) is prevalent in 2/3 >55 years, especially in smokers. PAD (defined by ankle brachial pressure index <0.9) can be asymptomatic, whilst the most common symptom is intermittent claudicatio (IC): *exertional calf pain caused by walking that resolves with rest*.

PAD increases cardiovascular morbidity and death 2-6 times due to the affection of coronary arteries, and patients' exercise performance is low and detrimental to their quality of life (QoL). Therapy and focus at risk factors is essential, and the options are pharmacological, conservative treatment (exercise and change of life style) or vascular surgery.

Earlier studies of pharmacological treatment has shown limited effect, whilst exercise is documented to be effective and has shown an increase in maximal walking distance up to 150% due to development of collaterals.

Caffeine has several physiological effects which could increase walking performance: CNS stimulation which reduce rate of perceived exertion, vasodilatation of skeletal muscles possibly effect on muscle endurance and reduced fatigue.

To our knowledge there are no studies on caffeine in IC, whereas an increased endurance and decreased experience of exhaustion is shown in healthy elderly.

Besides few objective data are found about the modern operative treatment of IC, and most studies have focused on only walking distances and not QoL in IC patients.

Aims

The first study is a review and meta-analysis of pharmacological management of IC to show effect estimates of improvements of walking distances.

Second we carried out two crossover intervention studies to investigate the effect of caffeine on physical capacity in patients with moderate IC.

The third study's aim was to evaluate effect of revascularisation and conservative treatment on QoL, functional status and physical performance for claudicants. Another aim of this study was to achieve relevant data for planning of robust randomized studies.

The design of the project was a combination of two randomized, double-blind, placebo-controlled crossover studies and a 3-months follow-up. In all 88 participated of whom 41 were revascularized after the first crossover study. Participants were tested in two rounds with one week interval between two tests, and the intervention was intake of caffeine (6 mg/kg) or placebo.

Summary of the results

The review shows that pharmacological management yet remains to be defined precisely. Statins showed the highest benefit and because of their dual benefits their importance for patients with PAD is re-enforced.

Both crossover studies showed that caffeine has potential benefits to improve physical performance: increased walking distance (pain-free and maximal), strength and muscular endurance were significantly improved.

The follow-up study shows that revascularization compared to conservative treatment significantly improved patients' health related QoL, and self-reported and measured walking distances.

Perspectives

Neither revascularization nor statins cure IC, so exercise is necessary and as increased walking distance is associated with QoL, caffeine can be a mean to improve their training possibilities and augment walking distance. How caffeine and training combines in practice and is implemented has to be explored to improve QoL for the growing number of IC patients. Revascularization increases both QoL and walking distance and thereby possibility for training. Measurement of QoL can be taken into account in a more liberal selection of patients to vascular surgery.

Danish summary

Projektet er udført ved Kirurgisk Forskningsafsnit, Regionshospitalet Herning i samarbejde med Karkirurgisk Afdeling, Regionshospitalet Viborg. Afhandlingen er baseret på en sammenfattende redegørelse samt tre artikler.

Baggrund

Åreforsnævring (aterosclerose) er hyppigste dødsårsag i den vestlige verden, og aterosclerose i benenes pulsårer, *Peripheral Arterial Disease* (PAD) kan påvises hos 2/3 >55 år, særligt hos rygere. PAD (defineret ved ankel brachial trykindeks <0,9) kan være asymptomatisk, mens det hyppigste symptom er intermitterent claudicatio (IC): *Reproducerbare smerter i benene udløst af gang, som svinder i hvile.*

PAD øger kardiovaskulær morbiditet og mortalitet 2-6 gange pga. samtidig affektion af koronarkar, og personernes daglige aktivitetsniveau og livskvalitet er oftest nedsat. Behandling er lige så vigtig som ved hjertesygdom og skal fokusere på risikofaktorerne, hvor mulighederne er medicinsk, konservativt (livsstilsændringer og gangtræning) og nogle personer tilbydes kirurgisk rekonstruktion.

Tidligere forsøg på farmakologisk behandling har vist begrænset og tvivlsom effekt. Derimod er gangtræning veldokumenteret og kan øge den maksimale gangdistance op til 150 % pga. iskæmibetinget udvikling af kollaterale arterier.

Koffein har flere biologiske virkningsmekanismer som kunne øge gangdistancen: En CNS-stimulerende effekt, der mindsker træthedsfølelse, vasodilatation i skeletmuskulatur og muligvis direkte muskeleffekt i form af øget styrke og udholdenhed.

Der findes ingen studier af effekten af koffein hos personer med IC, men der er hos raske ældre påvist øget udholdenhed og nedsat træthedsfølelse.

Ligeledes findes der ikke mange objektive data om den moderne operative behandling af IC, og de fleste studier har fokuseret på gangdistance frem for livskvalitet.

Formål

Første studie er en oversigtsartikel og meta-analyse af farmakologisk behandling af IC for at vise effektmål af ændring i gangdistance.

Andet studie er et klinisk interventionsstudie for at undersøge om koffeinindtagelse kan øge gangdistancen, IC patienters fysiske formåen og kognitive funktion.

Tredje studies formål var at undersøge effekten af karkirurgisk operation og konservativ behandling for deltagernes helbredsrelaterede livskvalitet samt gangdistance og fysiske formåen.

Projektets design var to randomiserede, dobbeltblinde, placebokontrollerede overkrydsningsforsøg samt opfølgning efter 3 måneder. I alt deltog 88, hvoraf 41 blev revaskulariseret efter første overkrydsningsforsøg. Deltagerne blev testet i to omgange med en uges interval mellem to test, og interventionen var indtagelse af koffein (6 mg/kg) eller placebo.

Resultater

Meta-analysen viser, at statiner har bedst effekt på gangdistancen og tilmed nedsætter risiko for hjertekarsygdom. Oversigtsartiklen viser, at der af talrige forsøg med farmakologisk behandling ikke har været signifikante fund med klinisk relevans for gangdistance.

Begge overkrydsningsforsøg viser effekt af koffein i fht. øget fysisk formåen: personernes gangdistance (smertefri og maksimal), maksimal styrke og udholdenhed i lårmuskler blev signifikant øget.

Opfølgingsstudiet viser, at revaskularisering i fht. konservativ behandling signifikant forbedrede personernes helbredsrelaterede livskvalitet, selvvaluerede og målte gangdistancer.

Perspektiver

Hverken revaskularisering eller statiner kurerer IC, livslang træning er nødvendig, og idet gangdistance er associeret med øget livskvalitet, kan effekten af koffein være et middel til at muliggøre den nødvendige træning. Hvordan det implementeres, og hvordan koffein og træning kan kombineres i praksis bør undersøges til gavn for den voksende gruppe med IC. Revaskularisering øger både livskvaliteten og gangdistancen og giver derved mulighed for træning. Mål for livskvalitet kan indgå ved en mere liberal selektion af personer til revaskularisering.

Reference List

- (1) Steinberg D. Atherogenesis in perspective: hypercholesterolemia and inflammation as partners in crime. *Nat Med* 2002 Nov;8(11):1211-7.
- (2) Dalager S. General and Site-Specific Feature of Atherosclerosis. 2007. Faculty of Health Sciences University of Aarhus.
- (3) Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;45 Suppl S:S5-67.
- (4) Kuiper N, Gordon M, Roake J, Lewis D. Treating claudication in 5 words (stop smoking and keep walking) is no longer enough: an audit of risk factor management in patients prescribed exercise therapy in New Zealand. *N Z Med J* 2006;119(1231):U1918.
- (5) Kugler CF, Rudofsky G. Do age and comorbidity affect quality of life or PTA-induced quality-of-life improvements in patients with symptomatic pad? *J Endovasc Ther* 2005;12(3):387-93.
- (6) Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001;104(22):2746-53.
- (7) Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;300(2):197-208.
- (8) McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA* 2009;301(2):165-74.
- (9) Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;326(6):381-6.
- (10) Feringa HH, Bax JJ, van W, V, Boersma E, Elhendy A, Schouten O, et al. The long-term prognostic value of the resting and postexercise ankle-brachial index. *Arch Intern Med* 2006;166(5):529-35.

- (11) Beebe HG. Intermittent claudication: effective medical management of a common circulatory problem. *Am J Cardiol* 2001;87(12A):14D-8D.
- (12) Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, Rodgers A, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;361(9359):717-25.
- (13) Regensteiner JG, Stewart KJ. Established and evolving medical therapies for claudication in patients with peripheral arterial disease. *Nat Clin Pract Cardiovasc Med* 2006;3(11):604-10.
- (14) Erb W. Über das "intermittierende Hinken" und andere nervöse Störungen in Folge von Gefäßerkrankungen. *13 Dtsch Z Nervenheilkunde*, 1-76. 1898.
- (15) Larsen OA, Lassen NA. Effect of daily muscular exercise in patients with intermittent claudication. *Lancet* 1966;2(7473):1093-6.
- (16) Wang J, Zhou S, Bronks R, Graham J, Myers S. Supervised exercise training combined with ginkgo biloba treatment for patients with peripheral arterial disease. *Clin Rehabil* 2007;21(7):579-86.
- (17) Tan KH, Cotterrell D, Sykes K, Sissons GR, de CL, Edwards PR. Exercise training for claudicants: changes in blood flow, cardiorespiratory status, metabolic functions, blood rheology and lipid profile. *Eur J Vasc Endovasc Surg* 2000;20(1):72-8.
- (18) Izquierdo-Porrera AM, Gardner AW, Powell CC, Katzel LI. Effects of exercise rehabilitation on cardiovascular risk factors in older patients with peripheral arterial occlusive disease. *J Vasc Surg* 2000;31(4):670-7.
- (19) Lumsden AB, Rice TW. Medical management of peripheral arterial disease: a therapeutic algorithm. *J Endovasc Ther* 2006;13 Suppl 2:II19-II29.
- (20) Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2008;(4):CD000990.
- (21) Connors MS, Money SR. Can claudication be improved with medication? *Semin Vasc Surg* 2002;15(4):237-44.

- (22) **Girolami B, Bernardi E, Prins MH, Ten Cate JW, Hettiarachchi R, Prandoni P, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. Arch Intern Med 1999;159(4):337-45.**
- (23) **Momsen AH, Jensen MB, Norager CB, Madsen MR, Vestersgaard-Andersen TB, Lindholt JS. Drug therapy for improving walking distance in intermittent claudication. A systematic review and meta-analysis of robust randomized controlled studies. Eur J Vasc Endovasc Surg 2009; 38(4):463-474.**
- (24) **Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee-summary of recommendations. J Vasc Interv Radiol 2006;17(9):1383-97.**
- (25) **Murphy TP, Soares GM, Kim HM, Ahn SH, Haas RA. Quality of life and exercise performance after aortoiliac stent placement for claudication. J Vasc Interv Radiol 2005;16(7):947-53.**
- (26) **Pell JP, Lee AJ. Impact of angioplasty and arterial reconstructive surgery on the quality of life of claudicants. The Scottish Vascular Audit Group. Scott Med J 1997;42(2):47-8.**
- (27) **Mori E, Komori K, Kume M, Yamaoka T, Shoji T, Furuyama T, et al. Comparison of the long-term results between surgical and conservative treatment in patients with intermittent claudication. Surgery 2002;131(1 Suppl):S269-S274.**
- (28) **Bosch JL, van der GY, Hunink MG. Health-related quality of life after angioplasty and stent placement in patients with iliac artery occlusive disease: results of a randomized controlled clinical trial. The Dutch Iliac Stent Trial Study Group. Circulation 1999;99(24):3155-60.**
- (29) **Aquarius AE, Denollet J, Hamming JF, Breek JC, De VJ. Impaired health status and invasive treatment in peripheral arterial disease: a prospective 1-year follow-up study. J Vasc Surg 2005;41(3):436-42.**
- (30) **Izquierdo-Porrera AM, Gardner AW, Bradham DD, Montgomery PS, Sorkin JD, Powell CC, et al. Relationship between objective measures of peripheral arterial disease severity to self-reported quality of life in older adults with intermittent claudication. J Vasc Surg 2005;41(4):625-30.**

- (31) Mehta T, Venkata SA, Chetter I, McCollum P. Assessing the validity and responsiveness of disease-specific quality of life instruments in intermittent claudication. *Eur J Vasc Endovasc Surg* 2006;31(1):46-52.
- (32) McDermott MM, Liu K, Guralnik JM, Martin GJ, Criqui MH, Greenland P. Measurement of walking endurance and walking velocity with questionnaire: validation of the walking impairment questionnaire in men and women with peripheral arterial disease. *J Vasc Surg* 1998;28(6):1072-81.
- (33) Coyne KS, Margolis MK, Gilchrist KA, Grandy SP, Hiatt WR, Ratchford A, et al. Evaluating effects of method of administration on Walking Impairment Questionnaire. *J Vasc Surg* 2003;38(2):296-304.
- (34) Verspaget M, Nicolai SP, Kruidenier LM, Welten RJ, Prins MH, Teijink JA. Validation of the Dutch version of the Walking Impairment Questionnaire. *Eur J Vasc Endovasc Surg* 2009;37(1):56-61.
- (35) Myers SA, Johanning JM, Stergiou N, Lynch TG, Longo GM, Pipinos II. Claudication distances and the Walking Impairment Questionnaire best describe the ambulatory limitations in patients with symptomatic peripheral arterial disease. *J Vasc Surg* 2008;47(3):550-5.
- (36) Graham TE. Caffeine and exercise: metabolism, endurance and performance. *Sports Med* 2001;31(11):785-807.
- (37) Bangsbo J, Jacobsen K, Nordberg N, Christensen NJ, Graham T. Acute and habitual caffeine ingestion and metabolic responses to steady-state exercise. *J Appl Physiol* 1992;72(4):1297-303.
- (38) Nehlig A, Daval JL, Debry G. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Res Brain Res Rev* 1992;17(2):139-70.
- (39) Spigset O. Pharmacological effects of caffeine. *Tidsskr Nor Laegeforen* 2001;121:3080-1.
- (40) Lindinger MI, Graham TE, Spriet LL. Caffeine attenuates the exercise-induced increase in plasma [K⁺] in humans. *J Appl Physiol* 1993;74(3):1149-55.
- (41) Jackman M, Wendling P, Friars D, Graham TE. Metabolic catecholamine, and endurance responses to caffeine during intense exercise. *J Appl Physiol* 1996;81(4):1658-63.

- (42) **Graham TE, Sathasivam P, Rowland M, Marko N, Greer F, Battram D. Caffeine ingestion elevates plasma insulin response in humans during an oral glucose tolerance test. Can J Physiol Pharmacol 2001;79(7):559-65.**
- (43) **Anselme F, Collomp K, Mercier B, Ahmaidi S, Prefaut C. Caffeine increases maximal anaerobic power and blood lactate concentration. Eur J Appl Physiol Occup Physiol 1992;65(2):188-91.**
- (44) **Poehlman ET, LaChance P, Tremblay A, Nadeau A, Dussault J, Theriault G, et al. The effect of prior exercise and caffeine ingestion on metabolic rate and hormones in young adult males. Can J Physiol Pharmacol 1989;67(1):10-6.**
- (45) **Christensen T. Postoperative fatigue. Dan Med Bull 1995;42(4):314-22.**
- (46) **Tverdal A, Stensvold I, Solvoll K, Foss OP, Lund-Larsen P, Bjartveit K. Coffee consumption and death from coronary heart disease in middle aged Norwegian men and women. BMJ 1990;300(6724):566-9.**
- (47) **Silletta MG, Marfisi R, Levantesi G, Boccanelli A, Chieffo C, Franzosi M, et al. Coffee consumption and risk of cardiovascular events after acute myocardial infarction: results from the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione trial. Circulation 2007;116(25):2944-51.**
- (48) **Lopez-Garcia E, Rodriguez-Artalejo F, Rexrode KM, Logroscino G, Hu FB, van Dam RM. Coffee Consumption and Risk of Stroke in Women. Circulation 2009;119(8):1116-23.**
- (49) **Graham TE, Spriet LL. Metabolic, catecholamine, and exercise performance responses to various doses of caffeine. J Appl Physiol 1995;78(3):867-74.**
- (50) **Falk B, Burstein R, Ashkenazi I, Spilberg O, Alter J, Zylber-Katz E, et al. The effect of caffeine ingestion on physical performance after prolonged exercise. Eur J Appl Physiol Occup Physiol 1989;59(3):168-73.**
- (51) **Laurent D, Schneider KE, Prusaczyk WK, Franklin C, Vogel SM, Krssak M, et al. Effects of caffeine on muscle glycogen utilization and the neuroendocrine axis during exercise. J Clin Endocrinol Metab 2000;85(6):2170-5.**
- (52) **Norager CB, Jensen MB, Madsen MR, Laurberg S. Caffeine improves endurance in 75-yr-old citizens: a randomized, double-blind, placebo-controlled, crossover study. J Appl Physiol 2005;99(6):2302-6.**

- (53) Park ND, Maresca RD, McKibans KI, Morgan DR, Allen TS, Warren GL. Caffeines enhancement of maximal voluntary strength and activation in uninjured but not injured muscle. *Int J Sport Nutr Exerc Metab* 2008;18(6):639-52.
- (54) Graham TE. Caffeine, coffee and ephedrine: impact on exercise performance and metabolism. *Can J Appl Physiol* 2001;26 Suppl:S103-S119.
- (55) Ryu S, Choi SK, Joung SS, Suh H, Cha YS, Lee S, et al. Caffeine as a lipolytic food component increases endurance performance in rats and athletes. *J Nutr Sci Vitaminol (Tokyo)* 2001;47(2):139-46.
- (56) Regensteiner JG, Hiatt WR. Current medical therapies for patients with peripheral arterial disease: a critical review. *Am J Med* 2002;112(1):49-57.
- (57) Carrero JJ, Grimble RF. Does nutrition have a role in peripheral vascular disease? *Br J Nutr* 2006;95(2):217-29.
- (58) Karmisholt K, Gotzsche PC. Physical activity for secondary prevention of disease. Systematic reviews of randomised clinical trials. *Dan Med Bull* 2005;52(2):90-4.
- (59) Momsen AH, Jensen BJ, Norager CB, Madsen MR, Vestersgaard-Andersen T, Lindholt JS. Caffeine improves walking distance in patients with intermittent claudication. A randomized, double-blind, placebo-controlled crossover study. *Arch Inter Med* 2009; Under review.
- (60) Farkouh ME, Fuster V. Meta-analysis of small trials: proceed with caution. *Nat Clin Pract Nephrol* 2008;4(3):115.
- (61) Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the Quality of Reports of Meta-Analyses of Randomised Controlled Trials: The QUOROM Statement. *Onkologie* 2000;23(6):597-602.
- (62) Berglund B, Eklund B. Reproducibility of treadmill exercise in patients with intermittent claudication. *Clin Physiol* 1981;1(3):253-6.
- (63) Perakyla T, Tikkanen H, von KJ, Lepantalo M. Poor reproducibility of exercise test in assessment of claudication. *Clin Physiol* 1998;18(3):187-93.
- (64) Altstaedt HO, Berzewski B, Breddin HK, Brockhaus W, Bruhn HD, Cachovan M, et al. Treatment of patients with peripheral arterial occlusive disease Fontaine stage IV with

intravenous iloprost and PGE1: a randomized open controlled study. Prostaglandins Leukot Essent Fatty Acids 1993;49(2):573-8.

- (65) Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1-12.**

- (66) McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. Ann Intern Med 2002;136(12):873-83.**

- (67) Coll AM, Ameen JR, Mead D. Postoperative pain assessment tools in day surgery: literature review. J Adv Nurs 2004;46(2):124-33.**

- (68) Rantanen T, Era P, Heikkinen E. Physical activity and the changes in maximal isometric strength in men and women from the age of 75 to 80 years. J Am Geriatr Soc 1997;45(12):1439-45.**

- (69) Spreen O, Benton AL. Comparative studies of some psychological tests for cerebral damage. J Nerv Ment Dis 1965;140:323-33.**

- (70) Armitage P, Berry G. Statistical methods in medical research. 2nd edition, 222-226. 1987. Blackwell Scientific Publications.**

- (71) Hand DJ, Everitt BS. The Statistical Consultant in Action. 1987. Cambridge University Press.**

- (72) Moher D, Schulz KF, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials 2001. Explore (NY) 2005;1(1):40-5.**

- (73) Tonnesen KH, Albuquerque P, Baitsch G, Gomez AA, Ibanez F, Kester RC, et al. Double-blind, controlled, multicenter study of indobufen versus placebo in patients with intermittent claudication. Int Angiol 1993;12(4):371-7.**

- (74) Guldager B, Jelnes R, Jorgensen SJ, Nielsen JS, Klaerke A, Mogensen K, et al. EDTA treatment of intermittent claudication--a double-blind, placebo-controlled study. J Intern Med 1992;231(3):261-7.**

- (75) Hiatt WR, Hirsch AT, Cooke JP, Olin JW, Brater DC, Creager MA. Randomized trial of AT-1015 for treatment of intermittent claudication. A novel 5-hydroxytryptamine antagonist with no evidence of efficacy. *Vasc Med* 2004;9(1):18-25.
- (76) Mohler-III-ER, Hiatt-WR, Creager-MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation*- 2003;108(12):1481-6.
- (77) Aronow WS. Lipid-lowering therapy in high-risk persons. *Comprehensive-Therapy* 2006;32(2):68-73.
- (78) Mondillo S, Ballo P, Barbati R, Guerrini F, Ammaturo T, Agricola E, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med* 2003;114(5):359-64.
- (79) Castano G, Mas FR, Fernandez L, Gamez R, Illnait J, Fernandez C. A long-term study of policosanol in the treatment of intermittent claudication. *Angiology* 2001;52(2):115-25.
- (80) Regensteiner JG, Ware JE, Jr., McCarthy WJ, Zhang P, Forbes WP, Heckman J, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *J Am Geriatr Soc* 2002;50(12):1939-46.
- (81) Strandness DE, Jr., Dalman RL, Panian S, Rendell MS, Comp PC, Zhang P, et al. Effect of cilostazol in patients with intermittent claudication: a randomized, double-blind, placebo-controlled study. *Vasc Endovascular Surg* 2002;36(2):83-91.
- (82) Moher D, Pham B, Ausejo M, Saenz A, Hood S, Barber GG. Pharmacological management of intermittent claudication: a meta-analysis of randomised trials. *Drugs* 2000;59(5):1057-70.
- (83) Goldsmith DR, Wellington K. Naftidrofuryl: a review of its use in the treatment of intermittent claudication. *Drugs Aging* 2005;22(11):967-77.
- (84) Mohler ER, III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003 ;108(12):1481-6.

- (85) Mohler ER, III, Beebe HG, Salles-Cuhna S, Zimet R, Zhang P, Heckman J, et al. Effects of cilostazol on resting ankle pressures and exercise-induced ischemia in patients with intermittent claudication. *Vasc Med* 2001;6(3):151-6.
- (86) Berthold HK, Unverdorben S, Degenhardt R, Bulitta M, Gouni-Berthold I. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. *JAMA* 2006;295(19):2262-9.
- (87) Mannava K. Current management of peripheral arterial occlusive disease: A review of pharmacologic agents and other interventions. *American-Journal-of-Cardiovascular-Drugs* 2007;7(1):59-66.
- (88) Rowlands TE, Donnelly R. Medical therapy for intermittent claudication. *Eur J Vasc Endovasc Surg* 2007;34(3):314-21.
- (89) de Backer TL, Bogaert M, Vander SR. Buflomedil for intermittent claudication. *Cochrane Database Syst Rev* 2008;(1):CD000988.
- (90) De-Backer-TL, Vander-Stichele-RH, Warie-HH, Bogaert-MG. Oral vasoactive medication in intermittent claudication: Utile or futile? *European-Journal-of-Clinical-Pharmacology* 2000;56(3):199-206.
- (91) Leizorovicz A, Becker F. Oral buflomedil in the prevention of cardiovascular events in patients with peripheral arterial obstructive disease: a randomized, placebo-controlled, 4-year study. *Circulation* 2008;117(6):816-22.
- (92) Creager MA, Pande RL, Hiatt WR. A randomized trial of iloprost in patients with intermittent claudication. *Vasc Med* 2008;13(1):5-13.
- (93) Amendt K. PGE1 and other prostaglandins in the treatment of intermittent claudication: a meta-analysis. *Angiology* 2005;56(4):409-15.
- (94) Robless P, Mikhailidis DP, Stansby GP. Cilostazol for peripheral arterial disease. *Cochrane Database Syst Rev* 2008;(1):CD003748.
- (95) Hiatt WR, Krantz MJ. Masterclass series in peripheral arterial disease. Antiplatelet therapy for peripheral arterial disease and claudication. *Vasc Med* 2006;11(1):55-60.
- (96) Labs KH, Nehler MR, Roessner M, Jaeger KA, Hiatt WR. Reliability of treadmill testing in peripheral arterial disease: a comparison of a constant load with a graded load treadmill protocol. *Vasc Med* 1999;4(4):239-46.

- (97) Money SR, Herd JA, Isaacsohn JL, Davidson M, Cutler B, Heckman J, et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg* 1998;27(2):267-74.
- (98) Hood SC. Management of intermittent claudication with pentoxifylline: Meta-analysis of randomized controlled trials. *Canadian-Medical-Association-Journal* 1996;155(8):1053-9.
- (99) Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev* 2007;(4):CD000123.
- (100) de Backer TL, Vander SR, Leher P, Van BL. Naftidrofuryl for intermittent claudication. *Cochrane Database Syst Rev* 2008;(2):CD001368.
- (101) Walker-GA, Mac-Hannaford-JC. A meta-analysis of randomized, double-blind, placebo-controlled studies of the effect of buflomedil on intermittent claudication. *Fundamental-and-Clinical-Pharmacology* 1995;9(4):387-94.
- (102) Ganio MS, Klau JF, Casa DJ, Armstrong LE, Maresh CM. Effect of caffeine on sport-specific endurance performance: a systematic review. *J Strength Cond Res* 2009;23(1):315-24.
- (103) Williams AD, Cribb PJ, Cooke MB, Hayes A. The effect of ephedra and caffeine on maximal strength and power in resistance-trained athletes. *J Strength Cond Res* 2008;22(2):464-70.
- (104) Beck TW, Housh TJ, Malek MH, Mielke M, Hendrix R. The acute effects of a caffeine-containing supplement on bench press strength and time to running exhaustion. *J Strength Cond Res* 2008;22(5):1654-8.
- (105) Norager CB, Jensen MB, Weimann A, Madsen MR. Metabolic effects of caffeine ingestion and physical work in 75-year old citizens. A randomized, double-blind, placebo-controlled, cross-over study. *Clin Endocrinol (Oxf)* 2006;65(2):223-8.
- (106) Franks HM, Hagedorn H, Hensley VR, Hensley WJ, Starmer GA. The effect of caffeine on human performance, alone and in combination with ethanol. *Psychopharmacologia* 1975;45(2):177-81.
- (107) Sattin A, Rall TW. The effect of adenosine and adenine nucleotides on the cyclic adenosine 3, 5-phosphate content of guinea pig cerebral cortex slices. *Mol Pharmacol* 1970;6:13-23.

- (108) **Graham TE, Hibbert E, Sathasivam P. Metabolic and exercise endurance effects of coffee and caffeine ingestion. J Appl Physiol 1998;85(3):883-9.**
- (109) **Collins TC, Suarez-Almazor M, Bush RL, Petersen NJ. Gender and peripheral arterial disease. J Am Board Fam Med 2006;19(2):132-40.**
- (110) **Jensen SA, Vatten LJ, Romundstad PR, Myhre HO. The prevalence of intermittent claudication. Sex-related differences have been eliminated. Eur J Vasc Endovasc Surg 2003;25(3):209-12.**
- (111) **Collins TC, Suarez-Almazor M, Bush RL, Petersen NJ. Gender and peripheral arterial disease. J Am Board Fam Med 2006;19(2):132-40.**
- (112) **Cachovan M, Rogatti W, Woltering F, Creutzig A, Diehm C, Heidrich H, et al. Randomized reliability study evaluating constant-load and graded-exercise treadmill test for intermittent claudication. Angiology 1999;50(3):193-200.**
- (113) **Brass EP, Jiao J, Hiatt W. Optimal assessment of baseline treadmill walking performance in claudication clinical trials. Vasc Med 2007;12(2):97-103.**
- (114) **Hiatt WR, Cox L, Greenwalt M, Griffin A, Schechter C. Quality of the assessment of primary and secondary endpoints in claudication and critical leg ischemia trials. Vasc Med 2005;10(3):207-13.**
- (115) **McDermott MM, Ades PA, Dyer A, Guralnik JM, Kibbe M, Criqui MH. Corridor-based functional performance measures correlate better with physical activity during daily life than treadmill measures in persons with peripheral arterial disease. J Vasc Surg 2008;48(5):1231-7, 1237.**
- (116) **Bendermacher BL, Willigendael EM, Nicolai SP, Kruidenier LM, Welten RJ, Hendriks E, et al. Supervised exercise therapy for intermittent claudication in a community-based setting is as effective as clinic-based. J Vasc Surg 2007;45(6):1192-6.**
- (117) **Feringa HH, Bax JJ, Hoeks S, van W, V, Elhendy A, Karagiannis S, et al. A prognostic risk index for long-term mortality in patients with peripheral arterial disease. Arch Intern Med 2007;167(22):2482-9.**
- (118) **Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. Eur J Vasc Endovasc Surg 1996;11(4):409-13.**

- (119) Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. *Angiology* 1997;48(4):291-300.
- (120) Regensteiner JG, Gardner A, Hiatt WR. Exercise testing and exercise rehabilitation for patients with peripheral arterial disease: status in 1997. *Vasc Med* 1997;2(2):147-55.
- (121) Mehta T, Venkata SA, Chetter I, McCollum P. Disease-specific quality of life assessment in intermittent claudication: review. *Eur J Vasc Endovasc Surg* 2003;25(3):202-8.
- (122) de VM, Ouwendijk R, Kessels AG, de Haan MW, Flobbe K, Hunink MG, et al. Comparison of generic and disease-specific questionnaires for the assessment of quality of life in patients with peripheral arterial disease. *J Vasc Surg* 2005;41(2):261-8.
- (123) Regensteiner JG. Exercise in the treatment of claudication: assessment and treatment of functional impairment. *Vasc Med* 1997;2(3):238-42.
- (124) Breek JC, De VJ, van Heck GL, van Berge Henegouwen DP, Hamming JF. Assessment of disease impact in patients with intermittent claudication: discrepancy between health status and quality of life. *J Vasc Surg* 2005;41(3):443-50.
- (125) Duprez DA. Pharmacological interventions for peripheral artery disease. *Expert-Opinion-on-Pharmacotherapy* 2007;8(10):1465-77.
- (126) Girolami B, Bernardi E, Prins MH, Ten Cate JW, Hettiarachchi R, Prandoni P, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. *Arch Intern Med* 1999;159(4):337-45.
- (127) Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. *J Vasc Surg* 2008;48(6):1472-80.
- (128) Daenens K, Schepers S, Fourneau I, Houthoofd S, Nevelsteen A. Heparin-bonded ePTFE grafts compared with vein grafts in femoropopliteal and femorocrural bypasses: 1- and 2-year results. *J Vasc Surg* 2009;49(5):1210-6.