Chelation therapy for Intermittent Claudication and Coronary Heart Disease

A Birmingham Technology Assessment Group Report

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West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

About InterTASC

West Midlands HTAC is a member of InterTASC which is a national collaboration with three other units who do rapid reviews: the Trent Working Group on Acute Purchasing; the Wessex Institute for Health Research and Development; York Centre for Reviews and Dissemination. The aim of InterTASC is to share the work on reviewing the effectiveness and cost-effectiveness of health care interventions in order to avoid unnecessary duplication and improve the peer reviewing and quality control of reports.

Contributions of Authors

Martin Connock was the main author. He was responsible for the day-to-day management of the report; undertook all searches; designed the protocol, designed and piloted study inclusion and data extraction; undertook assessment of study eligibility, validity and extracted and collated data; liased with external experts and wrote and collated the report.

Jayne Wilson undertook assessment of study eligibility; extracted data; read and edited the manuscript.

Chris Hyde and Fujian Song resolved problems relating statistical analyses, direction of the report and read and edited parts of the manuscript.

Catherine Meads was the project manager and took overall responsibility for the report. She advised on protocol development and all aspects of the report; assisted and advised on writing of the report and provided general statistical advice.

Conflicts of Interest

None.

West Midlands Development and Evaluation Committee Recommendation:

The recommendation for the use of chelation therapy for intermittent claudication and coronary heart disease chelation is:

Not supported

Randomised controlled trials have failed to generate convincing evidence of effectiveness. Only Level III evidence exists to indicate any effectiveness of chelation therapy

Anticipated Expiry Date

Valid until further notice

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Abbreviations and Acronyms

ABI	Ankle/brachial blood pressure index.
ACD	Absolute claudication distance.
ACAM	American College for Advancement in Medicine.
BMI	Body mass index.
CABG	Coronary artery bypass graft.
CHD	Coronary heart disease.
CLI	Critical limb ischaemia.
CRD	Centre for Research and Dissemination.
CT	Chelation therapy.
CVD	Cardiovascular disease.
EBCT	Electron beam computed tomography.
ECG	Electrocardiograph.
EDTA	Ethylenediamine tetraacetic acid.
GP	General practitioner.
IC	Intermittent claudication.
ICD	Intermittent claudication distance.
IVUS	Intra-vascular ultrasound.
MRI	Magnetic resonance imaging.
MWD	Maximum walking distance.
NO	Nitric oxide.
PAD	Peripheral arterial disease.
PFWD	Pain free walking distance.
PTCA	Percutaneous transluminal coronary angioplasty.
QUOROM	Quality of reporting of meta-analyses.
RCT	Randomised controlled trial.
SPECT	Single photon emission computer assisted tomography.
WD	Walking distance.

1. Summary

- Chelation therapy (CT) is a treatment proposed for coronary heart disease (CHD) and intermittent claudication (IC). A course of treatment consists of a series of intravenous infusions of a solution containing the chelating agent EDTA. Each infusion takes about 3 hours and infusions are repeated about twice a week, typically until 20 or 40 infusions have been administered.

- CHD and IC are manifestations of reduced local blood supply due to narrowing of arteries caused by atherosclerosis. CHD is responsible for about 25% of all deaths in the UK. CHD causes severe angina, heart attacks and heart failure. About 5.3% of men and 3.2% of women in the UK suffer from angina. People with IC may experience severe leg pain. Their condition is debilitating and associated with increased risk of death and of non-fatal heart attack and stroke. About 5% of people aged 55 to 74 years suffer from IC but prevalence data is limited. In the West Midlands approximately 200,000 people per year might be candidates for treatment with CT.

- This report examines whether CT is more clinically effective and cost effective than placebo for CHD and IC.

- Electronic data-bases, the Internet and current literature were searched to identify reviews, controlled studies of effectiveness, and economic studies on CT. Predefined eligibility criteria were applied to the recovered literature. Two RCTs for CHD, three RCTs for IC and six reviews of CT were included for analysis. One economic analysis was found but was unobtainable from the British library. Two reviewers independently extracted data.

- For CHD, neither of the two included RCTs showed a statistically significant difference in the primary outcome measures. For IC, all three RCTs were underpowered and one was very small (n=10). This RCT showed a statistically significant difference in favour of CT for the primary outcome measure whereas the other two showed no significant difference. Small effect sizes in favour of CT were observed in some secondary outcome measures.

- The quality of reviews was very variable and their conclusions in some cases extremely polarised. Deriving a consensus opinion on effectiveness from the included reviews could not be justified*.

- The cost of CT ranges from £1330 to £4775 per patient depending on the number of infusions administered. As there was no evidence of clinical effectiveness, a cost utility analysis was not performed.

- Currently there is little objective evidence that CT is effective for CHD or IC. Conversely there is little evidence that CT does harm. In order to establish the true level of effectiveness of CT, large numbers of patients would need to be enrolled in an RCT. This is very unlikely to be carried out.

* This part of the report (pp 37-50) does not assess the effectiveness of CT but examines the validity of other reviews; readers may wish to omit this section if their primary interest is in the effectiveness of the intervention.

2. Introduction

Peripheral arterial disease (PAD) and coronary heart disease (CHD) are arterial diseases with high prevalence in the UK. They are associated with considerable mortality and morbidity, high cost to the NHS and the erosion of quality of life for patients.

Treatment is based on drug therapies that address symptoms or reduce risk factors for vascular disease and on invasive surgical treatments that aim to replace or improve the function of affected arteries. Surgical procedures are costly, technically demanding, not always successful, and often require repetition. A non-invasive or less invasive therapy that achieved the same outcomes of symptom relief could have wide potential application. There are claims that EDTA-chelation therapy (CT) may represent such a treatment or an alternative to drug therapy. It involves the intravenous infusion over several hours of a solution of ethylenediamine tetraacetic acid (EDTA). A course of treatment consists of 20 or more infusions delivered at a rate of about 2 per week.

This report examines whether CT is effective and cost effective for the treatment of CHD and intermittent claudication caused by PAD.

3. Background and underlying health problem

3.1 Natural History

3.1.1 Arterial disease

Disease of the arterial wall is the major cause of cardiovascular disease (CVD) which includes diseases of the heart and circulatory system and represents the single most important medical condition in the UK.

The artery wall is a complicated structure. Outer layers contain muscle cells and fibres made of collagen. These make the artery elastic so it can resist the pressure of blood and can respond to signals that control diameter and the vessel's capacity to carry blood. The innermost lining is the endothelium that separates the rest of the arterial tissue from the blood. It is supplied with nerve endings. In response to nerve signals the endothelium releases nitric oxide (NO) that causes muscle cells in the artery wall to relax and the diameter of the artery to enlarge and a greater quantity of blood to pass along. This is one way in which blood supply can be tailored to meet demand, for example during physical exercise. An unhealthy artery with a damaged wall may be less able to respond in an appropriate way. Breach of the endothelium allows blood to contact collagen with the likelihood of blood clot (thrombus) formation.

Arteries become diseased by local changes in the thickness or strength of the artery wall. When locally weakened the channel may widen and the artery balloon to form an aneurysm. More commonly the wall thickens locally and the artery channel narrows (stenosis). By far the commonest cause of stenosis is atherosclerosis. Complete blockage (occlusion) is most often caused by atherosclerosis plus a thrombus. Narrowing of the channel reduces the supply of oxygenated blood to downstream tissues (ischaemia). Complete arterial blockage with severe ischaemia results in the death of that tissue (infarction).

3.1.2 Atherosclerosis

Atherosclerosis causes more deaths in the UK than any other medical condition.

It is a common and progressive deterioration of arterial structure and function characterized by fatty deposits, termed atheromas or plaques, which build up in the walls of major arteries. Atheroma progression has been classified into five phases on the basis of morphological characteristics.[1] Atheroma starts as a simple fatty streak or series of blobs that barely raise the inner surface of the artery lining. Streaks and blobs consist of living fat-laden cells (foam cells) that accumulate locally just below the endothelium. In westernized populations fatty streaks typically tend to progress insidiously over decades. They gradually form larger plaque structures of more complex composition that represent a serious medical condition.
Plaques are characterized by:-

- their accumulation of extra-cellular fatty deposits (predominantly cholesterol);
- fat-laden dead and dying foam cells;
- the production of collagen fibres;
- the multiplication of smooth muscle cells that may partially or wholly cap the plaque and separate it from the blood flow within the artery;
- their accumulation of calcium deposits (calcium hydroxyapatite).

Plaques and their cellular caps are not stable. Post mortem studies on persons dying from causes other than atherosclerosis indicate that plaques frequently fracture resulting in thrombus formation. This may cause occlusion and consequent infarction.

Calcium ions play an important role in calcification of plaques and also in thrombogenesis. Without bound calcium several proteins of the clotting cascade fail to function. Calcium ions can be removed from these proteins in freshly taken blood samples by use of strong chelating agents (e.g. citrate or EDTA); this will halt the clotting process and keep the blood liquid. The anticoagulant drug Warfarin reduces the calcium binding capacity of clotting proteins and so reduces the blood's clotting ability in an individual.

Several important risk factors for atherosclerosis have been identified. These include:-

- lack of physical activity (20 minute of vigorous activity on <12 occasions in last 4 weeks).
- obesity (BMI >30).
- raised blood pressure (>140/90 mmHg).
- smoking.
- raised blood cholesterol (> 5.2 mmol/l).

It is probable that only about half of the risk factors for atherosclerosis are known and many have yet to be discovered.[2]

3.1.3 Peripheral arterial disease and Coronary heart disease

The vast majority of peripheral arterial disease (PAD) and coronary heart disease (CHD) is caused by atherosclerosis.

PAD affecting the leg involves reduced arterial blood flow to the legs and can be associated with leg pain, compromised walking ability, anxiety and curtailment of normal life activities.[3,4]

Three categories of atherosclerosis-dependent PAD affecting the leg have been distinguished:-

- Asymptomatic PAD.
- Intermittent claudication (IC), the most common symptomatic PAD. Patients experience cramping leg pain induced by walking and relieved by rest. The pain may be in the buttock, thigh, calf or foot or in a combination of these sites. People with IC are only able to walk short distances pain-free.
- Critical limb ischaemia (CLI) is a rare and more severe symptomatic category characterised by rest pain accompanied by ulceration or gangrene. CLI may require limb amputation.

CHD involves reduction or complete obstruction of blood flow through the coronary arteries by narrowing due to atherosclerosis and/or a blood clot (thrombus).

CHD causes:-

- angina; [constricting chest pain occurring on exercise (stable angina); or recurring at rest or with increasing frequency and severity on exertion (unstable angina)].
- heart attack (myocardial infarction).
- irregular heart beat (arrhythmia).
- heart failure.

The impact of angina on a patient's quality of life can range from very mild pain on exertion to severe disabling pain at rest. On the basis of symptom severity, stable and unstable angina have been classified into 4 and 3 subcategories respectively.[5] Untreated CHD is progressive and leads to death from heart attack (acute myocardial infarction) or heart failure. Evidence indicates that when properly managed, progression of CHD can be slowed down and possibly reversed in some people.

3.1.4 Medical examination of arterial tree

3.1.4.1 Physical examination (pulse and blood pressure)

The pulse in an artery can be detected by placing a finger on the artery and feeling the throb beneath (palpation). A weak or missing pulse in an artery indicates the possibility of poor blood flow (arterial insufficiency). Pulse strength measured by palpation has been graded on arbitrary scales (e.g. 0 to 4).[6] Bilateral examination allows comparisons to be made but all such assessments are subjective, and prone to observer variation.[6]

During each pulse of blood flow the pressure exerted on the artery wall rises and then falls. The highest point of this pressure build up (systolic pressure) and the lowest (diastolic pressure) can be measured using a sphygmomanometer. Abnormally high values for systolic and diastolic blood pressure are indicative of someone at risk of arterial disease. Most frequently a superficial artery in the arm (brachial) is examined because it is accessible and the pressure there is similar to that in the aorta.

Measuring systolic pressure in peripheral arteries (e.g. the leg) can provide information on arterial health in various parts of the arterial tree. Low systolic pressure is indicative of

narrowing somewhere above the detection point. Under standard physiological conditions a pressure drop beyond an arterial narrowing is not expected until about 80% of the cross sectional area of the channel has become blocked (occluded). Segmental (upper thigh, above the knee, below the knee, above ankle and toe) blood pressure measurement in the arterial tree of the leg allows detection of narrowing. A ratio of ankle to brachial pressure of ≤ 0.9 is more than 95% -sensitive in detecting angiogram-positive arterial disease in the leg. Lower ankle/brachial blood pressure index (ABI) values are indicative of greater severity of disease.

Arterial disease can result in disturbances in the flow of blood near an abnormality; for example the flow may become turbulent rather than smooth. Turbulence can sometimes be detected as a murmur using a stethoscope.

3.1.4.2 Ultrasonic methods

Because some arteries of interest are small or deep their blood pressure and pulse may be difficult to investigate by sphygmomanometry or palpation. However, these parameters can be investigated using ultrasonic technology.

When used to investigate arteries some of the high frequency ultrasound bursts rebound from moving red blood cells in an artery. By using a Doppler ultrasound instrument the flow of blood in an artery can be detected and its velocity estimated. The values obtained can be compared with 'normal' values and to values measured for the corresponding artery on the other side of the body. The Doppler effect is especially useful for a small artery with a non-palpable pulse. Using an inflatable cuff connected to a pressure gauge together with a Doppler instrument to detect the return of systolic flow it is possible to measure systolic pressure in small peripheral arteries and obtain a value for ABI (see above). Alternatively the return of blood flow can be detected via a strain gauge transducer linked to a pulse volume recorder (plethysmograph).

In the "reactive hyperaemia test" the systolic pressure in an artery. Then the artery is closed with a pressure cuff at a standard pressure (e.g. 50 mm Hg above systolic) for a standard period of time (e.g. 5 minutes). After this the artery is opened again and bood pressure measured after a standard time has elapsed (e.g. 15 secs) after reopening. If the pressure estimated in this second measure is less than the pre-closure value then a "hyperaemic drop" has been observed. This test provides a measure that depends on the elasticity of the vessel wall. The size of the pressure drop is represented as a percentage fall from pre-test pressure.

Details of blood flow and turbulence can be detected using sophisticated ultrasound imaging that also locates and quantifies abnormalities. These "Duplex" instruments may incorporate multiple generator/detector assemblies. They combine Doppler and amplitude information. More recently phase and harmonic details in the echoes have also been incorporated into the analyses. By means of computer technology this information is integrated into real time two-dimensional colour images. These reveal details of the shape and dimensions of the arterial channel (e.g. any narrowing or widening), how the blood flows in the channel (e.g. speed, direction and turbulence characteristics through time), and information about the thickness of the wall. In some investigations the contrast in the image and its definition are enhanced by injecting agents which increase the harmonic content of the echoes.

Using duplex ultrasound the severity and location of stenoses in arteries can be estimated. Information helps in monitoring the progress of disease through time, the evaluation of

applied therapies and is a guide for future angiography used to pinpoint lesions prior to invasive therapies such as arterial bypass surgical interventions.

In the last decade intra-vascular ultrasound techniques (IVUS) have been developed. Instrumentation mounted on the tip of a catheter introduced into the coronary arteries allows sophisticated cross sectional imaging. Information on the lumen, thickness and tissue characteristics of an individual lesion in the artery wall can be obtained.

3.1.4.3 Magnetic Resonance Imaging (MRI)

MRI is a non-invasive method of mapping internal structures. It employs radio-frequency radiation and controlled magnetic fields to produce high quality images. The images depend on the spatial distribution of protons in tissue and on parameters relating to their motion.[7] Imaging of arteries employs procedures that discriminate between stationary tissue and flowing blood. A bolus of contrast agent is administered prior to imaging. MRI is more sensitive than ultrasound but more time consuming to perform and requires sophisticated apparatus of considerable capital cost.

3.1.4.4 Angiography

An even more precise but invasive method for detecting arterial disease involves injecting a chemical that can absorb X-rays (radio-opaque dye). The dye passes along the artery of interest while a beam of X-rays is directed at the site. The resulting X-ray picture (angiogram) illustrates the shape of the blood space within the artery. Abnormal narrowing or widening of the artery channel can be located and quantified and thickening of the artery wall identified and quantified.

3.1.4.5 Computed Tomography

Recent advances in computed tomography instrumentation have allowed ultra-fast imaging (e.g. 10 images / sec) that minimises the motion-interference that is a particular problem in investigating coronary arteries that change position with heart beat. In electron beam computed tomography (EBCT) the X-rays are generated from an electron beam impacting a tungsten target. Multiple images can be combined. Fat deposits and calcium deposits in the artery wall contrast strongly with other arterial tissue and it is possible to locate and quantify calcification. The precision and non-invasiveness of these methods recommend them, however EBCT scanners are more expensive than conventional scanners and are available at relatively few sites.

3.1.4.6 Exercise methods

Poor oxygen supply compromises physiological function. Muscle activity (i.e. exercise) is associated with greatly increased demand for oxygen and so it is especially susceptible to arterial insufficiency. Muscle subjected to arterial insufficiency is less capable of doing work and muscle pain may be experienced.

Isotonic exercise tests have been developed in which an individual performs measurable dynamic exercise on a treadmill or other similar machines. The exercise is designed to stress the muscle system under investigation. The performance of an individual in such tests can

help to diagnose the presence and extent of arterial and cardiac disease and its development through time with or without intervention.

Exercise testing can incorporate measures of oxygen consumption and/or imaging methods such as thallium single photon emission computer assisted tomography (SPECT). For example stress exercise on a treadmill is performed and at some time, usually near the end of the exercise stress, a radioisotope (e.g.^{82}Rhubidium or ^{201}Thallium) is injected into an artery. Scintillation detection of emitted gamma rays allows passage of blood through the myocardium (or other scanned region) to be imaged and monitored. This allows abnormalities in cardiac function to be detected.[8,9]

Arterial insufficiency in heart muscle results in altered contraction characteristics. These can be monitored, recorded and measured using ECG (electrocardiogram) apparatus coupled with heart rate and blood pressure measurements during specified exercise tasks. ST segment depression of the ECG is the most common manifestation of exercise-induced myocardial ischaemia. Vigilance is required during testing so as to minimise untoward events and complications secondary to testing.

3.1.5 Relevant outcome measures

Objective outcome measures frequently used in trials of therapies for PAD and CHD include the following:-

3.1.5.1 Exercise test outcomes

The most commonly employed exercise test involves walking on a treadmill. Usually the treadmill is set at constant speed (typically 1.5 to 2 mph or ~3.6 km/h). In constant-load tests the slope of the treadmill is kept constant during the test (typically 10^{o} or 12^{o}). In graded treadmill testing the slope of the treadmill is gradually increased (typically in increments of 3.5% or 2%) according to a set temporal programme. It has been claimed that constant-load tests are inferior to graded tests in several respects.[10] Graded tests have greater dynamic range so that few if any patients need to be excluded from a study; they show little evidence of improved performance with repeated testing and have a satisfactory within subject coefficient of variance. It is contended that graded tests relate closely to patient walking ability in everyday life and therefore small changes in performance in graded tests are likely to be clinically significant.

Various end points or measures are employed with treadmill tests. Usually the speed of the treadmill and the time spent walking on it are used to calculate the distance walked. For patients with intermittent claudication two outcome measures are made. These are:

- walking distance to the patient's first experience of claudication pain [Intermittent Claudication Distance (ICD); or Pain-free Walking Distance (PFWD)].
- walking distance to maximum level of bearable claudication pain [Absolute Claudication Distance (ACD) or Maximum Walking Distance (MWD)].

It is claimed that MWD and PFWD measured using treadmill exercise tests provide an objective assessment of severity of PAD.

For patients with angina a typical end point is the exercise time or work output to a detected change in the ECG signal (e.g. ST segment depression). A treadmill or bicycle ergometer (which can measure work and/or power output) is typically employed.

The Master's two step test[11-13] uses an apparatus of prescribed dimensions that consists of two ascending steps in tandem with two descending steps. The patient ascends two steps and descends two steps to complete one trip. The patient then turns through 180^{o} and repeats the process to complete a second trip. This activity is repeated until a predetermined number of trips have been completed in the prescribed period of time (usually 3 min). The number of trips to be completed by an individual patient (and therefore the rate of stepping) varies according to age and sex and is determined from a table of standards. The ECG signal is monitored before, during, immediately after, and at 2 and 6 min post-exercise. Used mainly for diagnosis, the test is adaptable as an outcome measure (e.g. Number of trips completed to onset of claudication).

3.1.5.2 Ankle / brachial blood pressure index (ABI)

Change in ABI (ankle/brachial blood pressure index) after treatment is a frequently used outcome measure in investigations of therapeutic interventions for PAD.

3.1.5.3 Angiographic measures

A more rarely employed outcome measure is change in angiograms obtained using X-ray contrast media. These are best coupled with systems for objective scoring of the artery lumen to determine degree of stenosis of identified vessels. The low throughput of samples coupled with the invasiveness of this methodology mean it has been used on a limited scale in trials.

3.2 Prevalence

3.2.1 Cardiovascular disease

3.2.1.1 Mortality

Diseases of the heart and vascular system (cardiovascular disease) are the main cause of death in the UK accounting for over a quarter of a million deaths in 1998 (Table 1) (Table 1.2 in Coronary Heart disease Statistics[14]).

Table 1 Deaths from cardiovascular disease in the UK in 1998 (all ages)

CAUSE OF DEATH	MEN	WOMEN	TOTAL
ALL CAUSES	298,767	327,384	626,151
CARDIOVASCULAR DISEASE	122,218 (40.9%)	134,492 (41.1%)	256,710 (40.0%)

Although the cardiovascular disease death rate has been falling since the 1970s it is still one of the main causes of premature death (death before age of 75) accounting for 38% of premature deaths for men and 30% for women. CHD is the major contributor to cardiovascular disease mortality.

3.2.1.2 Morbidity

According to the Health Survey for England 1998 [15] 27.9% of men and 27.8% of women self-reported cardiovascular disease conditions and 10% of adults reported long-standing cardiovascular disease.

3.2.2 PAD affecting the leg

3.2.2.1 Mortality

Peripheral arterial disease patients occasionally die as direct result gangrene in their leg, but this is an extremely rare event. People with critical limb ischaemia have widespread atherosclerosis and poor prognosis with 20% dead within 1 year of presentation and only 53% alive with both legs.[16,17] People with IC likewise have systemic atherosclerosis and have a high risk of mortality; between 30% and 50% of those referred to hospital being dead within 5 years (a rate ~3 times that of people without IC).[18,19]

3.2.2.2 Morbidity

About 30% of the UK population over 55 years old have PAD affecting the leg, but most of this is asymptomatic.[6]

Population surveys indicate that intermittent claudication (IC) is rare in people under 55 years old (less than 1%) but then increases with age. Overall prevalence for men and women between 55 and 74 years old is approximately 5%.[6,20,21] For pre-menopausal women prevalence is about half that of men of similar age.[22] After the menopause this sex difference disappears. Limited information suggests that the annual incidence in the UK is about 1.8% for 55 to 74 year olds.

In the general population ~40% of people with IC have angina (2 to 4 times the rate in people without IC). Of people with IC referred to hospital 90% were found to have coronary heart disease and they were at about two fold greater risk of non-fatal myocardial infarction or stroke than people without IC.[18,23]

Regional variations in prevalence of IC in the UK are uncertain, but as with coronary heart disease there is likely to be a North South divide and a progressively increasing prevalence with lower social class.[17]

Critical limb ischaemia (CLI) is rare; an incidence in the range 500-1000 per million people (0.05 to 0.1%) per year has been calculated.[24]

3.2.3 Coronary heart disease

3.2.3.1 Mortality

CHD accounts for about 25% of all deaths in the UK. The mortality rate increases rapidly with age and at any age is greater for men than for women. The rate is higher in men in manual occupations compared with those in non-manual and is higher than average for ethnic South Asians living in the UK.

Table 2 Deaths from CHD in 1998 in UK (all ages)

NUMBER OF DEATHS FROM CHD		
MEN	WOMEN	TOTAL
74,542	62,611	137,153

Mortality from CHD peaked in the 1970s and has steadily declined by about a third since then. This decline has been greater in the 16-64 age group than 65 to 74 age group.[14]

3.2.3.2 Morbidity

Information regarding the prevalence of coronary heart disease in UK is fragmentary. Existing monitoring systems have focussed on acute episodes and death rather than on disease burden. The Health survey for England 98 reported on prevalence estimated in two ways:- a) on the basis of doctor-confirmed diagnosis; b) on the basis of self reported symptoms obtained via questionnaire. The two methods yielded different results.

Doctor-confirmed angina had an estimated prevalence of 5.3% in men and 3.2% in women. Prevalence increased up to 75 years of age in both sexes and at all ages was higher in men than women. The current prevalence (i.e. that reported in the last 12 months) was estimated as 3.2% and 2.5% for men and women respectively.

3.2.4 West Midlands burden of angina and PAD affecting the leg

Using the estimated prevalence of doctor-confirmed angina in England (above) and the projected estimate of the West Midlands population for 2001, we estimate there are approximately 140,340 men and 86,240 women (total 226,580) with angina in the West Midlands region. Using data from the same source we estimate that about 152,100 (67%) of these people would suffer angina in a 12-month period and would consult their doctor. This corresponds reasonably with the 167,000 coronary heart disease consultations for the region in 1996 reported in “Key Health Statistics from General Practice”.

Based on this estimate about 150,000 people per year in the region might be suitable for chelation therapy for treatment of angina.

In the year 1999-2000 there were 28,400 admissions to West Midlands regional hospitals for which the primary or secondary diagnosis was PAD caused by atherosclerosis. If we assume that in the majority of these patients the disease affected the leg(s) then they account for about half of the 52,000 patients with intermittent claudication calculated from estimated prevalence (above). Many of these patients might be suitable for chelation therapy.

Adding angina and IC patients together a total approaching 200,000 possible candidates for chelation therapy per year is obtained. Lack of information prevents an estimate of how many of these possible candidates might seek or request chelation therapy. In the UK chelation therapy is administered almost exclusively outside of the NHS. No private clinics in the region offer this service. The nearest clinics are in Atherton (Lancashire) and London. The only clinic in the West Midlands region (Haseley Clinic in Warwick) closed recently and does not appear to have reopened.

3.3 Current service provision

3.3.1 PAD affecting the leg

The aims of primary care are to provide diagnosis, to control risk factors, to alleviate symptoms and to make appropriate referral.

Treatment modes to modify risk factors of cardiovascular disease in PAD patients include:-

- Life style changes emphasising cessation of smoking and uptake of exercise.
- Antiplatelet therapy; drug therapies for lowering blood lipid levels, for control of diabetes, and for the control of hypertension.

Modes of treatment aimed at relieving symptoms of IC include:-

- exercise programmes.
- Vasodilator and anticoagulant drug therapies, drugs that alter the flow properties of blood by modifying deformability of red blood cell membranes, other drugs with various proposed mechanisms of action.

Systematic reviews of the efficacy of the various available interventions for relief of IC indicate weak evidence and/or marginal effectiveness.[15,25-28]

Secondary care procedures for people with intermittent claudication and people with critical limb ischaemia include:-

- Transluminal operations performed mainly on femoral and iliac arteries.
- Iliac and femoral bypass operations.
- Limb amputation.

In England approximately 22,000 femoral artery and 4,000 iliac artery transluminal operations are performed annually.[29] Corresponding numbers for bypass operations are 5,500 (femoral) and 1000 (iliac).[29] Provision of this secondary care in the UK is diverse with the majority of the vascular surgery performed by general surgery units in district general hospitals rather than in tertiary centres.[17]

3.3.2 Angina

For most patients treatment remains with the GP. A small proportion are referred to secondary and tertiary centres. Treatment is aimed at relief of symptoms, at halting or slowing the progression of disease, and at reduction in risk factors. Treatment for angina includes:-

- Advice on life style:- cessation of smoking; adoption of exercise; avoidance of obesity.
- Administration of drugs:- anticoagulants and antiplatelet agents to reduce thromboses; agents to lower blood lipid levels; vasodilators; agents to lower blood pressure.
- Surgery:- coronary artery bypass graft (CABG); percutaneous transluminal coronary angioplasty (PTCA) with or without stents.
- Rehabilitation programmes for survivors of myocardial infarction.
- Alternative therapies:- including over-the-counter remedies such as garlic powder tablets, garlic oil capsules, fish oil capsules.

Prescription records show that during the ‘90s there was a steady rise in the proportion of patients given lipid lowering statins and aspirin. A similar increase in surgical interventions

occurred. The number of CABGs performed in the UK doubled over the 10 years 1987 to 1997 reaching 28,000 per year. The number of PTCAs increased at an even faster rate (about 7 fold) reaching 25,000 per year 1997-98.

3.3.3 Implications of service provision

In relation to disease burden consultation rates for peripheral vascular disease in the UK are extremely low (estimated at 82 per 10,000 people per year) and the disease probably under diagnosed. It is possible therefore that current service provision of surgery for IC in the UK is inadequate.

Under-provision of surgery for CHD in the UK is implicit in the National Service Framework's goal of doubling CABGs and PTCAs over the 5 years 1998 to 2003.

Chelation therapy has been particularly canvassed as an alternative to surgical intervention for CHD and IC patients. If shown to be effective it might help address the shortfalls described above.

3.4 Description of intervention:- Chelation therapy and its uses

3.4.1 Introduction

EDTA chelation therapy is one approach suggested for the treatment of atherosclerosis. It involves the intra-venous infusion of a solution of EDTA. It was introduced in the 1950s in the USA and was advocated for PAD, CHD and stroke patients. Early use of the therapy was haphazard with regard to dosage of EDTA, rates of infusion, and the frequency of repeat infusions. After an early flush of enthusiasm following its inception the value of chelation therapy for atherosclerosis became a topic of dispute. In many countries chelation therapy is now generally administered outside of mainstream state-supported or insurance scheme-supported medicine and has become classified under the umbrella terms of "complementary", "holistic" or "alternative medicine".

3.4.2 Chelating agents

Chelating agents react with metal ions to form a particular class of metal complexes called metal chelates. In this reaction at least two reactive groups ("chela" or "claws") of the chelating agent become fastened to the metal ion so as to form a heterocyclic ring (defined as a cyclic structure in which the participating atoms represent at least two different elements). Many chelating agents have been developed and some have found uses in medicine.

3.4.3 Concept of Chelation Therapy

Chelation therapy is the administration of a chelating agent as a form of treatment. In theory the chelating agent extracts unwanted metal ions from various cellular or extra-cellular sites, circulates in the blood stream with its bound metal ion, and reaches the kidney where it is voided in the urine. In this way unwanted metal may be eliminated from the body. Except for reaction with a stronger chelating agent, or replacement by a preferred metal, a metal ion fully bound to a chelating agent is unavailable for other chemical reaction; it effectively disappears from solution.

The most obvious circumstances in which chelation therapy might be useful are:

- when a toxic metal has inadvertently accumulated in the body (e.g. lead poisoning, accident with radioactive isotope, arsenical chemical warfare agent).
- when a pathological condition has resulted in an abnormal build up of a metal (e.g. copper build up in Wilson's disease, or iron accumulation after repeated blood transfusion for thalassemia).

In the 1950s it was widely recognised that calcium deposits accumulate in atherosclerotic arteries and attempts to remove these deposits by chelation therapy were started. The rationale for the therapy was that arteries would become less blocked by removal of accumulated calcium. After the 50s dominant theories minimised the importance of calcium in atherogenesis and viewed its accumulation as a late secondary event. Modern imaging techniques (e.g. Electron beam computed tomography; EBCT) and new methods of investigation have recently refocused attention on calcium. It is now realised that the extent of calcification in the coronary arteries is a good prognostic indicator for acute adverse events.[30] Calcification of atheromas is no longer viewed as a passive precipitation. Instead the same proteins and regulatory mechanisms that control bone deposition and resorption are thought to be involved. The relationship between plaque calcification and plaque stability and potential thrombosis is unknown. Whether decalcification of a plaque would stabilise or labilise its structure is uncertain.

Other mechanisms of action for chelation therapy have been suggested. These include the proposed lowering of blood cholesterol levels, and the removal of transition metal ions (copper and iron) thereby minimising the oxidative changes to blood lipoprotein particles that are currently thought to play a pivotal role in the development of atheromas.

3.4.4 Ethylene diamine tetra-acetic acid (EDTA)

EDTA is a chelating agent that is able to bind most metals. It has various applications in biology and medicine, the most familiar as an anti-coagulant for blood collection.

The binding affinity of EDTA for different metals has been estimated. Equilibrium constants for EDTA-metal chelates vary from lower values (lower affinity) of 10^7 to 10^{11} (for group IIA metals e.g. Calcium, Magnesium, Barium) to higher values (10^{19} to 10^{25}) for other biologically significant metals such as Iron and Copper. The most important factor determining the affinities of different metals is the pH of the medium. In biological materials most metals (other than Na and K) are bound to physiological chelating agents (especially proteins); EDTA will only remove these if it is a stronger chelator of the particular metal.

Which metals form chelates with Na_2-EDTA in a biological environment depends on their relative concentrations, their chemical state (freely ionised, inorganic precipitate, or bound to biological chelating agents), and their affinity for Na_2-EDTA in the prevailing conditions (e.g. of pH). The most abundant chelate formed on introduction of 3 g of Na_2-EDTA into the circulation is calcium chelate.[31] Na_2-EDTA chelates calcium to form five pentacyclic heterocycle rings that completely enclose the metal and create a complex with no net charge. This structure is represented in the diagram below (Fig. 1).

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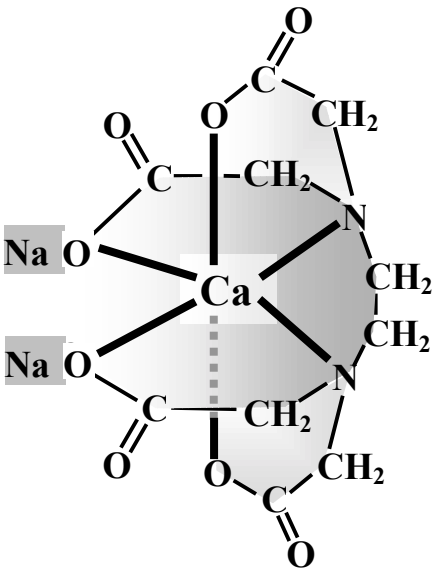
Fig. 1

The structure of the metal chelate formed between disodium EDTA and calcium.
The calcium ion is held in five pentacyclic rings and it's positive charge is neutralised.



Administration

The most common route of administration of EDTA is by intravenous infusion. This mode is an approved treatment for lead poisoning. Recently EDTA tablets have been marketed, but significant intestinal absorption is unlikely.

Free acid EDTA is poorly soluble and exerts an acid pH. The disodium salt of EDTA is more soluble and can be administered near to physiological pH. The American College for Advancement in Medicine[32] has recommended a protocol for EDTA therapy (Rozema 1997 [33]: "The protocol for the safe and effective administration of EDTA and other chelating agents for vascular disease and metal toxicity therapy"). A description of the protocol is available on the internet.[34] It involves the intra-venous infusion of 500 ml of solution containing 3 g disodium EDTA together with various additional substances including vitamins, magnesium chloride and sodium bicarbonate. The protocol does not specify the pH or osmolarity of the infusion mixture. Infusion lasts for 1.5 to 3 hours and typically 20 to 40 infusions are administered at a rate of about 2 per week. Minor variations on this protocol have been commonly used but have mainly concerned a larger volume of infusate (e.g. 1 litre for 500 ml) that quantitatively delivers the standard amount of chelator (about 3g EDTA). When magnesium chloride is included in the infusion virtually all the Na_2-EDTA will be administered as its magnesium chelate.

Depleted blood calcium levels are rapidly replenished from soft tissue stores, however very rapid infusions of Na_2-EDTA can precipitously lower serum calcium levels with a risk of tetany and death. Slow infusions have marginal effects while magnesium Na_2-EDTA infusions only mildly decrease serum calcium with rapid return to normal. Loss of ionised blood calcium stimulates release of parathyroid hormone which increases calcium reabsorption in the kidney, intestinal calcium uptake, and release of calcium from bone stores.

Theoretically 1g Na_2-EDTA can chelate a maximum of about 120 mg calcium. The quantity of ionised blood calcium removable as a result of the standard infusion of 3 g of EDTA is very small (maximum about 360 mg) relative to bone stores (typically about 1 Kg). Changes in parathyroid hormone induced by repeated infusions of EDTA could conceivably be relevant for persons at risk of osteoporosis (e.g. post-menopause women). EDTA and EDTA-metal chelates are not metabolised. After venous infusion of Na_2-EDTA, calcium-EDTA metal chelate is lost to the urine. Other metal chelates (e.g. zinc, copper, iron, cadmium, manganese, vanadium, and lead) are also voided in the urine as is unaltered Na_2-EDTA. All EDTA is voided in one form or another within ~24 hrs of administration.[35]

3.4.5 EDTA chelation therapy for atherosclerosis

EDTA chelation therapy has been claimed an effective therapy for many conditions. In recent reviews Olmstead[36] lists 39 separate conditions and Meyer[37] lists 28. In the UK its use for atherosclerosis started in 1985. Since then approximately 10,000 individuals have been treated. According to the Arterial Health Foundation this service is currently provided by eight doctors administering at 5 clinics (federated as "The Arterial Disease Clinic").

According to the Arterial Disease Clinic's web site[38] and promotional material the therapy may be suitable for patients with angina, claudication, memory loss due to PAD, and for stroke patients. It is not an approved therapy for these conditions and has been administered outside of the NHS with costs met by patients rather than health insurance schemes. The Arterial Disease Clinic lists three categories of patient that may be suitable for chelation therapy as follows:-

- Preventative cases; symptom-free individuals with a family history of cardiovascular disease and with risk factors (e.g. raised blood cholesterol).
- Moderate cases; people with clinical conditions that may lead to eventual surgery.
- Severe cases; usually people who have had surgery that has failed them or persons wishing to avoid surgery such as amputation.

According to Arterial Disease Clinic information a course of chelation therapy encompasses the following elements:-

- An initial examination that includes:- Doppler ultrasound examination of 24 arterial sites supplying the brain and legs; blood tests for kidney and liver function; urine analysis with creatinine clearance measurement to establish kidney function; physical examination; red cell magnesium; resting ECG test; atherosclerosis risk factor analysis (cholesterol, ferritin, fibrinogen, lipoprotein a, apo-lipoprotein E, and homocysteine).
- Venous infusion of EDTA solution according to the protocol of The American College for Advancement in Medicine (see above). An infusion lasts about 3.5 hours during which time the patient reclines in a chair and is free to eat, drink and chat. The procedure is closely monitored for cardiac function and blood pressure (avoidance of hypotensive episodes). Infusions are repeated at a rate of one a week to a total that depends on clinical judgement (typically 20 to 40 infusions).
- Oral vitamin supplements that form an integral part of the therapy.
- Interim and end of treatment tests including Doppler examination, and urine creatinine measurement.

Potential advantages of chelation therapy include:-

- Its low degree of invasiveness compared with CABG or PTCA.
- Its out-patient mode of administration contrasting with CABG.

- Its possible avoidance of surgery.
- Its lesser requirement for operator training.
- Its lack of requirement for cardiac surgery facilities in the vicinity of the clinic.
- Its relatively low requirement for high-grade technology and staff back-up.

Compared with other conservative management regimes such as oral drug therapy it suffers the disadvantage of being time consuming and involving travel by the patient.

Almost from its first use for cardiovascular diseases, considerable controversy has surrounded the question of whether EDTA chelation therapy is effective. Strong opinions have been expressed both for and against its use with the result that it has become a highly contentious topic. Both RCTs and reviews have been published about chelation therapy. There has been debate on whether systematic reviews or randomised controlled trials represent the best evidence that can be used when considering efficacy of an intervention[39-42]. Reviews, especially systematic reviews, have considerable opinion-forming influence. A review of reviews on chelation therapy has been included in the present report so as to summarise the direction of their conclusions and to assess their quality.

4. Questions addressed by this review

The question addressed in this review is what is the effectiveness and cost of EDTA-chelation therapy for the treatment of patients with intermittent claudication or coronary heart disease.

5. Methods

5.1 Clinical effectiveness

5.1.1 Search strategy

A scoping search was done in March 2001. For clinical effectiveness the detailed search strategy involved looking for randomised control trials (RCTs), case control studies, systematic and other reviews. Both index terms and text words were used. Embase (1980 to April 2001) and Medline (1966 to April 2001) were searched on Ovid. No language restrictions were applied. Further searches of Medline and Embase were done in July 2001 to check for any recent papers.
Searches were: -

1. for RCTs using the NHS CRD[43] search strategy for RCTs and the search terms exp. chelation therapy, EDTA, ethylenediamine tetraacetic acid, exp. Chelating agents, exp. Edetic acid.
2. for case control studies, using the search terms exp. Cohort studies, exp. Case control studies, exp. chelation therapy, exp. Chelating agents, exp. EDTA, exp. Edetic acid.

The following additional sources were searched during April 2001;

- Cinahl.
- Grateful Med.
- Cochrane Library.
- CHID online (The Combined Health Information Data Base).
- NCCAM website (National center for complementary and alternative medicine).

- Internet Search Engine (Google, Dogpile).
- Web of Science (MIMAS).
- Biomednet.
- Reference lists in review articles, meta-analyses and RCTs.
- Hand search of current literature available online at Birmingham University and held in the University library; this included specialised and general journals publishing papers on atherosclerosis:- JAMA, NEJM, BMJ, Lancet, Circulation, Atherosclerosis, Annals of Internal Medicine. The issues searched covered from Sept 2000 up to July 2001; earlier publications were assumed to have been entered onto Medline and Embase data bases.
- Practitioners of chelation therapy and colleagues were consulted for references and web sites.

5.1.2 Inclusion criteria

5.1.2.1 Primary studies of clinical effectiveness

- Study design:- RCTs. Other controlled studies were accepted if >100 people were included.
- Population:- Atherosclerosis causing PAD with IC, or CHD.
- Intervention:- Chelation therapy involving repeated infusion of EDTA solutions containing at least 1 g EDTA per infusion with a total of at least 10 infusions.
- Comparator:- RCTs:- Placebo or other interventions that were not chelation therapy. Case control studies:- matched untreated controls.
- Outcomes:- A measure of effectiveness determined using an exercise test.

5.1.2.2 Reviews of clinical effectiveness + meta-analyses

Systematic reviews, critical reviews and other reviews were included if they attempted a critical analysis of quantitative primary data on efficacy of EDTA chelation therapy for atherosclerosis causing peripheral arterial disease with intermittent claudication, or coronary heart disease. Meta-analyses were included if they reported a summary estimate of effectiveness of chelation therapy for IC or angina.

5.1.3 Exclusion criteria

All studies: Atherosclerotic cerebral disease. Studies involving chelation therapy with chelating agents other than EDTA.
Reviews: uncritical reiteration of conclusions from papers reporting primary data.

5.1.4 Quality assessment strategy

The following factors were considered when evaluating RCTs:-
- The method of randomisation used, concealment of allocation and how this might effect outcomes.
- Whether baseline characteristics were similar between groups.
- Whether groups were treated similarly except for the randomised intervention.
- The extent of treatment crossover.
- The nature and extent of loss to follow up.
- The extent of blinding of assessment.

- Whether the analysis was carried out on intention to treat basis.
- Whether the conclusions match the results.

In addition RCTs were scored on a scale based on that proposed by Jadad.[44]

The following factors were considered in evaluating reviews:-
- The degree to which QUOROM guidelines[45] were fulfilled.
- Whether statements were matched by the references given in their support.
- Whether statements were errors, misrepresentations or unsubstantiated by evidence.

Meta-analyses were evaluated in terms of the following factors[46]:-
- Study protocol in advance.
- Complete literature search.
- Selection of studies objective and reproducible.
- Analysis of individual patient data when results found in different settings are combined.
- The need for future studies defined.

5.1.5 Data extraction strategy

Two reviewers independently extracted the data from all the included studies into predefined tables. One discrepancy was resolved by discussion.

5.2 Economic analysis

5.2.1 Search strategy

For economic evaluation the NHS CRD (Centre for Reviews and Dissemination) search strategy ["All Databases" (DARE, NHS Economic Evaluation Database, HTA)] was used.[47] Medline and EMBASE were also searched on Ovid in July 2001. Search terms included: exp economics; exp economics, hospital; medical/or exp economics; nursing/ or economics; pharmaceutical; exp costs and cost analysis; exp cost of illness; exp economic value of life; exp health care costs; exp economics, medical/; exp "fees and charges"/; (costs or costs or costed or costing).mp.;
No language restrictions were applied.

5.2.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria were applied as for the clinical effectiveness section (5.1.2.1 and 5.1.3). In addition, included studies must include either assessment of resource implications and or costs. There were no language restrictions. Inclusion and exclusion criteria were applied by two reviewers.

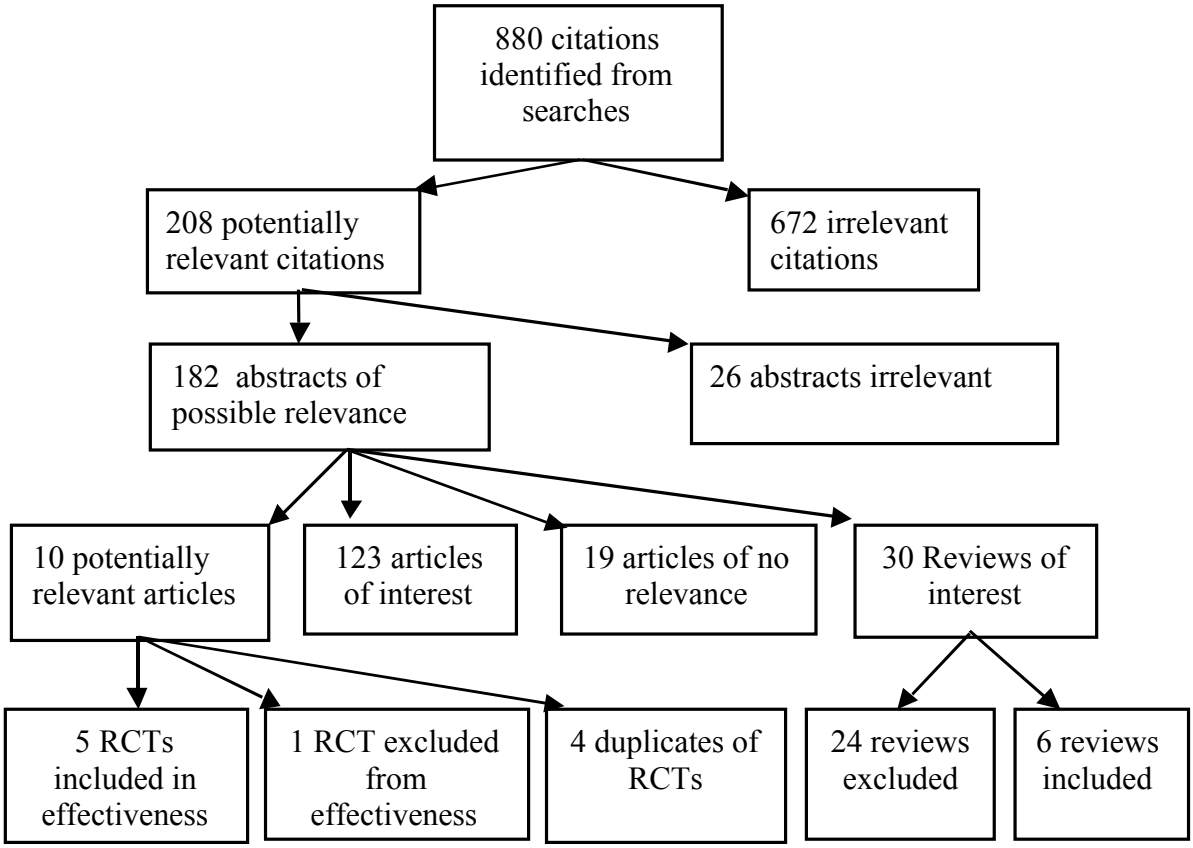
5.2.3 Economic evaluation

The economic evaluation was a cost study of chelation therapy. The analysis was done from the perspective of the NHS. This was so as to gauge the cost impact of the therapy should it be adopted within the NHS.

6. Quality, direction and strength of the evidence (clinical effectiveness + reviews)

6.1 Number and types of studies

The outcome log of the studies identified from literature searches is shown in the diagram below:



6.2 Randomised controlled trials

6.2.1 Studies found

Six RCTs were found.[48-53] No other controlled trials or case control studies were found. One RCT (Kitchell et al 1963[48]) was excluded because no objective measure of outcome was reported. In this RCT four intervention and five placebo patients received 12 weeks of initial treatment in a cross-over design study. At 6 and 12 weeks post initial treatment they were evaluated in terms of "benefit" or "no benefit". The patients then returned to a further 12 weeks of treatment in cross over mode. At least three of the nine patients failed to complete this second phase of treatment. The authors remarked that no valid conclusions could be drawn from their study.

Table 3 Details of studies found

Type of study	Number of studies	Source
R C T	3	Embase,Medline or Biomednet
R C T	1	Internet [Alberta Heritage Foundation]
R C T	2	Referenced in Journal

6.2.2 Randomised controlled trials of CT for PAD patients with IC

6.2.2.1 Studies found and trial design

Three randomised controlled trials were found.[51-53] One of these trials was reported several times.[53-57] All three trials compared EDTA chelation therapy with placebo. They employed an exercise test (walking distance) as the primary outcome. Details of trial designs are shown in the Table 4.

Table 4. Design of RCTs of chelation therapy for peripheral arterial disease

	TRIAL		
	Olszewer et al.,1990	**Guldager et al.,1992†**	**van Rij et al.,1994**
Patient Group	Men with PAD 41-53 years old (mean 47). Stable intermittent claudication. Pain-free walking distance 100 to 300 metres. Ankle/brachial BPI 0.75 - 0.4.	>40 years old (mean 65), 65% men. Stable intermittent claudication for ≥12 months. Pain-free walking * 50-200m. Ankle/brachial BPI <0.8	>45 years old (mean 67), 82% men. Intermittant claudication. Arteriographically-confirmed PAD. ≤20% variation in pain-free walking distance.
Interv-ention	Infusion 10 ml solution containing 1.5 g Na_2 EDTA + 1 g $MgSO_4$ + vitamins & heparin in Ringer's lactate [Ringer's lactate not defined]. 10 infusions. Time unspecified.	3-4 h infusion of 1000 ml isotonic solution containing 3g Na_2 EDTA + 8.4 g NaCl. 20 infusions over period of 46 days (31-69 days).	3-4 h infusion of 500 ml isotonic solution containing 3g Na_2 EDTA + 0.76 g $MgCl_2$ + 0.84g $NaHCO_3$, in "normal" saline + vitamins. 20 infusions at 2 / week for 10 weeks
Comp-arator	As intervention but minus Na_2 EDTA. 10 infusions	Isotonic NaCl (minus Na_2 EDTA). 20 infusions over period of 46 days (range 27-63 days).	500 ml "normal" saline + vitamins. 20 infusions at 2 / week over period of 10 weeks.
Primary outcome	"Walking distance" test [+ Master's two step test††, + bicycle exercise test]. Comparison between baseline and after 10 infusions.	Pain free and maximal walking distances on a treadmill. Differences between baseline and various time points calculated. Comparison in differences CT v. placebo.	Pain free and maximal walking distances on a treadmill. Differences between baseline and various time points calculated. Comparison in differences CT v. placebo.
Second-ary outcomes	Blood pressure measurements.	Subjective evaluation by patients. Change in ankle/brachial BPI before v after treatment. Side effects during treatment period.	Many measures (n≥14) covering arterial & cardiac function, quality of life & mood state, & patient assessment of treatment.
No. at start	10; CT= 5 & PL=5	159; CT=80 & PL=79	32; CT=15 & PL=17
No. at end	10 ; CT= 5 & PL=5	153; CT=75 & PL=78	32; CT=15 & PL=17
Follow up time	Not reported	3 mo. n=149; CT=66 & PL=67 6 mo. n=123; CT=51 & PL=56	3 mo n=32; CT=15 & PL=17

CT = chelation therapy. PL = placebo. PAD = peripheral arterial disease. BPI = blood pressure index. † this was a multicentre trial. †† Master's two step exercise test described by Master and Oppenheimer 1929.[11]

The Olszewer trial did not describe the method of measurement of walking distance and it is assumed that maximum walking distance only was estimated. In Guldager and van Rij trials a fixed incline-constant speed treadmill was employed to measure walking distance. Two

measures were made:- 1] the pain-free walking distance (PFWD), which is the distance walked up to the first onset of claudication; 2] the maximum walking distance (MWD), which is the distance walked up to the point when the patient cannot continue despite a severe whipping, various inducements and other encouragement.

6.2.2.2 Trial quality assessment

The quality of trials was assessed according to criteria described in Methods and set out by Jüni et al (2001).[58]

i] The Olszewer trial[52]

The method of randomisation was not described. Patients and investigators were effectively blinded to treatment allocation. Treatment crossover was planned after the tenth infusion but because of dramatic improvements in all intervention but no placebo patients cross over and blinding were abandoned and the study continued as an open label trial of the intervention for all patients. Baseline characteristics were similar between groups but demographic details were meagre. Patients were treated similarly except for the randomised intervention. There were no losses to follow up.

ii] The Guldager trial[53]

Block randomisation was used but no further details of the randomisation procedure were supplied. Baseline characteristics were similar between groups except that the placebo group maximum walking distance standard deviation was very large (169% of the mean) compared with that for the intervention group (32% of the mean). Such large variance precludes a significant difference between means but might indicate some difference between groups. The placebo group standard deviation value is large compared with values reported for this outcome measure in a representative selection of other trials (see Appendix 1). Groups were treated similarly except for the randomly allocated intervention.

Patient numbers completing to each stage of the study were stated but their distribution between groups is not clear and not all withdrawals are accounted for. Numbers of patients stated to have completed to each stage do not correspond with the numbers contributing outcome data. Observations on some patients were said to be “censored” and their data excluded from analysis. Clear reasons for censoring were not provided. Numbers of censored data were stated to be small but in fact exceed 10% as shown in Table 5.

Table 5 Patient numbers at each stage of the Guldager trial

STAGE	Stated no. of patients	Losses from previous stage‡	Losses fully accounted for	Number that contributed data‡	% of data "censored" ‡
Baseline	159	0		153	4%
10'th infusion	?	?	0	143	?
Post treatment	153	6	6	135	12%
3 month follow up	149	10	0	133	11%
6 month follow up	123	26	8	101	18%

‡ Calculated from data tables of Guldager trial.

Blinding was broken at the end of treatment so that investigators were aware of patient allocation during outcome measurements at 3 month and 6 month follow up. Of 123 patients that completed the study only 36% were still blinded. How and when blinding was broken for the other 64% was not stated. No reason was provided for why blinding was abandoned.

iii] Van Rij trial[51]

Block randomisation was used but no further details of the randomisation procedure were supplied. Baseline characteristics were similar for both groups. Blinding procedure was described and both investigators and patients were blinded to treatment allocation throughout the study. There were no losses to follow up and all patient data was used for analysis.

6.2.2.3 Trial size and study power

Walking distance of claudicants is variable. With repetitive testing it tends to increase.[10] Better designed trials carry out pre-trial tests to recruit patients with reproducible walking of known variance. A calculation should then be done to estimate suitable trial size. Only van Rij described pre-trial tests and performed a calculation for trial size. However the calculation was flawed and the trial underpowered by a factor of ~10 (see Appendix 2).

The Vascular Clinical Trialists[10] have recommended trial sizes for trials of pharmacological agents for intermittent claudication. They estimate that, using a walking performance end point, for a 25% difference between control and intervention to be detectable at $P < 0.05$ the trial would require ~200 patients. According to this all three of the trials under consideration here were underpowered except for detection of >25% differences between treatments.

6.2.2.4 Summary of trial quality

A summary of quality aspects[58,59] of the three RCTs is shown in Table 6.

Table 6. Summary of study quality of RCTs of CT for PAD

QUALITY ASPECT	TRIAL		
	Olszewer et al., 1990	Guldager et al.,1992	van Rij et al., 1994
Qualitative criticisms	Duration time of treatment not specified. Timing of outcome measure unclear	Placebo and intervention groups may have differed at start of the trial§	Power calculation for trial size either flawed or ill-described.
Trial size	Very small (10)	Moderate (159)	Small (32)
Pre-trial estimate of likely outcome variance and calculation of trial size required	No	No	Yes
Population inclusion & exclusion criteria adequately described	Yes	Yes	Yes
Demographic details given	Inadequate	Yes	Yes
Groups similar at start	Probably	Probably	Yes
Blinding method described	No	No	No
Blinding maintained	Yes, up to the 10'th infusion‡	Not during follow up‡‡	Yes
Full description of Treatment	No	Yes	Yes
Description of outcome methods	Incomplete	Complete	Complete
Full account of losses to follow up	Yes	No	Yes
Non-complier results carried forward	NA	No	NA
Data presented allow calculation of authors' end point conclusion	Uncertain	No	No
Jadad-based summary score. [0 (worse) -5(best)]	3	2	4

NA: Not Applicable (no withdrawals occurred in these trials). ‡ Original trial planned cross over after 10 infusions but this design abandoned then together with blinding. ‡‡ Blinding of investigators abandoned at end of treatment, that of patients (74%) at indeterminate times after end of treatment. § Very large SD for maximum walking distance at baseline for placebo group.

6.2.2.5 Results of randomised control trials of CT for patients with IC

In the three RCTs of EDTA-chelation therapy for patients with intermittent claudication the primary outcome was based on walking distance at one or more time points during or after treatment and on comparison of these distances with those observed at baseline.

i] The Olszewer trial

Olszewer measured WD at baseline and after 10 infusions (end of treatment) for a total of 10 patients randomised to CT or placebo. Olszewer rounded walking distances to the nearest 10 metres (all distances quoted are a multiple of 10). Mean and SD of measures were not reported. We have calculated these and they are shown in Table 7.

Table 7 Mean and SD‡ of walking distances measured in Olszewer trial

OUTCOME	Intervention				Placebo			
	follow up no.	Distance (m) at baseline mean (SD)	Distance (m) at post-treatment mean (SD)	Change Mean (SD)	follow up no.	Distance (m) at baseline mean (SD)	Distance (m) at post-treatment mean (SD)	Change Mean (SD)
Walking distance	5	160 (59)	424 (110) ‡	264 (51.8)	5	192 (29)‡	212 (49) ‡	20 (20.5)

‡ All means and SD values were calculated from published data of Olszewer.

Olszewer reported in the text a 2.2 and 1.04 fold increase in walking distance for the intervention and placebo groups respectively. The correct value (shown in table 2 of Olszewer) should be 2.65 (i.e. 424/160). This increase is substantial. Olszewer reported a significant difference ($P<0.05$) between intervention and placebo groups. Their statistical procedure is not clearly described and not easily identified. We used Olszewer's data for individuals to calculate 95% confidence interval for mean walking distance for each group. We did this for walking distances and also log transformed walking distances. The results are shown in the Table 8.

Table 8 Olszewer trial calculated 95% CIs for walking distance and log walking distance measurements

GROUP	Time of outcome measure-ment	95% CONFIDENCE INTERVAL‡ WD in metres	Inter-group significant difference*	95% CONFIDENCE INTERVAL‡ Log WD‡‡	Inter-group significant difference*
INTERVENTION	Pre-T	87-233	NO	4.58 to 5.47	NO
PLACEBO	Pre-T	155-229		5.05 to 5.44	
INTERVENTION	Post-T	287-561	YES	5.73 to 6.33	YES
PLACEBO	Post-T	152-272		5.02 to 5.64	

WD = walking distance. Pre-T = pre-treatment (i.e. baseline). Post-T = post treatment.
= no overlap in 95% CIs between intervention and placebo groups.
‡ All values calculated from appropriate data in Olszewer.
* $P<0.05$ intervention v placebo.
‡‡ nb. These values are not merely ln (95% CI of WD in metres) but 95% CIs of ln WD.

Using these methods of analysis the intervention is significantly more effective than placebo.

We also used log WD to calculate the ratio of change (intervention/placebo) from pre- to post-treatment (effectiveness ratio) and it's 95% CI. The result was: 2.5 (95% confidence interval: 2.1 to 2.97). Again according to this result the intervention is significantly more effective (2.5 fold) than placebo. The reliability of this result is called into question because of the small size and low quality of the trial.

ii] Guldager trial

Guldager measured pain-free and maximum walking distance. Measures were made at baseline, mid-treatment (10th infusion), end of-treatment, and at 3 and 6 months follow up. Means and standard deviations were tabulated. Guldager also tabulated the effectiveness ratio with 95% CI (ratio of intervention/placebo for % change in WD from baseline) calculated from log transformed data for individuals. Should the lower 95% CI value for effectiveness

ratio be greater than one then the intervention is significantly more effective than placebo (at P= 0.05 level). At no time was there a significant difference between placebo and intervention. Table 9 shows the results for baseline, post-treatment and 3 months follow up.

Table 9. Guldager trial results at pre- & post-treatment & 3 months follow up

		INTERVENT-ION			PLACEBO			Effectiveness Ratio and (95% CI)†
OUTCOME	TIME	*n*	mean	(SD)	*n*	mean	(SD)	
Pain-free WD	Pre-T	*75*	74	(25)	*78*	82	(36)	NA
Pain-free WD	Post-T	*68*	93	(40)	*67*	109	(56)	0.91 (0.79 to 1.04)
Pain-free WD	3 months follow up	*66*	95	(48)	*67*	102	(42)	0.98 (0.85 to 1.13)
Maximum WD	Pre-T	*75*	119	(38)	*78*	157	(266)	NA
Maximum WD	Post-T	*68*	159	(99)	*67*	206	(239)	0.92 (0.81 to 1.05)
Maximum WD	3 months follow up	*66*	162	(101)	*67*	204	(248)	0.94 (0.82 to 1.08)

† According to Guldager calculated from antilog of ratio of means of ln (% change in individual walking distances)[60] NA = not applicable. PreT = pre-teatment. Post-T = post-treatment.

Guldager stated that the values they log transformed were the % change from baseline of each individual's walking distance. A complex variance model was used to take into account the effect of several covariates in estimating differences between groups. Because of this complex treatment and lack of individual patient data the calculation of the effectiveness ratio and its confidence interval cannot be checked directly. However Guldager's 95% CIs for effectiveness ratios appear much narrower than would be expected (see Appendix 3). The 95% confidence intervals quoted are reasonable only when it is assumed that the effectiveness ratio was calculated from the "change in the log WD" of individuals or from "change in log of % WD" (where 100% is defined as pre-treatment WD) rather than from "log % change in WD" (as stated by the authors). Whatever statistical handling of the available results is employed no significant difference between the two groups is found.

There was no significant difference between groups with regard to side effects or adverse events.

iii] van Rij trial

van Rij measured pain-free and maximum walking distance. Measures were made for 32 randomised patients at baseline, end of-treatment, and at 3 months follow up. Means and standard deviations were tabulated. Non-significant increases over baseline walking distance were observed for intervention and placebo groups. There was no significant difference **between** groups in walking distance at any time point or between groups in **change** in walking distance at any time point relative to baseline.

van Rij log transformed walking distances. The method used to calculate effect sizes is not clear. The authors state "*effect sizes were calculated to standardise comparison of changes in mean values of variables following treatment*". However they did not report effectiveness ratios or effect sizes of any form. We were unable to calculate effectiveness values from the van Rij paper because individual patient data was not presented. We calculated 95% confidence intervals for group walking distances and checked for within group and between group significant differences. The results for pre- and post-treatment are shown in the Table 10. The considerable overlap in 95% confidence intervals for WDs indicate a likely lack of within group or between group significant differences and this is confirmed by the 95% CIs of differences between means (which all span zero).

Table 10. Pre- and post-treatment results of the van Rij trial

		INTERVENTION	PLACEBO	Between group 95% CI of difference between means††		Within group 95% CI of difference between means†	
OUT-COME	TIME	*n* mean (SD) [95% CI]	*n* mean (SD) [95% CI]‡	Pre-treat	Post-treat	Interv-ention	Placebo†
Pain-free WD	Pre-Treat	*15* 92 (64) [57 – 127]	*17* 98 (67) [64 – 132]	-53 to +41	-73 to +33	-52 to+34	-78 to +32
Pain-free WD	Post-Treat	*15* 101 (50) [73 – 129]	*17* 121 (89) [75 – 167]				
Maximum WD	Pre-Treat	*15* 185 (117) [120 – 250]	*17* 196 (121) [134 – 258]	-97 to +75	-118 to + 88	-117 to +71	-122 to +67
Maximum WD	Post-Treat	*15* 208 (135) [133 – 283]	*17* 223 (149) [146 – 300]				

‡ Calculated from data in van Rij trial report.
WD = walking distance. Pre-Treat = pre-treatment (ie baseline). Post-Treat = post treatment.
† Tests within group for difference between pre- and post-treatment means.
†† Tests between intervention and placebo groups for difference between means.

Subsequent to publication of the van Rij trial the maximum walking distances for all patients at pre-treatment and at 3 months were published by Godfrey and Chappell[61] (Appendix 4). They noted that a single placebo patient accounted for 80% of the group's total increase relative to baseline. They suggested that this individual be considered an outlier and excluded from statistical analysis but they did not offer a new statistical analysis. We log transformed the data for individual patients and calculated the effectiveness ratio (intervention / placebo) with 95% CIs. We did this both including and excluding the so-called outlier, although excluding an outlier of this sort is not justifiable.[62] The results are shown in table 11.

Table 11. Effectiveness ratio and 95% CIs at 3 months follow up compared to baseline calculated for van Rij trial

CALCULATION TYPE‡	With or Without "outlier" patient	Effectiveness Ratio (CT / placebo)	95% confidence interval
Log (change in walking distance)	Without	1.17	0.82 to 1.67
Log (change in walking distance)	With	1.13	0.79 to 1.61
Log (% change in walking distance)	Without	2.44	0.18 to 33.4
Log (% change in walking distance)	With	1.91	0.14 to 25.4

‡ Calculated changes for individual patients were used.

The results show that in the van Rij trial intervention and placebo did not differ significantly and that inclusion of the outlier has little effect on this result. The 95% confidence intervals are much wider if log "% change in walking distance" (rather than change in log walking distance) is used for calculation.

Van Rij measured numerous secondary outcomes (32, including 18 relating to life style). With so many in a study we might expect chance to yield inter-group significant differences. Ankle-brachial blood pressure index (measured in each leg at rest) significantly improved in intervention relative to placebo group. The fact that this occurred independently in both legs implies a result not due to chance. There was also a non significant trend for greater improvement in the intervention group ABI in the worse leg after exercise (that is measured immediately after treadmill test for walking distance). Whether the authors specified ABI blood pressure indices as a primary outcome is unclear. Improvement of femoral artery

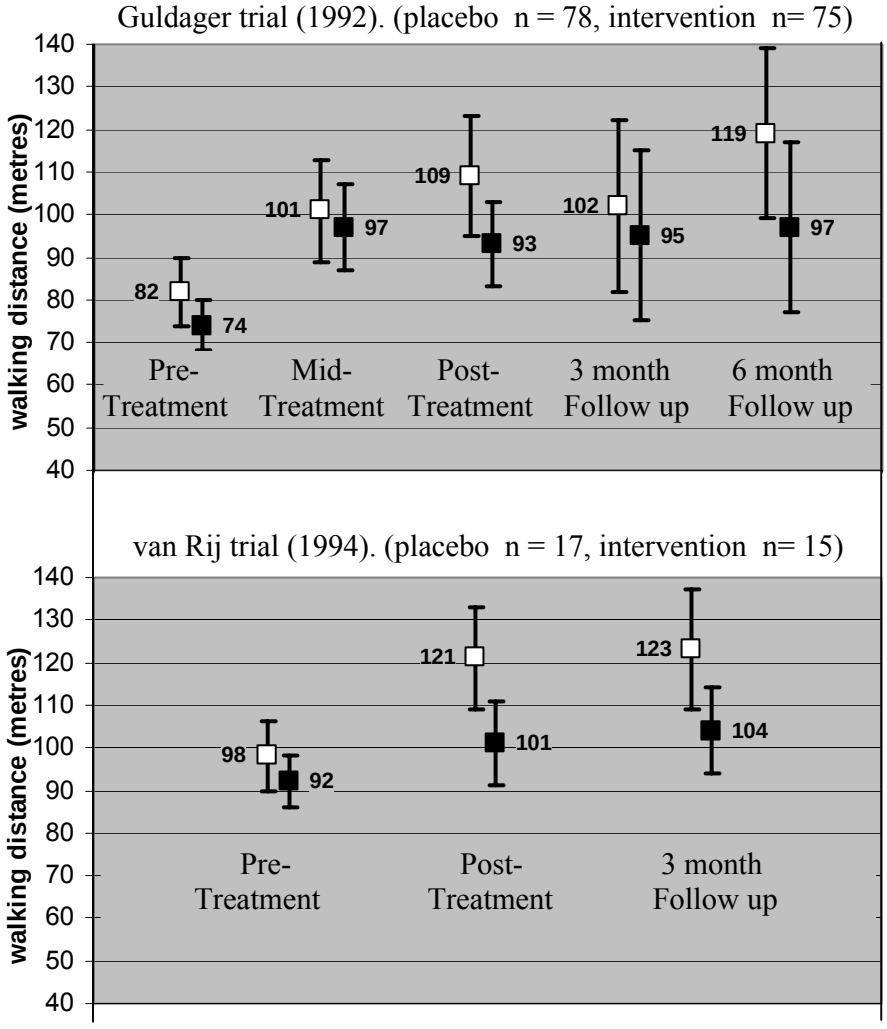
pulsatility in the worse leg was significantly greater in the intervention group. Similar but non significant trends were observed for the better leg and for tibial artery pulsatility indices.

There was no significant difference between groups with regard to side effects and adverse events.

The van Rij trial report mentioned 12 month follow up data to be published elsewhere. When we contacted the author he confirmed that the data had never been published and sent a brief summary of the results. His e mail is reproduced in Appendix 5.

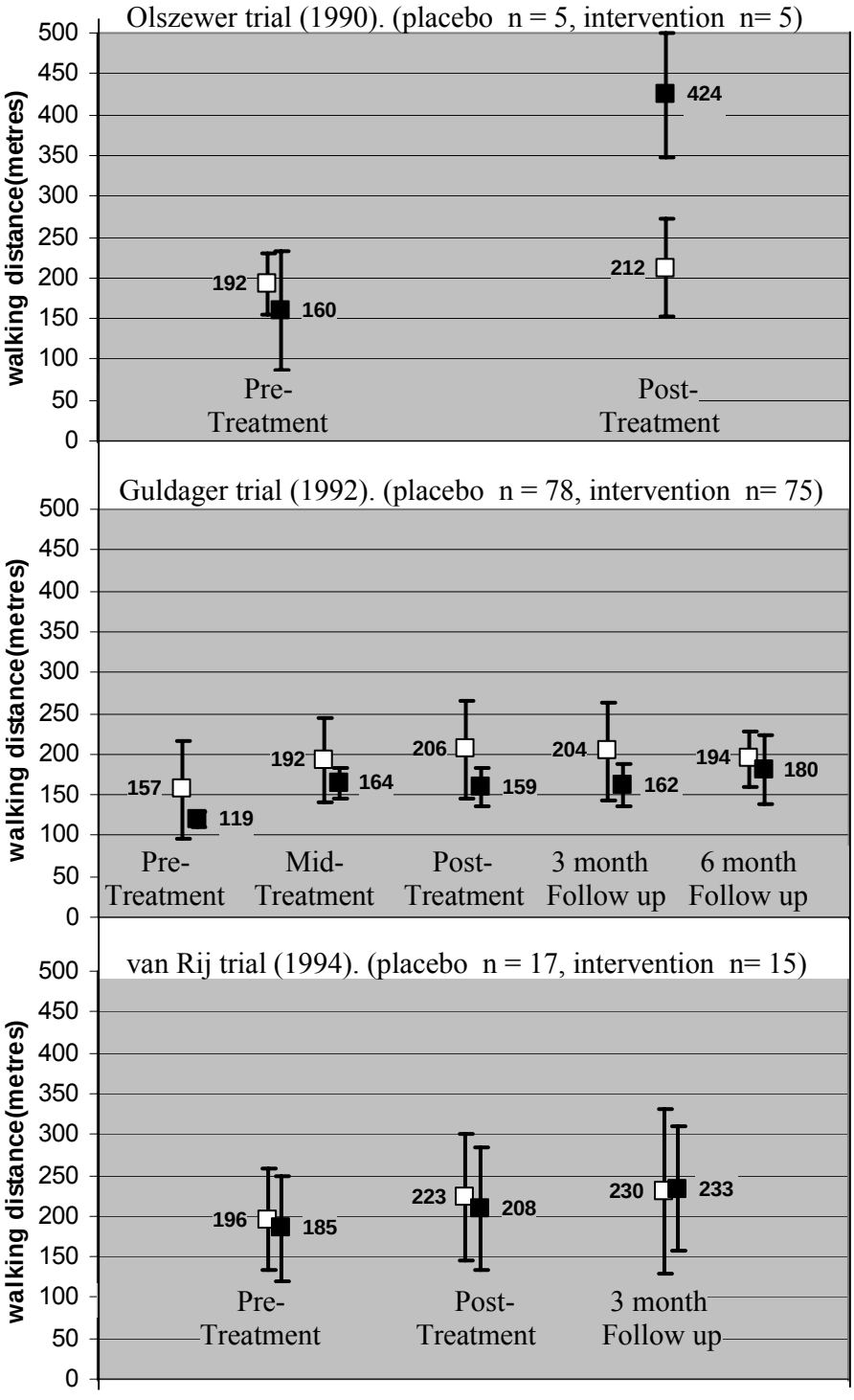
6.2.2.6 Summary of results of CT for IC

A graphical summary of the primary outcome results is shown in Figs 2 and 3.



Graphical summary of Pain Free Walking Distance measures reported in RCTs of chelation therapy for intermittent claudication. Error bars represent 95% confidence intervals. ■ = intervention. □ = placebo.

Fig. 2



Graphical summary of Maximum Walking Distance measures reported in RCTs of chelation therapy for intermittent claudication. Error bars represent 95% confidence intervals. ■ = intervention. □ = placebo.

Fig. 3

The very small trial of Olszewer[52] (n=10) shows striking benefit of chelation therapy relative to placebo and statistical difference ($P<0.05$) between treatments. The largest trial (Guldager et al[53] (n=153) and the intermediate-sized trial (van Rij et al[51] (n=32) indicate no benefit of chelation therapy relative to placebo.

Any conclusions drawn from these results will depend on the weight given to each study. This in turn depends on quality assessment of the three trials. All three trials performed reasonably well when tested against the pre-set criteria listed in the Methods section. Individual analysis of each trial has revealed some failures of design, reporting and statistical analysis. These failures are summarised as follows:-

a] Olszewer trial.

- Intervention and placebo intravenous infusion solutions not clearly described.
- Methods of outcome measurement very poorly described with some features nonsensical (claudicants operating an exercise bicycle at 50 km/hr for 3 to 6 min).
- Duration of study not stated.
- Incorrect calculation of improvement factor for intervention group.
- Statistical analysis obscure/absent.
- Implausible intervention results: all CT patients improve dramatically and all placebo patients remain essentially unchanged or deteriorate; after cross over to CT the original placebo group all improve dramatically and original CT group crossed over to placebo all improve further (carry over effect).

b] Guldager trial

- Blinding abrogated before end of study.
- Results from about 10% patients “censored”; “last result” not brought forward for analysis.
- Non-compliers incompletely accounted for.
- 95% confidence intervals for primary outcome (effectiveness ratio) implausibly narrow and indicative of misreporting of calculation method.

c] van Rij trial

- Power calculation incorrect or at best obscure and trial severely underpowered to test proposed hypothesis.
- No quantitative value given for relative effectiveness of intervention (merely a statement that $P > 0.05$, but statistical procedure unclear).

In view of the very low quality and small size of the Olszewer trial its findings are overwhelmed by the results of the other two trials. These failed to demonstrate that CT has a beneficial effect with regard to the primary outcome. The direction of evidence indicates that CT may completely lack benefit .

That some secondary outcomes in the van Rij trial were in favour of chelation therapy might imply that further study is justified. Such a study might require very large numbers of patients (500 to1000) to demonstrate if such marginal effectiveness was real. The clinical significance for claudicants of small gains is controversial.[27,63,64] The proposed funding for an RCT of CT was recently estimated for the NIH by Goertz to be $ 3 million[65] The NIH research fund for alternative medicine has recently increased substantially.[66]

The trials were of relatively short duration. Two of the trials included follow up periods of 3 or 6 months that extended beyond treatment. Trial groups were seriously ill patients with life threatening atherosclerosis. Adverse events and side effects of treatments were observed. Neither study reported a significant difference in these between groups. One patient in the Guldager study died, however there was no indication in the report of the cause or to which group the individual belonged. Consideration of the evidence brought to bear on the question of safety of chelation therapy is included in section 6.3.

6.2.3 Randomised controlled trials of CT for coronary heart disease patients

6.2.3.1 Studies found and trial design

Three RCTs[48-50] were found one of which[48] was excluded because it lacked an objective measure of effectiveness using an exercise test. The two included trials Hopf et al. (1985)[49] and Knudtson (2002)[50] had only been published in abstract at the time of searching. On request we received a 68 page report[67] of the Hopf trial. This account is in German and is a dissertation prepared by one of the trial authors as part of her qualification for "Doktorgrades der Medizin des Fachbereichs Humanmedizin". The Knudtson trial was submitted for publication early in 2001. Requests for a fuller account than the abstract were unsuccessful because of the trialists' respect for journal policy. The authors informed us of imminent publication in Dec 2001 and publication occurred in the 23 Jan 2002 issue of *JAMA* (it is not represented in the "potentially relevant papers box" of the outcome log on p 24).

Characteristics of the two trials are shown in Table 12.

Table 12. Characteristics of available RCTs of chelation therapy for CHD

	TRIAL

Characteristic	Hopf et al.1997† Single centre.	Knudtson et al. 2002*. Multi-centre
Patient group	Men with angina on effort and with angiographically confirmed CHD. Age range 43-64 (mean 59.5).	Men and women >21 years of age with proven ischaemic heart disease & stable angina. Non-candidates for re-vascularisation & no previous CT. Ability to perform exercise test. No abnormal renal or liver function.
Intervention	Infusion of solution containing 3 to 4g Na_2EDTA in isotonic sterile saline with 10 m eq $MgCl_2$. Delivered every third day for 20 infusions.	Infusion of 500 ml Na_2EDTA (40 mg/Kg) solution†† over 3 hr delivered 2 / week for 15 weeks and then once / month for total of 33 treatments‡‡.
Comparator	As intervention but minus EDTA.	As intervention but isotonic saline substituted for EDTA‡‡.
Primary outcome	Exercise stress test:- [a] Time (min) able to perform work (at maximum individual output, Watt) up to 6 min maximum, while monitored for ST depression of ECG trace; [b] "Ischaemic score"‡.	Time to ischaemia (ECG detection of ST segment depression) on a graded-stress treadmill test. Differences between baseline and 27 weeks post-randomisation calculated. Comparison in differences CT v. placebo.
Timing of primary outcome measures	Before and immediately after treatment, and at 3 to 6 months after treatment.	At baseline and at 15 and 27 weeks post-randomisation.
Secondary outcome(s)	Patient well-being + side effects; Lab: measures:- Blood Ca, calcitonin, PTH, electrolytes, creatinine, lipids. Angiographic coronary scores. ^{201}Tl scintillography of myocardium; Ventricular ejection faction using ^{99}Tc gamma camera.	Exercise functional reserve†††; quality of life assessment (Seattle Angina Questionnaire; Duke Activity Status index; Health Status Survey Short Form-36); clinical events.
No. at start	16 CT = 8 PL = 8	84 CT = 41 PL = 43
No. at end	15 at end of treatment; 7 at follow up.	78 CT = 39 PL = 39‡‡‡
Follow up time	3 to 6 months	12 months for clinical events.

CT = chelation therapy. PL = placebo. ECG = electrocardiogram. PTH = parathyroid hormone. * Details from full paper . † Details extracted from report by M. Gleuβner.[67] †† Solution cotained 5% dextran, 80 mg Lidocaine, 5 g ascorbic acid, 0.7 g magnesium sulphate, and sodium bicarbonate to titrate to physiological pH. ††† calculated from maximum oxygen consumption and time to anaerobic threshold . ‡ Ischaemic score = [(100 x mm ST depression) / (Watt x F)] where F = fraction of 6 min that excerise was performed. ‡‡ Both groups received oral vitamins on non-treatment days. ‡‡‡ Intention to treat analysis.

6.2.3.2 Quality assessment

i] Hopf trial

The randomisation method was not described. Assessors were blinded. Treatment of patients was delivered by a "believer" in chelation therapy. It is not clear if this individual was also an assessor. It is likely patients were effectively blinded to treatment. Baseline charactistics were provided including patient history of MI and bypass grafts, grade of angina, and scores for number and extent of main coronary artery branches with stenosis (2.6 and 2.1 for placebo intervention group respectively). It is unlikely the two groups differed significantly at baseline.

The method of primary outcome measurement was fully described in the dissertation report as follows:- patients operated an exercise machine at their maximum individual power output capacity while linked to an ECG recorder that monitored ST segment depression (mm).

Exercise was continued for up to 6 min or such time that the patient discontinued because of angina, breathlessness or exhaustion. The machine allowed measurement of power output (Watt). The assessor recorded duration of exercise (t; in min), power output (P; in Watt) and maximum ST depression on ECG trace (D; in mm). If ST depression was observed then an ischaemia score was calculated:-
Ischaemia score = (100 x D) / (P x [t/6]); [a measure of ST depression per fractional work performed].

The numerous methods used to measure secondary outcomes were also described. Pre- and post-treatment outcome measures were made but the exact timing of follow up measures was not given (between 3 and 6 months after treatment). One placebo group patient did not complete treatment (withdrew for bypass operation) and did not contribute post treatment data. From the variance in the primary outcome measure at pretreatment it is clear the study was underpowered except for detection of large changes in the primary outcome.

ii] Knudtson trial

The Knudtson trial full paper provides trial details lacking in the abstract. The method of randomisation was partially described (randomisation in blocks of ten) and the fact of allocation concealment from investigators was stated and the method indentified. Extensive baseline characeristics were tabulated and there were no statistically significant differences between groups; however the chelation group had experienced more myocardial infarctions (20/41 v.12/43) and more individuals in the placebo group were receiving nitrate therapy (19/43 v. 10/41). Similarity in baseline characteristics indicated successful randomisation.

Therapy was described as “nurse-supervised”. Apart from the substitution of saline for EDTA both groups received the same treatment. Infusion solutions were indistinguishable by colour or labelling. Infusions were slow and contained Lidocaine to minimise the possibility of unblinding (EDTA infusion might be distinguished from saline because of stinging sensation). It is likely therefore that care was the same for both groups. Losses to follow up were low (less than 10%) and were similar between groups. All losses were accounted for. Blinding of patients was safeguarded by slow infusion, use of Lidocaine, blinding of investigators and similar appearance of infusion solutions. Methods of outcome measurement were clearly described and intention to treat analysis (last observation carried forward) was employed. A power calculation was performed prior to the study and the study was adequately powered for the primary outcome measure.

This study was judged to be of high quality and scored 5 on a Jadad-based scale (range 0-5).

6.2.3.3 Results of RCTs of chelation therapy for patients with CHD

i] Hopf trial

The abstract of this trial provided values for mean change of work duration from baseline to end of treatment for the two groups. These results are shown in table 13.

Table 13. Summary of results of Hopf trial as presented in abstract

TRIAL	Group	n at start	n at finish	OUTCOME† Mean increase in time of work duration (at end of treatment v baseline) Value (min)	Statistical significance (Placebo v intervention)
Hopf et al., 1997	Intervention	8	8	1.2	No difference between groups
	Placebo	8	7‡	1.1	

† Mean group power output during work was similar in the two groups (106 and 94 Watt in intervention and placebo groups respectively). ‡ number obtained from report not abstract.

It is unclear how these results were derived from the fuller data provided in the dissertation report. We have recalculated the means and 95% confidence intervals using data for individual patients in the dissertation. They are shown in Table 14. No significant difference between groups in the mean change from baseline was observed for any primary outcome. Secondary outcomes were also not significantly different.

Table 14. Summary of primary outcome results of Hopf trial based on dissertation data

OUTCOME		INTERVENTION			PLACEBO		
		n	mean	95% CI	n	mean	95% CI
Duration of exercise test (min)‡.	before†	8	4.6	3.1 to 6.0	7	4.4	3.4 to 5.5
	after††	8	5.3	4.2 to 6.4	7	5.3	4.4 to 6.2
	change*	8	+ 0.75		7	+ 0.86	
Ischaemic score‡‡.	before	7	2.3	1.22 to 3.37	7	2.1	0.97 to 3.23
	after	5	1.8	0.89 to 2.65	6	1.9	0.78 to 2.97
	change		– 0.53			– 0.22	
Watts x FD**	before	8	80.9	48 to 114	7	74.6	47 to 102
	after	8	95.1	65 to 126	7	88.3	69 to 108
	change	8	+ 14.2		7	+ 13.7	

‡ Times were measured to the nearest half minute, the means we have calculated are the same as reported in the dissertation.
‡‡ The mean we calculated for the intervention group after treatment differs from that in the dissertation because one patient's data was omitted from the latter.
† Before treatment. †† After treatment. * Mean of individual changes (before treatment minus after treatment). ** FD = fractional duration of maximum 6 minutes.

ii] Knudtson trial

This trial was sufficiently powered to detect as statistically significant a difference between groups of 60 sec for change in mean time to ischaemia (pre-treatment to end of treatment; see Appendix 6). This represents an increase over pre-treatment time to ischaemia of ~20% for the intervention group.

Both groups significantly improved to the same extent their performance in the primary outcome measure (time to ischaemia). Thus the time to ischaemia at post-treatment (27 weeks) was significantly different from baseline (by about 10%) for both placebo and intervention groups. However there was no significant difference between groups for change in outcome (end of treatment relative to baseline). These results are shown in the Table 15.

Table 15. Summary of results of the Knudtson trial

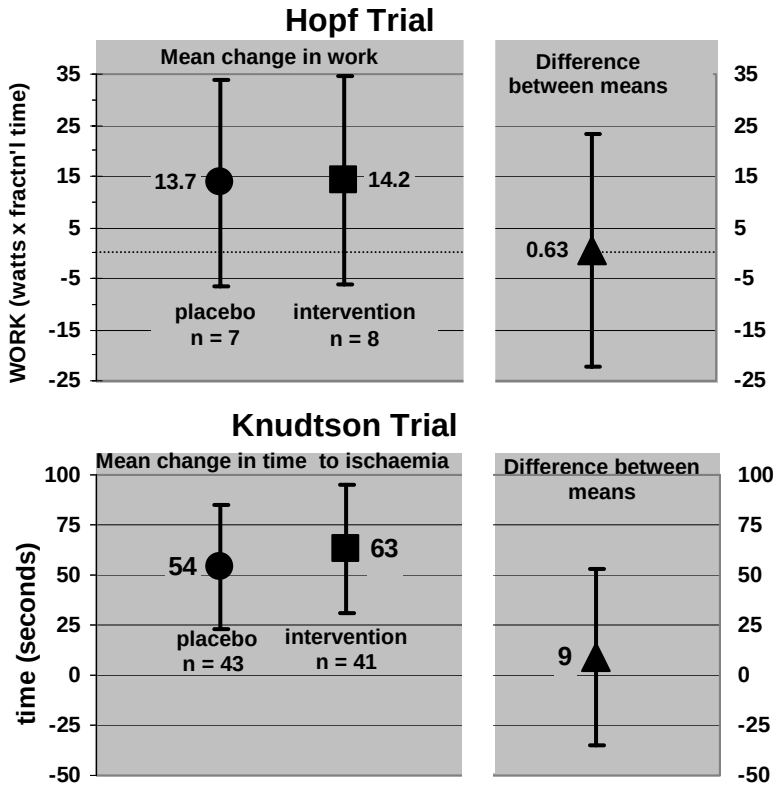
Group	n at start*	BASELINE Mean time (sec) to ischaemia [SD]	OUTCOME† Mean increase in time (sec) to ischaemia at 27 weeks v baseline Value [95% CI]	Statistical significance (P values 27 weeks v baseline)	Statistical significance (P value Placebo v. Intervention)
PLACEBO	43	572 [172]	54 [23 to 84]	<.001	
EDTA	41	589 [186]	63 [29 to 95]	<.001	
Difference between groups			9 [-36 to 53]		.69

* Number completed = 39 in each group, last observation carried forward. † Treatment ceased at week 27 at which point primary outcome measure was made. 95% CI = 95% confidence interval.

Similarly there were no statistically significant differences between groups in any secondary outcomes. The intervention group did show a significant increase in maximum oxygen consumption (baseline v. 27 weeks P = 0.03) whereas the control group showed a non-significant increase, however again there was no significant difference in change between groups. Clinical events observed over the 12 month follow up period did not differ between groups.

6.2.3.4 Summary of results of RCTs of chelation therapy for CHD

A graphical summary of the primary outcome results is shown in Figs 4.



Summary of outcome measures reported in RCTs of chelation therapy for CHD. Error bars represent 95% confidence interval. ● = placebo ■ = intervention ▲ = difference between placebo and intervention.

Fig. 4

The Hopf trial was small (only16 patients). The reported difference between groups in mean number of stenosed coronary branches at the start of the trial was unlikely to have invalidated the trial. Variances in the primary outcome measures were large and the trial was under-powered except for detection of large changes. No significant affect of chelation therapy was found.

The Knudtson trial was of moderate size (78 patients completed). It was well designed and conducted. It was sufficiently powered to detect an effect size of 20% which by consensus represents a minimally important clinical improvement. No statistically significant effect of chelation therapy was found. The authors concede that generalization of their findings should be restricted to a population of similar characteristics to the study group (i.e. patients with stable angina, non-candidates for revascularization and able to perform on a treadmill). Since both intervention and placebo groups received oral multivitamins daily the authors could not exclude the possibility that these supplements might be partially responsible for the improvements observed in both groups. A Hawthorne effect provides an alternative explanation.

6.3 Reviews of chelation therapy for PAD and CHD

6.3.1 Reviews found and characteristics of included reviews

Thirty potentially relevant reviews were found. These dated from 1976 to 2001. They are listed in the Table 16.

Table 16. Details of Reviews found

Type of study	Number of studies	Source
Systematic & other Reviews	19	Embase,Medline or Biomednet
Systematic / Critical Reviews	2	CHID
Systematic / Critical Reviews	5	Referenced in Journal or cited in Web of Science
Systematic / Critical Reviews	2	Cinahl
Meta-analyses	2	Referenced in Journal

Of the 30 reviews found 24 were excluded for reasons tabulated in the Appendix 7.

The six included reviews[36,68-72] all attempted a critical analysis of primary data. They span 1993 to 2000 and therefore were able to evaluate at least two of the published RCTs of chelation therapy. Main features of these reviews are shown in Table 17.

Table 17. Summary and characteristics of reviews for chelation therapy for PAD and CHD

Authors [study type]†	Objective of Review††	Search strategy and outcome**	Inclusion exclusion criteria.	Results
Grier & Meyers 1993 [review article]	To determine safety & efficacy of EDTA chelation for atherosclerosis	Electronic Medline search + citation searches. Cited all RCTs to date of publication; also 14 of the 21 uncontrolled studies to 1993 retrieved and listed in Ernst 2000§.	Criteria not stated; all types of study of CT efficacy included.	Best evidence shows therapy is ineffective. EDTA CT should not be used in clinical practice to treat atherosclerosis.
Chappel & Janson 1996 [historic review]	Review research literature, current evidence of effectiveness, & potential mechanisms of action of EDTA	Strategy not described. Cited all RCTs to date of publication; also 7 of the 22 uncontrolled studies retrieved and listed in Ernst 2000§.	Criteria not stated; all types of study of CT efficacy included.	CT is a valuable therapeutic option for vascular disease.
Ernst E. 1997 [systematic review]	Review evidence from RCTs regarding safety and effectiveness of CT for PAOD	Extensive electronic and other searches. Cited all RCTs to date of publication.	Only RCTs admitted.	CT for PAOD is not superior to placebo, is associated with considerable risks and costs and should be considered obsolete
Elihu et al. 1998 [therapeutic review]*	Assess if there is sufficient evidence for the clinical use of CT in CVD	Strategy not described. Cited all RCTs to publication date except 1 abstract; also 4 of the 22 uncontrolled studies retrieved and listed in Ernst 2000§.	Criteria not stated; all types of study of CT efficacy included.	More controlled studies are required* to determine efficacy in CVD before broad use in clinical practice.
Olmstead 1998 [critical review]	Provide … critical analysis of evidence for and against efficacy of EDTA chelation.	Strategy not described. Cited all RCTs to publication date except 1 abstract; also 19 of the 22 uncontrolled studies retrieved and listed in Ernst 2000§.	Criteria not stated; all types of study of CT efficacy included.	More "balanced" controlled studies are required to determine efficacy.
Ernst 2000 [systematic review]	Summarize all the clinical evidence for or against effectiveness and efficacy of CT for CHD.	Extensive electronic and other searches. Cited all RCTs to publication date. 22 uncontrolled studies found and listed dating from 1955-93.	All clinical studies of intravenous CT for CHD	Given the potential for CT to cause adverse effects, this treatment should now be considered obsolete.

CT = chelation therapy. CVD = cardiovascular disease. CHD = Coronary heart disease. PAOD = peripheral arterial occlusive disease. RCT = randomised controlled trial.
† The study type as stated in the text or page header of the publication concerned.
†† As stated explicitly by authors. * This review considers several chelating agents in addition to EDTA.
** We assume that we have identified all RCTs published in full or abstract form.
§The included reviews have considered several types of study whereas our search strategy was aimed at controlled studies; we have therefore used the list of found studies in Ernst 2000 as a basis to compare reviews.

6.3.2 Quality assessment of reviews according to QUORUM check list

The included reviews were assessed according to the criteria set out in the Methods section. The QUORUM checklist is a list of the most important elements thought necessary for good reporting of a systematic review or meta-analysis.[45]

Two of the reviews (Ernst 1997[71] and Ernst 2000[68]) were formally identified as systematic and one other, Grier & Meyers 1993[72], was also systematic although not formally identified as such. The remaining reviews were not systematic but since their aim was identical to that of the others they were also assessed against the QUORUM checklist. The results are shown in the Table 18.

Table 18. Six included reviews assessed according to the QUORUM checklist

Heading	Subheading	Description	REVIEW †	Reported? (Y/N/I) G & M	C & J	E1	El et al	Olm	E2
Title		Identify the report as a meta-analysis [or systematic review] of RCTs……		N	NA	Y	NA	NA	Y
Abstract		Use a structured format……		Y	N	NA	N	N	Y
		Describe							
	Objectives	The clinical question explicitly……		Y	N	NA	Y	Y	Y
	Data sources	The databases (ie, list) and other information sources……		Y	N	NA	N	N	Y
	Review methods	The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication…….		Y	N	NA	Y	N	Y
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses		N	N	NA	N	I	Y
	Conclusion	The main results……		Y	Y	NA	Y	Y	Y
		Describe							
Introduction		The explicit clinical problem, biological rationale for the intervention, and rationale for review ……		Y	Y	Y	Y	Y	Y
		Describe							
Methods	Searching	The information sources, in detail (e.g., databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status,l anguage of publication)……..		Y	I	Y	N	N	Y
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design Validity assessment The criteria and process used (e.g., masked conditions, quality assessment, and their findings)……		N	N	Y	N	Y*	Y*
	Data abstraction	The process or processes used (completed independently, in duplicate)		N	N	N	N	N	N
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, &c, and how clinical heterogeneity was assessed……..		Y	N	Y	N	Y	Y
	Quantitative data synthesis	The principal measures of effect (e.g., relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias….		NA	NA	NA	NA	NA	NA
		Describe							
Results	Trial flow	Provide a meta-analysis profile summarising trial flow (see figure) ……		NA	N	NA	NA	NA	NA
	Study Characteristics	Present descriptive data for each trial (e.g., age, sample size, intervention, dose, duration, follow-up period) ……		Y	N	Y	Y	Y	Y
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (e.g. 2x 2 tables of counts, means and SDs, proportions) ……		I	N	I	N	Y	Y
Discussion		Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (e.g., publication bias); and suggest a future research agenda ……		Y	N	Y	Y	Y	Y

G & M = Grier and Meyers, 1993; **C & J** = Chappell and Janson, 1996; **E1** = Ernst 1997; **El et al** = Elihu et al, 1998; **Olm** = Olmstead 1998; **E2** = Ernst 2000. † Only in Ernst 1997 and Ernst 2000 was the body of the text formally subdivided into Introduction, Methods, Results and Discussion sections; Elihu et al, 1998 and Olmstead, 1998 lacked an Abstract; for the latter review the summary sections 5.1.4 and 5.2.7 were taken to be equivalent for an Abstract. * These reviews included all types of studies.
Some Descriptors in the QUORUM table have multiple elements, with respect to these Y = all or nearly all elements reported in the review; N = none or very few of the elements reported in the review; **I** = incomplete i.e. some elements only reported in the review. NA = not applicable.

6.3.3 Results of Reviews and analysis of Review Quality by additional criteria

6.3.3.1 General considerations

The individual reviews were assessed according to whether statements were matched by references given in their support and whether statements were errors, misrepresentations or

unsubstantiated by evidence quoted in their support. Also we examined the reviews for the direction and strength of their conclusions. The studies that were considered by the assessed reviews are shown in the table below.

Table 19. Studies considered in reviews of chelation therapy

		STUDIES CONSIDERED IN REVIEWS							
		Kitchell et al. ‡	**Olszewer et al.**	**Sloth-Nielson et al.‡‡**	**Guldager et al.**	**Van Rij et al.**	**Hopf et al.**	**Knudtson et al.†**	**Uncontrolled studies.**
REVIEW	DATE	1963	1990	1991	1992	1994	1997	2002	
Grier & Meyers	1993	YES	YES	NO	YES	PAR	PAR	PAR	YES
Chappell & Jansen	1996	YES	YES	YES	YES	YES	PAR	PAR	YES
Ernst	1997	NA	YES	YES	YES	YES	NA	PAR	NO
Elihu et al.	1998	NO††	YES	NO	YES	YES	NO	PAR	NO††
Olmstead	1998	YES	YES	YES	YES	YES	NO	PAR	YES
Ernst	2000	YES	NA	NA	NA	NA	YES	PAR	YES

‡ This RCT was excluded in the present report because it did not satisfy inclusion criteria. ‡‡This study[57] was excluded in the present report because it represents a subgroup study of the larger RCT of Guldager et al 1992.
† This RCT is tabulated because it was an included RCT in the present report.
†† Referenced but not assessed.
NA = not applicable (review considered only PAD or only CHD). PAR = published after the review.

6.3.3.2 Grier and Meyers (1993) review[72]

I] Material reviewed

This systematic review was written after the RCTs of Kitchell[48], Olszewer, and Guldager were published and all these trials were assessed. The subgroup study of Sloth-Nielson was either not found or not considered a separate RCT. Uncontrolled studies were reviewed. Other RCTs (van Rij, Hopf, Knudtson) were published after the review.

II] Review's conclusion

The reviewers concluded that the Guldager RCT of 1992 was the only scientifically successful trial completed, their only criticism was that it may have been underpowered. By implication other RCTs mentioned (Olszewer and Kitchell) were judged scientifically unsuccessful. They considered that published case reports were of limited scientific value. They concluded that the best evidence favoured lack of efficacy; the therapy could not be recommended for clinical use but should not be totally rejected because it's potential mechanisms of action were enticing and warranted animal studies. They judged the therapy safe if administered in doses of no more than 3 g EDTA per infusion.

III] Analysis of the review

The date of the Olszewer trial was given as 1989 throughout. The correct date should be 1990. The results table (Table 1) asserted that the outcome measure in this trial was "..*symptoms*.." and that results were "..*not reported*..". In fact symptoms were not a stated outcome. The stated outcome measures were three exercise tests and blood pressure measurements. The

individual patient data for the three exercise tests were reported in full and group results for other outcomes were also reported.

The results table misrepresents the Guldager trial by quoting distances walked as though they were gains in distance walked.

Although the review mentioned the violation of blinding in the Olszewer trial the abandonment of blinding in the Kitchell trial and during follow-up in the Guldager RCT were not mentioned.

6.3.3.3 Chappell and Janson (1996) review[69]

I] Material reviewed

This review was written after the RCTs of Kitchell, Olszewer, Guldager and van Rij were published. These were all considered together with the subgroup study of Sloth-Nielson[57] which was partly reviewed as a separate trial. Uncontrolled studies were also reviewed.

II] Review's conclusion

These reviewers strongly endorsed the efficacy of chelation therapy. The findings reported in uncontrolled case studies were judged valid and of scientific value. The negative RCTs of Guldager and van Rij, and the subgroup study of Sloth-Nielson, were criticised but also used as evidence for effectiveness of chelation. The reviewers concluded that chelation therapy was valuable ("*..87% of patients demonstrate improvement with objective testing..*") and safe. They further considered it might be reasonable to treat healthy persons who ask for chelation therapy since it removes potentially toxic heavy metals to which most people have been exposed.

III] Analysis of the review

The reviewers stated "*..Olszewer completed a small blinded cross-over study...that demonstrated significant improvement in both walking distance and ankle/brachial index measurements..*". This statement was not qualified in any way. It is misleading and misrepresents the trial because the cross over study design was not completed but abandoned at cross over at which point blinding was also violated.

The Guldager trial and the Sloth-Nielson subgroup study were criticised for claiming to use, but not actually using, the ACAM protocol for infusion of EDTA. In fact this claim was not made in the trial reports. Guldager stated that they omitted magnesium sulphate ($MgSO_4$) from the infusion (and therefore did not exactly follow the ACAM protocol). It is also explicit that vitamins that are included in the ACAM infusion protocol were given separately to trial patients as a daily tablet. No mention of the ACAM protocol occurred in the paper of Sloth-Nielson et al.

The van Rij trial was criticised for having compared two chelating solutions rather than one chelating solution v. a placebo. The two chelating solutions were described as "*..one with EDTA and the other with thiamin and ascorbate..*". This is misleading since both placebo and intervention infusions contained equal amounts of ascorbate and thiamin. The essential difference between intervention and placebo was the presence in the former of 3 g of

disodium EDTA, a well known chelating agent. It is true that ascorbate does have some chelating abilities although these are weak compared with EDTA.

Of the van Rij trial the reviewers stated *"..both groups of patients showed significant overall improvement (EDTA 60% versus thiamin / ascorbate 59%)..".* There are several reasons why this statement is misleading:- (a)"*..overall improvement..*" was not defined. It implied the combining of outcomes into a single measure of improvement, a procedure not performed in the review itself or in the trial report. (b) The "*60*" and "*59%"* cannot refer to degree of improvement. The degree of improvement in walking distances were actually only in the range 6 to 20%; all blood pressure changes were less than 10%; among 18 different life style measures no improvement was greater than 32%. Increases in "subjective walking distances" were > 100%, but these values have no clinical significance whatsoever since they merely represent the patient's guess as to how far they walked. (c) The van Rij study did report increased (not "improved") walking distance (whether maximum or pain-free walking distance is unclear) in 60 and 59% of intervention and placebo patients at a single time point. They did not comment on proportions of patients with respect to any other outcome measure or time point. Since the degree of increase in the patients was not specified and because there is random variation in any measure, we would expect that (with null-effect treatments) on average about half of the patients would increase and half would decrease their walking distance. Thus an increase in walking distance in 59 or 60% of patients is about what would be expected by chance. The fact that the degree of improvement is unspecified renders the unqualified statement made in the review at best meaningless and possibly misleading.

The reviewers stated that in the trials of Sloth-Nielson, Guldager and van Rij "*..50 to 60% of patients improved..*". It is not clear if this refers to one or all three of the trials. It is impossible to justify this statement from the data published in the trials since, except for a single secondary outcome (transcutaneous oxygen tension) in one study[57] no individual patient data was presented. Again, since the degree of improvement is not specified, we would expect by chance that on average about half of the patients to change in one direction and half in the other direction. The statement is at best meaningless and at worst misleading.

6.3.3.4 Ernst (1997) review[71]

I] Material reviewed

This systematic review was about RCTs of chelation therapy for peripheral occlusive arterial disease. It was written after the RCTs of Olszewer, Guldager and van Rij were published. All three were considered in the review together with the subgroup study of Sloth-Nielson[57] which was treated as a separate study. Uncontrolled studies were not included.

II] Review's conclusion

The Sloth-Nielson paper was acknowledged to be a subgroup study of the larger Guldager RCT, but it was nevertheless treated as an independent investigation. The positive trial of Olszewer was judged of such poor quality as to preclude interpretation. The three negative RCTs of Guldager, Sloth-Nielson and van Rij were found to be of "*..outstanding methodological rigour..*" yielding results that "*..clearly and conclusively show that .. chelation therapy does not ameliorate symptoms of the disease, nor .. change objective signs of the disease..to a greater extent than placebo..*". Lack of demonstrable efficacy and the

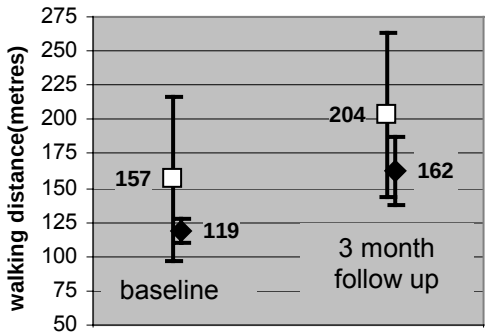
possibility of "*..severe, life-threatening adverse effects..*" led this reviewer to the emphatic conclusion that the therapy should considered obsolete.

III] Analysis of the review

The reviewer remarked on the subgroup study *"..in this sub-population there was a (non-significant) trend for the MWD and the peripheral arterial pressure to increase to a greater extent in the placebo group than in the EDTA group..*". This statement is not supported by the data (see Fig 1 & 2. of Sloth-Nielson et al[57]) and is unjustified because the full data from the study of 153 patients were available to the reviewer. Sloth-Neilson et al. commented "*..in this study the walking distance improved equally in both groups during the first ten infusions …after this the walking distances were similar..*". Maximum walking distance data for the full study is shown in the diagram below (Fig. 5); it fails to demonstrate any such trend.

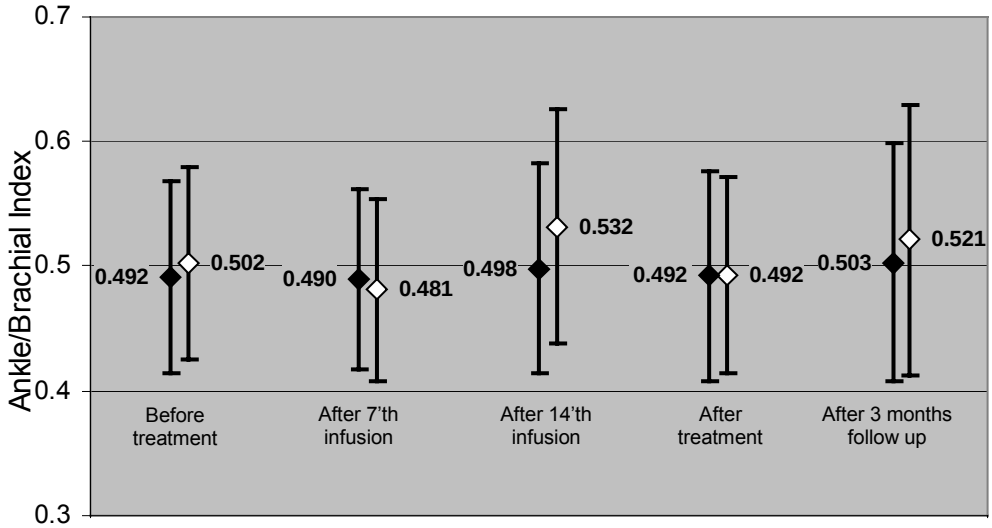
Fig. 5

Guldager MWD at baseline and at 3 months follow up. (open symbol placebo, filled symbol intervention). Error bars represent 95% confidence intervals of the mean.



Sloth-Nielson did not report peripheral arterial pressures but provided ankle/brachial blood pressure measures in a graph. Sloth-Nielson commented "*..ankle-brachial indices were constant in both groups during the study period..*", and "*..ankle/brachial indices before treatment, after 7 infusions, after 14 infusions, after a total of 20 infusions and after 3 months follow up are shown in Fig2. The curves are horizontal and are not significantly different..*". We have redrawn the data from the trialists' Fig 2 and this is shown below (Fig. 6). It does not support the reviewer's comment.

Fig. 6



◆ = intervention, ◇ = placebo. We have attempted to reproduce the error bars of the original figure pro-rata. It is assumed they represent standard deviation of the mean, but this was not stated. Data calculated from the graph shown in figure 2 of Sloth-Nielson et al.

Van Rij was quoted as stating that 59 and 60% patients "*improved*" in the two groups. In fact van Rij states that 59% and 60% increased their walking distance (type unspecified) at 3 months follow up.

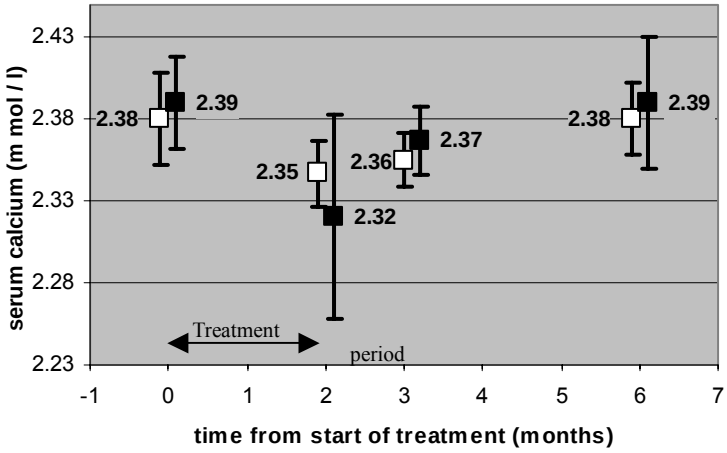
The reviewer pointed out that authors of the Olszewer trial were "*..unclear as to the method of data analysis..*" and that they had stated "*..there were no intergroup differences at the end of the double blind phase*..". The review's summary Table lists the result of the Olszewer trial as "*..no intergroup difference*..". However, whatever the shortcomings of the trialists' data analysis, or of their statements based on these, reviewers are empowered to conduct their own analysis because individual patient data was reported.[73] When this is done the between group significant difference in walking distance after ten infusions (the end of the double blind phase) is obvious (see fig 1 top panel page 31 and Table 8 page 28). Therefore the results of this trial are not reliably represented in the review.

The Sloth-Nielson subgroup study was referenced in support of the statement:- *"..in one trial, 6 patients of the experimental group showed clinical signs of (potentially lethal) hypocalcemia*..". However this reference did not mention hypocalcaemia and with regard to side effects of treatment the authors commented:- "*side effects of treatment were non specific and there was no difference between the two groups*". Among *"..side effects during treatment..*" the full Guldager trial report does list 6 intervention patients, but also 2 placebo patients (left unmentioned in the review), as exhibiting "*hypocalcaemic symptoms*". Hypocalcaemic symptoms were not defined. Neither whole group or individual patient blood calcium measures were provided. According to the text, "*..eight patients (5 intervention and 3 placebo) received intravenous calcium gluconate*.." . Why 5 intervention and 3 placebo patients should be treated when hypocalcaemic symptoms were observed in 6 and 2 respectively is unclear.

Another subgroup study[55] (not Sloth-Nielson) did report serum calcium levels in a single-centre subgroup (n=55) of the full Guldager trial (n=153). This paper was not referenced by the reviewer. In this study there was no significant difference between intervention and placebo groups for their change of serum calcium levels in response to treatment. Individual patient data was not provided and there was no mention of the number of patients with hypocalcaemia, "*..potentially lethal..*" or otherwise. We have calculated 95% confidence intervals for serum calcium concentrations reported in this subgroup study and these are shown in the figure below (Fig. 7). Because of the overlap of 95% confidence intervals for the intervention group data the authors' contention that a significant fall in serum calcium was observed in this group at end of EDTA treatment appears questionable.

Fig. 7

Serum calcium concentrations in subgroup of patients from the Guldager trial[53]. Solid symbols = intervention, hollow symbols = placebo. Error bars are 95% confidence intervals calculated from the data presented in Guldager et al. 1993.[55]



The review asserted that:- "*..through it's chelating action EDTA treatment is associated with severe life threatening events..*" This was referenced with Guldager et al.,1992[53] and Meltzer et al., 1961[74]. The former is an RCT in which the authors described side effects that "*..were generally non-specific and showed no preponderance in any of the groups..*" . Lack of clarity in the description of drop-outs means we are unable to allocate to which group all the patients suffering the serious adverse events (one death, two strokes) belonged. This reference does not support the assertion.

The other reference[74] offered in support described uses of EDTA from more than 40 years ago. It reported on 2000 infusions of 3g Na_2 EDTA administered on alternating days over a two year period to 81 consecutive patients. No cases of nephrotoxicity were observed. Prothrombin time was prolonged by about 30% but no adverse haemorrhagic events were noted and prothrombin time returned to normal within twelve hours of infusion. Other side effects considered included hypotension, vitamin deficiency syndromes, hypothyroidism, gastrointestinal problems, abdominal pain and local pain during infusion. The incidence of side effects was rare. The authors concluded *"..we have found no serious side effects or toxicity with use of EDTA when administered as a 3 g dose and infused as a 0.5% solution over 2.5 to 3 hours. It is therefore our opinion that the drug can be used without danger over prolonged periods.."* . This reference does not support the review's statement above.

Proponents of chelation therapy were accused of an.. "*outdated understanding of atherogenesis*".. in attempting to .."*deblock arteries*".. by.. "*extracting calcium*".. from …"*plaques*".. they were adhering to.. "*pathophysiological models…in overt discordance with present knowledge*". This accusation is unjustified. Firstly modern theories of plaque pathogenesis focus on metal ion-dependent free radical damage to LDL particles which, in theory at least, might be treatable via chelating agents (as is claimed by proponents). Secondly, calcification of plaques[61,75] has recently become detectable by sensitive non-invasive techniques and evidence has been presented that it predicts severity of atherosclerosis as indicated by adverse events.[30,75,76] This implies, but does not establish, a role for calcification in pathogenesis of plaques.

6.3.3.5 Elihu et al. (1998) review[70]

I] Material reviewed

This review was about the efficacy of several chelating agents for cardiovascular disease. The Hopf trial was either not found or left unconsidered because it was only available as an abstract. The existence of the Kitchell trial was referenced but it was not reviewed. Uncontrolled studies are mentioned but not assessed. As no completed RCTs of EDTA for CVD were included Elihu reviewed the PAD studies of Olszewer, Guldager and van Rij. The Sloth-Nielson subgroup study was either not found or not considered a separate trial.

II] Review's conclusion

There was no explicit comment on the relative quality of the RCTs. It was pointed out that the largely negative van Rij trial had reported "*.small improvements...at 3 months post chelation*.." in ankle/brachial blood pressure index and femoral artery pulsatility. The reviewers concluded that "*..there are conflicting results even within well-controlled trials*..". They considered serious side effects worrisome but commented that few adverse effects had

been reported when the AMCAM guidelines were followed. They concluded that too few controlled studies had been performed to warrant clinical use of EDTA for cardiovascular disease. With respect to PAD they were non-committal, commenting merely that 2 of 3 RCTs had revealed no benefit compared to placebo.

III] Analysis of the review

We did not identify erroneous or unsubstantiated statements in the parts of the review that considered EDTA.

6.3.3.6 Olmstead (1998) review[36]

I] Material reviewed

This review was written after the studies of Kitchell, Olszewer, Sloth-Nielson, Guldager, van Rij and Hopf were published. All except Hopf were considered. Uncontrolled studies were also reviewed. The review was not published in a peer-reviewed journal. It was initiated by a commission from the National Institute of Health's Office of Alternative Medicine (USA).

II] Review's conclusion

Available clinical data on EDTA therapy for CHD was judged scant and of poor quality. In the author's opinion only future prospective controlled clinical trials could firmly establish if EDTA was effective for symptoms of CHD or could alter the natural history of the disease.

With regard to PAD the reviewer assessed the quality and results of the Olszewer, Guldager, van Rij trials and the Sloth-Nielson subgroup study.

The Olszewer trial was judged inadequate in many respects and the outcome tests were described as scientifically invalid.

The Guldager trial was judged underpowered; in addition this trial was severely criticised for: a) poor retention of patients; b) inability to account for all dropouts; c) violation of blinding; d) inadequate effort to establish reproducibility in outcome measures prior to commencement of the trial; e) failure to employ intention to treat analysis; f) inappropriate statistical procedures. Despite the trialists' conclusion that chelation therapy did not result in improvement of intermittent claudication the reviewer stated ".. *the presented data, questionable as they are, indicated the mean MWD increased in the EDTA group*..". and pointed out that at 6 months the intervention group MWD was 51.3% increased from baseline whereas the placebo group was increased by 23.6% (see Fig 1, page 31).

The under-powering of the van Rij trial was described as " ..*a major failing*..". Otherwise the trial was judged well conducted. The statistically significant superiority of chelation therapy in improving ankle/brachial blood pressure index and femoral artery pulsatility was described as having clinically uncertain but intriguing implications. In the reviewer's opinion these findings indicated that EDTA chelation may improve non-invasive parameters of leg perfusion in patients with PAD.

The Sloth-Nielson subgroup study was criticised for :- a) it's small numbers (n=30); b) lack of blinding of investigators in measurement of walking distance; c) the use of arteriograms

assessed subjectively rather than by a quantitative method; d) lack of information concerning the timing of the follow up arteriograms. The arteriograms were dismissed as representing little more than opinion.

The poor quality of RCTs so far published (1998) and the hints of therapeutic effectiveness evident to the reviewer in these studies led him to the opinion that effectiveness of EDTA chelation for vascular occlusive disease was still an open question that awaited the outcome of a well conducted adequately powered RCT.

III] Analysis of the review

This critical review is by far the most extensive review we included here. It covered all aspects of EDTA chelation therapy. We did not identify erroneous or unsubstantiated statements in those parts of the review that considered efficacy of EDTA therapy for intermittent claudication or CHD.

6.3.3.7 Ernst (2000) review[77]

I] Material reviewed

This systematic review was about EDTA chelation therapy for coronary heart disease. It was written after the RCT report of Kichell (1963) and abstract of Hopf (1997) were published. These, together with 22 uncontrolled studies, were reviewed. The Abstract and full report of the RCT by Knudtson were published after the review.

II] Review's conclusion

The RCT reports of Kitchell 1963 and of Hopf 1997 were described as far from satisfactory. It was judged that these and the 22 uncontrolled studies found provided no reliable evidence of benefit. The risks, including the possibility of death, were considered substantial. The safety of the more recent protocols (presumably ACAM, but not specified) was judged not established and unconvincing. The review concluded that chelation therapy for CHD should be discarded and considered obsolete.

III] Analysis of the review

Data in the review were said to be presented in " .. *predetermined, standardized format (Tables I and II)..*". Only one table was published. All data may not have been presented.

The reviewer asserted ".. *when angiographic verification is sought in case studies of chelation therapy the results are negative…*" . This was supported by two references.[78,79] Each of these describes a single patient. One was a 57 year old man with PAD who received 30 EDTA infusions and whose angiographic results deteriorated; the other a 65 year old man with chronic angina who received 50 infusions of EDTA and one month later developed total occlusion of the right coronary artery. The case study of McDonagh & Rudolph (1993)[80], which reports angiographically determined improvement in a single patient after EDTA infusion, was not mentioned. These appear to be the only published angiographic studies of chelation therapy in which objective measures were made. It is misleading to only mention the negative reports.

The reviewer's statement "*.. several deaths have been reported with little doubt about the causal role of chelation therapy..*" was supported by one reference.[81] This paper provided details of only one patient, an 81 years old woman treated with EDTA for intermittent claudication. During the course of treatment she developed leg pain at rest and early lower leg gangrene (a natural history observed many times for the disease). Arteriography showed occlusion of the distal aorta and iliac arteries. Endarterectomy and an aortobifemoral bypass operation were performed. The patient developed renal failure "*..in the post-operative period… and died 5 days later*..". The time that elapsed between the end of chelation and surgery and death was not clear. No information on the dose level of EDTA, the duration or the frequency of dosage was provided. The author stated "*..post-mortem examination of the kidneys showed that renal failure was due to acute tubular necrosis*", and "*..useless therapy may have been responsible for the fatal complication*..". It is arguable that death could have resulted from complications of surgical intervention rather than chelation therapy. This reference also contained the statement *"..it is known that three other deaths have occurred during therapy.."*. Details were lacking and such information can only be viewed as anecdote.

In support of the statement "*..the risks associated with chelation therapy are substantial..* " the reviewer provided 7 references.[37,69,71,72,79,82,83] Three of these were other reviews. Two of these made the following statements with regard to safety :- "*.. EDTA chelation therapy is a safe and valuable addition to treatment protocols for all types and severity of vascular disease..*"[69]; "*.. EDTA does appear safe when used in doses < 3 g per infusion..*"[72]. It must be questionable whether these references support the reviewer's statement. The third review quoted in support was the author's own systematic review of chelation therapy for peripheral arterial occlusive disease[71] (see earlier). In this other review the references used in support of the statement "*..EDTA treatment is associated with severe life threatening adverse effects*.." were the Guldager RCT [53]and the 1961 report of Meltzer et al.[74] The lack of support provided by these has already been discussed above.

Three of the remaining four supporting references for risks with chelation therapy were:-

- Wirebrough and Garaets 1990[79] (Referenced as "Winebrough" and Garaets in most papers) presented one case study and "*..reviewed reports that substantiate lack of efficacy in treatment of coronary atherosclerosis*..". The report documents progression of the disease in one patient despite chelation therapy. The focus of the reference is lack of efficacy and information on safety is anecdotal.
- One reference[83] listed those medical bodies that considered in 1983 that EDTA therapy was of questionable safety especially for patients with coronary heart disease. This reference is a list of opinions, has no bibliography and provides no primary data or sources of data on safety.
- Peterson (1983)[82] speculated that adverse events resulting from EDTA therapy had been under-reported. He described a single patient who, treated with EDTA, developed life-threatening vasculitis. He also alluded to another recipient of EDTA therapy treated by a colleague. These patients were judged to suffer the manifestation of "*..autoimmune episodes..*" induced by EDTA therapy. Allergic reactions to many medications are widely recognised today, can be life threatening and are generally interpreted as rare individualistic responses that practitioners should be alert to. This reference does little to substantiate the reviewer's inference.

6.3.3.8 Summary of quality of reviews

The quality of the included reviews was variable.

The three systematic reviews were marred by statements that were not matched by references given in their support, were in error, or were misrepresentations unsubstantiated by evidence quoted in their support. To avoid bias the conclusions drawn by reviewers should flow from the results obtained. In the reviews by Ernst the style in which the results were presented appeared to have been influenced by the conclusion arrived at. This also appeared to be the case in the review of Chappel and Jansen, but here the bias was in favour of chelation therapy rather than against it.

The reviews of Olmstead (1998) and Elihu et al (1998) were by comparison free of these markers of poor quality. The latter review was brief and rather superficial. The former review was extensive and, in the parts relevant to the present report, was of higher quality than the other included reviews.

6.3.4 Summary of results of reviews

Reviewers did not identify their methods of quality assessment of individual RCTs. The assessments ranged from superficial to very detailed. The outcomes of assessment of RCTs varied greatly. A single RCT was described as having "*..outstanding methodological rigour*.." by one reviewer while another reviewer found that it was "*..characterized by inadequate planning, flawed design, inappropriate execution and improper statistical analysis..".* Several reviews argued that the conclusions expressed by authors of RCTs were unjustified or wrong. All RCTs were severely criticised in at least two reviews.

A summary table of the reviewers' assessments of the RCTs they considered when determining the efficacy of chelation therapy for peripheral arterial disease is given in Appendix 8.

The reviews were polarised in their opinions on the effectiveness and safety of chelation therapy. At one extreme Chappell and Jansen concluded that CT was valuable, effective and safe. At the other extreme Ernst concluded that it was likely unsafe, certainly ineffective and should be abandoned. Between these extremes the other reviewers judged the therapy as administered according to ACAM protocol probably safe. With regard to effectiveness the earliest review considered that animal studies were warranted, another reviewer considered clinical use of EDTA (for CHD) unjustified but that chelation therapy in general might hold promise, while the remaining reviewer considered effectiveness to be an open question and awaited a quality RCT to settle the issue.

7. Economic analysis

The electronic searches yielded 446 hits all of which were excluded. One potentially useful economic study was found by checking citation lists.[84] This book entitled "The cost effectiveness of alternative medicines" was not obtained at the time of completion of this report.

The cost of a course of chelation therapy depends on the number infusions administered during a course of treatment and the cost of initial and final medical assessments of the patient.

The likely number of infusions is 10, 20 or 40 depending on clinical judgement. The infusions are associated with the following obligatory costs:-
[i] £102 per intravenous infusion.

[ii] £30 medical monitoring after every fifth infusion of the series (other than the last infusion).

[iii] £55 follow-up medical assessment at the end of the series of infusions.

[iv] £29 vitamin supplements.

Thus the obligatory costs associated with infusions are:-
For 10 infusions £1105
For 20 infusions £2185
For 40 infusions £4345

Initial Medical Assessment of the patient includes ECG, Blood/Urine tests and doctor's assessment costing £225. Additionally patients may receive Bi-directional Doppler Ultrasound examination (£75) or Ultrasound heart scan (£130). It is likely IC patients would receive the former option, and angina patients the latter, however it is conceivable that an individual patient might receive both options. The possible costs associated with this initial examination are thus: £225 (no doppler or heart scan), or £300 (with doppler), or £355 (with heart scan), or £430 (with both doppler and heart scan).

The possible combined costs of an infusion course + initial medical assessment are as follows:-

- For 10 infusions £1330, £1405 or £1535
- For 20 infusions £2410, £2485 or £2615
- For 40 infusions £4570, £4645 or £4775

After a course of treatment some patients later return for further therapy. There is no information about the proportion of patients that receive further courses of therapy or about the time lapse between repeated courses of infusion.

For purposes of comparison with the above costs the mean cost to providers (NHS Trusts) of CABG and PTCA are shown below (data taken from the NHS Reference costs 2000[85]).

Table 20. Mean cost of CABG and PTCA in NHS Trusts

PROCEDURE	HRG†† code	Mean cost (£)†		
		Elective	Non-elective	Day case
CABG	E04	4956	5206	572‡
PTCA	E15	2369	2478	1267

† Data relates to period 1998-1999. West Midland NHS Trust average costs are lower than the national mean. †† Health Resource Group. ‡ Very few day-case CABG are performed.

8. Conclusions

Uncontrolled studies are of no use for judging effectiveness of chelation therapy because:-

- Descriptive studies (e.g. case series) are inherently incapable of demonstrating a cause-effect relationship[86] (such as that CT is effective for CHD or IC).
- A pronounced placebo effect has been reported in many controlled studies that investigated various interventions for intermittent claudication and CHD.
- The most commonly used outcome measures (walking distance or exercise performance) tend to improve with repeated testing irrespective of intervention.
- Many uncontrolled studies have employed subjective, ill defined, or poorly validated outcome measures.

Three RCTs investigated whether chelation therapy was effective for IC. They did not provide convincing evidence of effectiveness of the therapy. One trial was small and of such poor methodological quality that the declared results carry no weight. The other two trials were underpowered and provided no statistically significant evidence for effectiveness with respect to the primary outcome measure.

Trials were so few and so underpowered that subgroup analysis could serve no purpose. The possibility that intermittent claudication patients who have progressed to critical limb ischaemia might benefit from chelation therapy is never likely to be addressed in an RCT since recruitment of appropriate numbers would represent an insurmountable problem. Some of these patients are judged inoperable while others eschew surgery. Uncontrolled studies have claimed that chelation therapy benefits some of these patients. The question arises should the NHS, in the present and future absence of strong evidence of effectiveness, provide chelation therapy for these few extreme and inoperable patients should they request it?

Two RCTs investigated the effectiveness of chelation therapy for CHD. Neither study provided evidence for effectiveness. One study was considerably underpowered. The other study was adequately powered and well conducted. It represents the only RCT of chelation therapy that contained sufficient participants to test the hypothesis in question. Details of this study became available in Jan 2002. This trial provided no evidence that EDTA chelation therapy was effective. Like the two better quality trials for IC this trial provided oral multi-vitamins for both intervention and placebo groups.

A major ingredient of CT is EDTA. This agent is responsible for nearly all the chelating power of the infusion and its properties are responsible for the title by which the therapy has become known and marketed. It is the only ingredient of the treatment that requires intra-venous infusion; all other components (other than heparin, which was presumably first introduced to avoid clotting problems) can be more simply administered by mouth. Thus if EDTA was shown to be ineffective it would be reasonable to expect that intravenous administration should be abandoned.

Proponents of CT reject this position. They view CT as a “holistic therapy” encompassing many active ingredients that might have synergistic interactions (thus any demonstration that EDTA on its own was ineffective would not be persuasive because possible synergisms would

have been ignored). They also argue that it has never been tested in a properly conducted RCT. According to this stance either published RCTs have failed to employ the definitive ACAM protocol because the intervention infusion has lacked essential ingredients (e.g.vitamins), or RCTs have made an inappropriate comparison because intervention and placebo groups have both received essential ingredients (e.g. multivitamins that should have only been components of the intervention). The four RCTs that failed to demonstrate effectiveness of EDTA each included oral multi-vitamins in both arms of the trial. Thus if synergisms between EDTA and these ingredients exist they would have contributed to any superiority of intervention versus placebo. Since no superiority was detected in any of these trials such potential synergisms would seem unlikely.

Several of the included reviews of EDTA chelation therapy were highly polarised in their conclusions with regard to effectiveness. A consensus conclusion derived from the included reviews cannot be justified. The least biased of the reviews concluded that more research was required.

In conclusion there is no convincing objective evidence that chelation therapy is effective for IC or CHD. Published RCTs represent the only available objective evidence on CT and fail to demonstrate effectiveness; however, these trials do not demonstrate that the therapy is ineffective. Most trials were underpowered, or there were hints of small positive effects, or it was desirable that a wider patient group was addressed. The Knudtson trial of CT for CHD was adequately powered but, as pointed out by the authors, the generalizability of its findings limited.

The cost of a course of chelation therapy ranges from £1330 for ten infusions to £4775 for forty infusions.

Further research : Further adequately powered RCTs are required to determine the ineffectiveness or effectiveness of CT for CHD and IC. From the small effect sizes observed in completed studies it is clear that a further RCT employing the same primary outcome measures would require a very large number of participants to test the hypothesis that chelation is more effective than placebo. A study with these numbers is unlikely to be undertaken because it would require considerable funding; it is questionable whether the small effect sizes that may exist have any clinical significance. A smaller study employing a validated primary outcome measure that was associated with less variance might be feasible, but no such measure appears to exist. To avoid ambiguity of findings it would be necessary for the intervention to contain EDTA plus other ingredients encompassed in the “holistic” therapy advocated by practitioners of CT, while the placebo arm should lack these ingredients. It would avoid confusion if such trials were described as investigating the effectiveness of “holistic chelation therapy”, or if the therapy was renamed to more accurately reflect the philosophy of its practitioners.

Appendix 1 - Variance of measures of maximum walking distance

Medline and Embase were searched from 1990 to the present for meta-analyses of studies of claudication. Those in which maximum walking distance was a measured outcome were included. Two meta-analyses were found.[26,27] Means and standard deviations of maximum walking distances (MWD) summarised in these papers were taken as representative values and tabulated for comparison with those reported in the Guldager and van Rij trials.

MWD mean (metres) and standard deviation (SD) in studies of therapies for claudication

Study	N	mean	SD	SD as % of mean		
Larsen and Lassen.,1966 [87]	7	233	149	64	Plac‡	post†
Porter and Baur., 1982 [88]	40	250	172	69	Plac	post
Di Perri and Guerrini.,1983 [89]	12	215	98	70	Plac	post
Volker 1983 [90]	26	290	86	30	Plac	post
Roekaerts and DeLeers.,1984 [91]	8	190	85	45	Plac	post
Trubestein et al., 1984 [92]	50	314	176	56	Plac	post
Reilly et al 1987 [93]	10	191	159	83	Plac	post
Gillings et al.,1987 [94]	61	193	105	54	Plac	post
Rudofsky et al., 1989 [95]	79	287	215	75	Plac	post
Lindgarde et al., 1989 [96]	74	200	138	69	Plac	post
Lundgren et al.,1989 [97]	21	570	349	61	Plac	post
Adhoute et al., 1990 [98]	42	337	171	51	Plac	post
Hiatt et al.,1990 [99]	9	381	156	41	Plac	post
Mannarino et al.,1991 [100]	10	115	34	30	Plac	post
Guldager et al., 1992 [53]	78	157	266	169	Plac	pre††
Guldager et al., 1992 [53]	67	206	239	116	Plac	post
Ernst et al., 1992 [101]	20	420	229	55	Plac	post
van Rij et al., 1994 [51,102]	17	196	121	62	Plac	pre
Regensteiner et al., 1996 [102]	8	392	145	37	Plac	post

‡ Placebo group. † Post treatment value. †† Pre treatment value.

Appendix 2 - Power calculation for study size in van Rij trial

Walking distance of individual claudicants is variable. Better designed studies carry out pre-trial measures to estimate this variance and then perform a power calculation to determine suitable trial size. van Rij explicitly described pre-trial tests and performed a power calculation. Unfortunately this power calculation was flawed and the study consequently underpowered.

Four pieces of information are required for a power calculation:-

- the effect size expected.
- the SD of the outcome measure.

- the alpha value required; essentially this is the acceptable probability (in the opinion of the trialists) that observations which deviate (by the expected effect size) from the null hypothesis are due to the play of chance. Usually alpha is set at 0.05 (i.e. the trialist rejects the null hypothesis if the results obtained would only occur by chance on 1 in 20 occasions).
- the beta value required; Beta is the tolerable probability (in the opinion of the trialists) of accepting the null hypothesis when it is in fact false (i.e. type 2 error; failure to reject the null hypothesis when it is false). Beta is usually set at 0.2 (the trialist is willing to accept a probablitiy of 0.2 that play of chance will lead to false acceptance of the null hypothesis).

From the SD and the effect size the "Standardised Effect Size" (SES) can be calculated (SES = effect size / SD). Using the value of SES, of alpha and of beta, the number of patients required in each group of the trial can be read off from published tables. The larger the standardised effect size the greater the number of participants required in the trial (alpha and beta remaining unchanged).

van Rij fixed alpha and beta at 0.05 and 0.2 respectively. The SD value for the calculation was not stated. The effect size is ambiguously stated once as 0.2 and on another occasion as 10% (i.e. 0.1). It is possible, but unclear, that either or both numbers actually refer to Standardised effect Size. The number of patients for each group was then calculated by van Rij to be 15 and the actual number of patients used in the trial was 32 (15 +17).

In the table below we have calculated participant numbers using standardised effect sizes of 0.1 and 0.2 (rows 1 and 2). The results are approximately 3000 and 800 respectively.

Alternatively van Rij may mean that effect size is 0.1 or 0.2; with these values we used the standard deviation of the placebo group maximum walking distance at pre-treatment (mean MWD 196 metres [SD = 121 metres]) to make the calculation. Effect sizes of 0.1 and 0.2 then correspond 20 metres and 40 metres respectively giving Standardised Effect Sizes of:- 20/121 and 40/121, or 0.165 and 0.33 respectively. With alpha and beta set at 0.05 and 0.2 these Standardised effect Sizes generate participant numbers of approximately 1000 and 300 respectively (rows 3 and 4 in the table).

It is possible to use the actual participant number used by van Rij (i.e. 32) to calculate the Standardised Effect Size detectable at alpha 0.05 and beta 0.2. The result is 0.7. Given that the standard deviation observed for the outcome measure is 121/196 = 0.62 the effect size (ES) detectable (at P 0.05) in the trial is approximately 0.89 [i.e. a 89% increase in walking distance] (bottom row in the table).

A further ambiguity in the van Rij paper complicates the issue of the power calculation. It is possible that the effect size the authors actually considered refers to the difference between intervention and placebo in the **change** in walking distance after treatment. This is not made clear in the report. If this is the case then the trial was more underpowered than calculated above.

	Mean Walking distance in metres	SD	Effect Size (ES)	Standardised effect Size = [effect size] / SD	α	β	Number of patients required in each arm of study
				0.1	0.05	0.2	1570
				0.2	0.05	0.2	393
	196 m	121 m	20 m	20/121 = 0.165	0.05	0.2	(393-698) ~500
	196 m	121 m	40 m	40/121 = 0.33	0.05	0.2	(98 – 174) ~150
Calculated effect size [% change in walking distance] for actual numbers used	196 m	121 m OR 121/196 = 0.62	0.89 = 89%	SD / ES = 0.7 0.62 / ES = 0.7 ES = 0.62 / 0.7 ES = 0.89	0.05	0.2	(17+15)/2 =16

‡ van Rij assumed 80% power (β = 0.2) to avoid a Type II error and maximum chance of a type I error of 5% (α = 0.05); The calculation assumes a null hypothesis that after chelation therapy the maximum walking distance is the same as after placebo.

Appendix 3 - Confidence intervals in the Guldager study

Guldager et al. stated that they calculated effectiveness ratio (ER) using the logged % change in individual walking distances. They quote (ER) and 95% confidence intervals (CIs). For example at 3 months follow up for MWD:-

ER and (95% CIs) = 0.94 (0.82 to 1.08)

The confidence intervals reported are surprisingly narrow relative to the large standard deviations quoted for group mean walking distances and when compared with those calculable from individual patient walking distances available from the van Rij study (Godfrey and Chappell 1996[61]).

It is not possible to check the Guldager CIs directly because individual walking distances of patients were not provided. However it is possible to back calculate a value for the SD of 'the % mean change from baseline of the groups', and to then compare this with the actual standard deviation quoted for the mean of the groups MWD; as follows:-

Since Guldager log transformed "% change in individual WDs" we take the natural log of the ER and CIs giving: -

(ln ER) = -0.061875; and (ln CIs) = lower CI -0.198451 and upper CI = 0.076961

The difference between (ln ER) and (ln CI) is given by:

(ln upper CI) – (ln ER) = 0.13886‡
(ln lower CI) – (ln ER) = 0.13657‡
[‡ these differ slightly because of rounding in the Guldager report]

Taking the average difference we have:- (0.13886 + 0.13657) / 2 = 0.1377

The difference between ln ER and ln CI (0.1377) = SE x ***t***
Where SE is :- the standard error of the difference between means (intervention v. placebo) of "ln % change in WD of individual patients".

Guldager quote patient numbers as:
n_1 (placebo group) = 67 n_2 (CT group) = 66
Thus the degrees of freedom = 131; giving a ***t** value* = 1.978

Since SE x ***t*** = 0.377 we have SE = 0.377 / 1.987 = 0.0693

SE is related to "pooled SD of difference between means" (SDp) as follows:
$SE = SDp \times \sqrt{(1/n_1 + 1/n_2)}$

Thus $SDp = SE / \sqrt{(1/n_1 + 1/n_2)} = 0.06962/0.17342 = 0.401$
The pooled SD (SDp) relates to the SD values for mean % individual change in WD for the two groups (intervention and placebo) as follows:

$$SDp = \sqrt{[(SD_1)^2 \times (n_1 - 1) + (SD_2)^2 \times (n_2 - 1)] / (n_1 + n_2 - 2)}$$

Where SD_1 and SD_2 are the SD values for the two groups.
If we assume equal variance in the two experimental groups ($SD_1 = SD_2$), which is a reasonable assumption if patients were successfully randomised to groups, then

$$SDp = \sqrt{[(SD)^2 \times (n_1 - 1) + (SD)^2 \times (n_2 - 1)] / (n_1 + n_2 - 2)} = \sqrt{SD^2 \times 131 / 131}$$

$= \sqrt{SD^2} = SD$ THUS:-

SD_1 and SD_2 = SDp = 0.401

This value is **the SD of the natural log of the mean % change** in the individual patient WD at 3 months follow up compared to baseline. The antilog = 1.5%.

This implies that if the individual change in walking distances averaged 33% then the SD of this mean would be approximately 1.5% (indicating that 68% of the individuals changed their walking distance by between 31.5% and 34.5%). This range is extremely narrow and is implausible especially in view of the very large SD of MWD for groups (shown below), and when compared with the SD calculated using individual data provided in the other study (van Rij).
Group results from the Guldager trial (MWDs):-

Pre-treat MWD Mean (SD)	3 month MWD Mean (SD)	% change MWD	ln % change	
119 (38)	162 (101)	36%	3.58	intervention
157 (266)	204 (248)	30%	3.4	placebo

The contrast between confidence intervals stated in the Guldager report and those calculated from individual data of the van Rij study is highlighted when normal distributions are drawn using appropriate means and SDs; as can be seen below (Fig.8) the Guldager distribution is extremely narrow compared to the van Rij distributions.

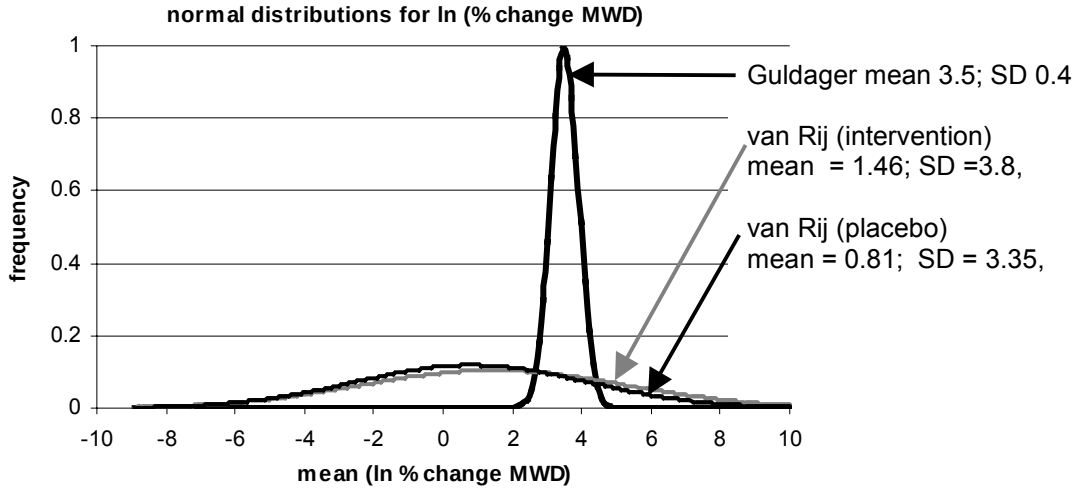


Fig. 8

It is likely Guldager actually log transformed % WDs of individuals (not % change in WD). To do this baseline WD would be designated = 100% (ln 100 = 4.60517).
The post-treament walking distance is then calculated as a % of that at baseline and the natural log taken (e.g. log 80% = 4.382 OR log 120% = 4.78749).
The change in log % WD for an individual is then given by:{ ln (% WD post-treatment) — ln 100}; e.g. (4.382 — 4.60517) or (4.78749 — 4.60517) ; i.e. — .22314 OR + 0.18232 .
This treatment would generate confidence intervals more commensurate with those quoted in the Guldager report.

Analysis of individual patient data from the van Rij trial

After the publication of the van Rij trial the maximum walking distances of individual patients at pre-treatment and 3 months follow up became available (Godfrey and Chappell [61]). Van Rij did not report an effect size of chelation therapy on walking distance (the primary outcome measure). They stated that "walking distances were log transformed" and that "effect sizes were calculated to standardise comparison of changes in mean values following treatment".

The individual patient data is tabulated below and is used to calculate an effect size as an effectiveness ratio. This has been done by three methods:-

1. Using changes in log of walking distance for each individual.
2. Using log of % changes in walking distance (according to the statement in the report of the Guldager trial). In this case the sign (+ or -) of the % change in walking distance was ignored for the logarithmic process.
3. Using the chage in the log of the % walking distance having defined the walking distance before treatment as 100%.

Individual patient data for intervention group of van Rij trial.

	Walking distance of individuals (metres)								
Patient no.	**Before treatment**	**3 months post treatment**	**Change from before to post**	**% change from before to post**	**ln (% Change)**	**Change in ln (%WD)** *[before treatment = 100%]*	**ln WD before treatment**	**ln WD 3 months post treatment**	**change in ln WD**
1	168	449	281	167.3	5.12	0.983	5.12	6.11	0.98
2	384	521	137	35.68	3.575	0.305	5.95	6.26	0.31
3	57	67	10	17.54	2.865	0.162	4.04	4.20	0.16
4	281	133	-148	-52.67	-3.964	-0.748	5.64	4.89	-0.75
5	141	345	204	144.7	4.975	0.895	4.95	5.84	0.89
6	152	308	156	102.6	4.631	0.706	5.02	5.73	0.71
7	54	92	38	70.37	4.254	0.533	3.99	4.52	0.53
8	116	203	87	75	4.317	0.560	4.75	5.31	0.56
9	301	301	0	0	0	0	5.71	5.71	0.00
10	253	174	-79	-31.23	-3.441	-0.374	5.53	5.16	-0.37
11	124	103	-21	-16.94	-2.829	-0.186	4.82	4.63	-0.19
12	97	187	90	92.78	4.53	0.656	4.57	5.23	0.66
13	129	302	173	134.1	4.899	0.851	4.86	5.71	0.85
14	426	255	-171	-40.14	-3.692	-0.513	6.05	5.54	-0.51
15	88	62	-26	-29.55	-3.386	-0.350	4.48	4.13	-0.35
Mean	**185**	**233**	**48.7**	**44.6**	**1.457**	**0.232**	**5.0332**	**5.2652**	**0.232**
SD	**117**	**138**	**129**	**73.1**	**3.81**	**0.564**	**0.6389**	**0.6674**	**0.564**

As can be seen from the table above normalising the before-treatment individual walking distances to 100%, calculating post-treatment walking distance as a %, taking logarithms, and then calculating the change in log % (post minus pre-treatment) gives the same result as merely taking logarithms of the walking distances and then calculating log post-treament minus log pre-treatment values.

Individual patient data for placebo group of van Rij trial

	Walking distance of individuals (metres)								
Patient no.	**Before treatment**	**3 months post treatment**	**Change from before to 3 months post**	**% change from before to 3 months post**	**ln % Change**	**Change in ln (%WD)** *[before treatment = 100%]*	**ln WD before treatment**	**ln WD 3 months post treatment**	**change in ln WD**
1	346	263	-83	-24	-3.18	-0.274	5.85	5.57	-0.27
2	424	903	479	113	4.727	0.756	6.05	6.81	0.76
3	317	261	-56	-17.7	-2.87	-0.194	5.76	5.56	-0.19
4	292	320	28	9.589	2.261	0.092	5.68	5.77	0.09
5	226	292	66	29.2	3.374	0.256	5.42	5.68	0.26
6	104	156	52	50	3.912	0.405	4.64	5.05	0.41
7	113	218	105	92.92	4.532	0.657	4.73	5.38	0.66
8	141	143	2	1.418	0.35	0.014	4.95	4.96	0.01
9	109	272	163	149.5	5.008	0.914	4.69	5.61	0.91
10	341	285	-56	-16.4	-2.8	-0.179	5.83	5.65	-0.18
11	340	262	-78	-22.9	-3.13	-0.261	5.83	5.57	-0.26
12	87	110	23	26.44	3.275	0.235	4.47	4.70	0.23
13	53	52	-1	-1.89	-0.63	-0.019	3.97	3.95	-0.02
14	80	61	-19	-23.8	-3.17	-0.271	4.38	4.11	-0.27
15	107	117	10	9.346	2.235	0.089	4.67	4.76	0.09
16	174	90	-84	-48.3	-3.88	-0.659	5.16	4.50	-0.66
17	79	112	33	41.77	3.732	0.349	4.37	4.72	0.35
Mean	**196**	**230**	**34.4**	**21.7**	**0.809**	**0.112**	**5.0849**	**5.1973**	**0.112**
SD	**121**	**195**	**133**	**41.3**	**3.35**	**0.416**	**0.6539**	**0.7039**	**0.416**

In order to calculate ER according to the methods described we extracted appropriate means and standard deviations from the results tables above. These are presented in the table below.

	INTERVENTION		PLACEBO	
	MEAN	(SD)	MEAN	(SD)
Individual change in (ln of WD)	0.23193	0.56376	0.11234	0.41609
Ln (% individual change in WD)	1.457	3.81	0.809	3.35
Change ln % walking distance	0.23193	0.56376	0.11234	0.41609

To calculate the difference between means and 95% confidence intervals for the difference the software (CIA) accompanying "Statistics with Confidence"[60,103] was used.

The print outs from these tests are shown below:-

1] Using change in (log WD) all patients in the placebo group (including postulated outlier).

```
Unpaired Sample
                              Sample EDTA    Sample Placebo
Sample size                          15          17
Mean of individual log WD          .231932     .112338
Standard Deviation of above        .5637652    .4160887
Difference between sample means             0.11959400
Standard Error of difference                   0.174
d.f.       30   t    2.042
95% Confidence Interval for the difference between means   -0.235  to   0.474
EXP of above diff between means and 95% CI = 1.127  95% CI 0.791 to 1.61
```

Thus the ER and 95% confidence intervals are:- 1.127 (0.79 to 1.6)

2] Using change in (log WD) excluding the postulated outlier in the placebo group (patient 2).

```
Unpaired Samples: VAN RIJ DIFF OF LOG WD AT 3 MO MINUS LOG WD AT BASE LINE
                             Sample EDTA    Sample PLACEBO (minus patient#2)
Sample size                     15             16
Mean                           .231932         .07211
Standard Deviation             .5637652        .3941149
Difference between sample means             0.15982200
Standard Error of difference                   0.174
d.f.       29   t    2.045
95% Confidence Interval for the difference between means   -0.196  to    0.515
EXP of difference between means and 95% CI =  1.1733  95% CIs  0.822  to  1.674
```

Thus the ER and 95% confidence intervals are:- 1.173 (0.82 to 1.67)

3] Using log (% change in individual WD) and including the postulated outlier in the placebo group (patient 2).

```
Unpaired Samples
                              Sample EDTA        Sample Placebo
Sample size                         15              17
Mean                              1.457             .809
Standard Deviation                3.812            3.353
Difference between sample means               0.6480
Standard Error of difference                   1.266
d.f.       30   t    2.042
95% Confidence Interval for the difference between means   -1.938  to   3.234
EXP of the difference between means and 95% CI = 1.9117  95% CIs 0.144  to  25.4
```

Thus ER and 95% CIs are 1.9 (0.14 to 25.4)

4] Using change in " log % individual WD" (relative to pre-treatment WD =100%)

```
Unpaired Samples
                                    EDTA    placebo
Sample size                          15          17
Mean                               .231932     .112338
Standard Deviation                 .5637652    .4160887
Difference between sample means             0.11959400
Standard Error of difference                   0.174
d.f.       30   t    2.042
95% Confidence Interval for the difference between means   -0.235  to    0.474
EXP of the difference between means and 95% CI = 1.127  95% CIs  0.79  to  1.606
```

Thus ER and 95% CIs are 1.127 (0.79 to 1.606)

Appendix 4 - Follow up results from van Rij trial

The e mail from Professor van Rij in response to our query with regard to follow up results in the van Rij trail is given below.

Date sent: Tue, 5 Jun 2001 11:01:10 +1200
To: "MJ Connock" <M.J.Connock@bham.ac.uk>
From: Andre van rij <andre.vanrij@stonebow.otago.ac.nz>
Subject: Re: chelation therapy

>Hi Martin

thanks for your enquiry. Unfortunately we did not get around to publishing the additional data. There was not much to it. The longer term followup was no different to what we published for the early followup. The lipid work suggested some improvement in the lipid profile with chelation but with the numbers this was borderline and for some not readily apparent reason fasting glucose was marginally better in the chelated group. None of these observations were sufficient to extend the study and were not consequential for our major study aim i.e. the impact on peripheral vascular performance.

Sorry that I have not much to contribute further in your assessment report.

yours sincerely

Andre van Rij

Appendix 5 - Trial size and power of the Knudtson Trial

Knudtson reported mean (and 95% CIs) for "mean change in time to ischeamia" as:-

Placebo = 57.2 sec (23.5 to 90.9) Intervention = 65.5 sec (31 to 100).

From this one confidence interval can be computed as:-

Placebo = 33.7 (n =39) Intervention = 34.5 (n=39)

Since CI = t x SE and ***t*** at 38 degrees of freedom = 2.024
we calculate SE as:
Placebo = 16.65 Intervention = 17.045

Since $SE = S/n^{0.5}$ (where S = standard deviation of the mean) we calculate the standard deviations as:

Placebo = 103.98 Intervention = 106.45

From these mean and S values we calculate the difference between the means and the 95% confidence intervals for this difference.

We did this using CIA software [104]

The answer obtained = –8.3 (95% CIs –55.758 to 39.158). This agrees with the report by Knudtson.

The pooled standard deviation for this difference between means can be calculated to be 105.16 as follows:-

One confidence interval = (55.758 + 39.158) / 2 = 47.458 = ***t*** x SE
With 78 –2 degrees of freedom ***t*** = 1.992
Thus SE = 23.8243 and = SD x $[(1/39 + 1/39)^{0.5}]$ = SD x $[(2/39)^{0.5}]$ = SD x 0.2264
Where SD is the pooled standard deviation of the difference between the means.
Thus SD = 23.8234 / .2264 = 105.16 (units are sec).

Using the above values we calculated the smallest effect size (i.e. difference between group means for increase in time to ischaemia) required to reach significance as follows:-
Assuming a two tailed null hypothesis that there is no difference in effect between intervention and placebo.
Given group sizes to be 39 for placebo and intervention;
Adopting the probability of a type I error (α value) of 0.05 and a power of 80% (β=0.2) not to commit a type II error (i.e. fail to detect a difference between means when one actually exists).
Then from tables the standardised effect size required is between 0.6 to 0.7.
Since standardised effect size = Effect size / SD , and SD = 105 sec
we have an effect size = (0.6 to 0.7) x 105 sec = 63 to 73 sec.

Thus the Knudtson trial was capable of detecting a difference of about 1 minute between group mean time increases to ischaemia.

Since administration of placebo resulted in an increased time to ischaemia of about 1 minute (from the baseline time of about 10 min) the increase required in the intervention group (to reach significance with respect to placebo) = 1 min + 63 to 73 sec = ~ 2 min. This is approximately double the increase actually observed for the intervention group and corresponds to a 20% increase from the baseline time to ischaemia of ~10 min.

Appendix 6 - Excluded reviews

Twenty four reviews were excluded because they lacked a critical analysis of primary data or because they did not consider EDTA for atherosclerosis. They are listed in chronological order in the table below.

Table of excluded reviews

First author(s)	TITLE	Paper type	Reason for exclusion	Comments
Soffer 1976[105]	Chihuahuas and laetrile, chelation therapy, and honey from Boulder, Colorado.	Editorial	No critical analysis of objective primary data.	
Casdorph 1983[106]	Chelation therapy: a reappraisal	Letter	No critical analysis of objective primary data.	
Pentel et al. 1984 [107]	Chelation therapy for the treatment of atherosclerosis. An appraisal.	Narrative review	No critical analysis of objective primary data.	
Rathmann & Golightly 1984[108]	Chelation therapy of atherosclerosis.	Review	No critical analysis of objective primary data.	
Cortese 1992[109]	Chelation therapy. The bypass alternative?	Review	No critical analysis of objective primary data.	
Chappell & Stahl 1993[110]	The correlation between EDTA Chelation Therapy and improvement in Cardiovascular Function: A met-analysis.	Meta-analysis & review	Unjustifiable combination of different disease conditions, different study designs and different outcome measures.	84% of patients from a single study with unique outcome measure.
Chappell, Stahl & Evans 1994[111]	EDTA Chelation Therapy for vascular disease: a Meta-analysis using unpublished data.	Meta-analysis & review	Unjustifiable combination of different conditions and different outcome measures for purposes of analysis.	80% of patients provided by a single study with unusual outcome measure.
Hershko 1994[112]	Control of disease by selective iron depletion: a novel therapeutic strategy utilizing iron chelators.	Review	No consideration of EDTA for atheroscerosis.	
Mulcahy et al. 1994[113]	Lasers, burns, cuts, tingles and pumps: a consideration of alternative treatments for intractable angina.	Editorial	No critical analysis of primary data.	
Chappell 1995[114]	EDTA chelation therapy should be more commonly used in the treatment of vascular disease.	Review	No critical analysis of primary data.	Tandem review with Margolis. 1995
Margolis 1995[115]	Chelation therapy is ineffective for the treatment of peripheral vascular disease.	Review	No critical analysis of primary data.	Tandem review with Chappell. 1995
Conti 1995[116]	Chelation therapy for atherosclerosis: one man's view.	Editorial	No critical analysis of primary data.	
Mikaelsen 1995[117]	EDTA in the treatment of arteriosclerosis.	Review	No critical analysis of primary data.	In Norwegian; exclusion based on English Abstract.
Vecchio et al. 1995[118]	Management of cardiac complications in patients with thalassemia major.	Review	No consideration of EDTA for atherosclerosis.	
Chappell 1997[119]	Applications of EDTA chelation therapy.	Review	No critical analysis of primary data.	
Lewin 1997[120]	Chelation therapy for cardiovascular disease.	Review and [editorial].	No critical analysis of primary data	
Oliver 1997[121]	MDs remain sceptical as chelation therapy goes mainstream in Saskatchewan.	Review	No critical analysis of primary data	
Johnson & Eckerly 1998[122]	Complementary approaches to combating atherosclerosis.	Review	No critical analysis of primary data.	
Kidd 1998[123]	Integrative cardiac revitalization: bypass surgery, angioplasty, and chelation. Benefits, risks, and limitations.	Review.	No critical analysis of primary data	
Gundling & Ernst 1999[124]	Complementary and alternative medicine in cardiovascular disease: what is the evidence it works?	Review.	Duplicates other reviews {Ernst 1997, Ernst 2000}	
Lamas & Ackermann 2000[125]	Clinical evaluation of chelation therapy: is there any wheat amidst the chaff?	Editorial	No critical analysis of primary data.	

Lee 2000[126]	Ask the doctor. My neighbour has atherosclerosis in his leg arteries and he has been getting chelation therapy. He swears it has made a huge difference and thinks I should try it for my coronary artery disease. Your advice?	Review	No critical analysis of primary data.	Long title, brief text ~ 500 words.
Hiatt 2001 A[64]	Drug therapy - Medical treatment of peripheral arterial disease and claudication.	Review	Does not consider EDTA chelation therapy	
Hiatt 2001 B[127]	New treatment options in intermittent claudication: the US experience.	Review	Does not consider EDTA chelation therapy	

The two meta-analyses[110,111] did not meet inclusion criteria because they did not analyse IC and CHD separately; rather, studies of different diseases (IC, other PAD conditions, angina, stroke) were combined to obtain a spuriously precise but misleading estimate of the overall effect of treatment. This estimate was in the form of a correlation coefficient. A single case series[128] accounted for more than 80% of patients (19,000) in both analyses; this series employed a unique outcome measure (thermography) which was not used in any of the other studies included in the meta-analyses and which appears not to have been validated. This large case series was available to the meta-analysts as a pre-publication release. It does not appear to have been subsequently published. Faced with the problem of no controls the authors proceeded to "*simply consider the existing study data* (i.e. case series reports) *to be data for the treatment group and compare the improvement in cardiovascular function of the treatment group to a control group defined to have no improvement in cardiovascular function".* They further asserted:- *"It needs to be shown that the assumption of a no-treatment with no improvement control is reasonable. This meta-analysis will use the blinded study of Olszewer, Sabbag and Carter[52] to show this."* The invention of a null-effect control group in this way is clearly invalid and renders the meta-analysis meaningless. The assumption of a no treatment-control group with no improvement was claimed to be reasonable because a particular RCT showed no improvement in the control group. However this trial only had 5 control subjects (compared with a total of 22,675 subjects considered in the meta-analysis). Other RCTs that have reported a placebo effect in the control group were not taken into account.

Appendix 7 - Reviewers' assessment of RCTs

Quality of published RCTs of Chelation therapy according to included reviews

Review and review type		Randomised Control Trial Assessed and RCT conclusion					
		Kitchell et al.,1963	Olszewer et al., 1990	Guldager et al.,1992	van Rij et al., 1994	Hopf et al.,1997	Knudtson et al.,2001
		No valid conclusion can be drawn (study number too small; drop out rate too high)	EDTA improved clinical status of patients at a significance level of P<0.05	Study failed to demonstrate evidence of any effect of CT in patients with IC. CT does not have a potential role in the clinical therapy of PAD.	CT has no significant beneficial effects over placebo in patients with IC. Previous encouraging reports of CT not substantiated.	CT was not found effective in slowing the progression of coronary heart disease.	No evidence to support a beneficial effect of CT in patients with IHD.
Grier & Myers 1993	SR NR	Unsuccessful study	Unsuccessfull study	Only scientifically valid trial published to date, well designed but may have insufficient power.	NA	NA	NA
Ernst 1997 & Ernst 2000	SR	Study extremely small lacking sufficient detail for objective assessment.	Study of poor quality that lacks methodological data essential for interpretation.	Study of outstanding methodological rigor.	Study of outstanding methodological rigor.	Study of high methodological standard but not reported in sufficient detail to allow fair evaluation.	NA
Lewin., 1997	NR	Assessment purely descriptive		Assessment purely descriptive	Assessment purely descriptive.		NA
Elihu et al., 1998	NR	Not assessed &/or not found.	Assessment purely descriptive	Assessment purely descriptive	Assessment purely descriptive.	NA &/or NF	NA
Olm-stead 1998	CR		Statistical analysis unrecognisable as an accepted biostatistical procedure. A 100% clinical response rate reported which challenges the credulity of clinicians.	Flawed study with respect to inadequate planning, flawed design, inappropriate execution and inappropriate statistical analysis.	A well conducted but poorly planned study. Lack of power in the study precluded an effective test of the hypothesis put before it.	Not assessed	NA

"Assessment purely descriptive" refers to an account that reiterates or paraphrases the results and conclusions of the RCT without addressing its quality.
NA not assessed; NF not found; SR systematic review; CR critical review; NR narrative review.

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