Intermittent Claudication (IC).

The art of medicine consists of amusing the patient while nature takes its course.
Voltaire - François-Marie Arouet (1694 – 1778)

Claudication comes from the Latin word which was used to describe a lame horse, some say after Emperor Claudicus. Charcot first described the syndrome in 1858. In humans, limb pain is brought on by exercise and relieved by rest. Immediate onset with exercise and/or immediate relief on rest suggests causes other than arterial disease. The pain is caused by an exercise induced supply-demand mismatch. The functional effects result in neurological, skeletal muscle, metabolic and gait changes with associated deconditioning of the patient.

Table 1. Rutherford classification of chronic ischaemia.

Category	*Clinical description*	*Objective tests*
0	Asymptomatic	
1	Mild claudication	Completed treadmill test and post exercise ankle pressure of more than 50mmHg
2	Moderate claudication	
3	Severe claudication	Failed exercise test and ankle pressure of less than 50mmHg
4	Rest pain	Resting ankle pressure less than 40mmHg
5	Minor tissue loss	
6	Major tissue loss	

9% of the western population have peripheral arterial disease (PAD) on duplex scan but only 2.5% are symptomatic. The Edinburgh Artery Study showed that between the ages of 55 to 74 years, 4.5% had symptomatic claudication, 8% had major asymptomatic disease and 16.6% had abnormal haemodynamic variables indicative of PAD. Although most studies have shown a male predominance, a study from Norway showed equal prevalence of IC in males and females (*EJVES* March 2003).

Disability is the actual walking distance. Handicap is the way this affects the patient. The assessment of handicap is difficult but fundamental to treatment. Claudication distance (CD) is the distance walked till onset of symptoms. Absolute claudication distance (ACD) or maximum walking distance (MWD) is the distance patients can walk until they have to stop walking.

<u>Natural history of intermittent claudication.</u>
Survival is related to the severity of PAD as measured by the ankle brachial pressure index (ABPI). Within 5 years, 30% who present with IC will be dead and 20% will experience a non fatal vascular event. 70% of those with IC have ischaemic heart disease and their 10 year mortality is 50% (3.8 times higher than those without PAD).

1 - 5% of patients with IC will develop a threatened limb per year. Dormandy's study (1991) showed that at one year, the amputation risk was 1.6% and 5.5% required intervention. McAllisters study showed that over 6 years, 50% improve spontaneously, 30% remain unchanged, 20% deteriorate and 7% go on to have an amputation i.e. 1% per year. The best predictor of a deterioration of PAD is an ABPI of less than 0.5, with a hazard ratio of more than 2. In those patients with IC who have an ankle pressure of less than 60mmHg, the risk of progression to sever ischaemia or amputation is 8.5% per year so this may be an indication for more aggressive intervention.

Exercise in those with IC causes a neutrophilia and neutrophil activation (low grade ischaemia reperfusion injury) which may account for the increased morbidity and mortality. Angioplasty can reduce systemic changes induced by exercise.

The strongest risk factor for developing IC is smoking. The diagnosis of PAD is made 10 years earlier in smokers compared to non smokers and the severity of PAD increases with the number of cigarettes smoked. A major amputation rate of 6 – 11% is found in smokers with IC vs. 0% in non smokers with IC. The 5 year mortality for IC patients who continue to smoke is 40 – 50%. Cessation of smoking is associated with an improvement in claudication symptoms. Continued smoking is associated with a greater likelihood of developing disabling claudication, limb threatening ischaemia and amputation. Patency rates are lower and survival less following revascularisation in those who continue to smoke.

IC is twice as common in diabetics compared to non diabetics. Diabetics with IC have a 21% risk of major amputation compared to 3% in non diabetics. Thus good diabetic control is important.

Differential diagnosis.

- Spinal claudication – Due to lumbar spinal stenosis (LSS). LSS results from narrowing of the lumbar nerve root canal, spinal canal, or intervertebral foramen, causing compression of the spinal cord. The most significant clinical symptom in patients with LSS is neurologic intermittent claudication (NIC) which has been shown to be helped by Gabapentin (Yaksi *Spine* 2007).
- Nerve root entrapment
- Osteoarthritis.
- Nocturnal Cramps – quinine was commonly prescribed for cramps but in Australia, since 2004, this has been removed as an indication for use. Despite this it still is commonly prescribed. Quinine can be complicated by thrombocytopenia with fatal consequences.

Secondary prevention of atherosclerotic disease.

Given the fact that atherosclerosis is a systemic condition and those with IC are more likely die from MI and strokes, all patients with IC should be on aspirin, ACE inhibitor and a statin. Blood pressure and glycaemia should be well controlled. See chapter on medical management of atherosclerosis.

Exercise.

Several mechanisms for the benefits of exercise have been reported including increased collateral blood flow, changes in microvascular and endothelial function, improved oxidative metabolism and oxygen extraction, improved walking economy/dynamics and central cardiovascular effects (fitness) as well as improvements in atherosclerotic risk factors (glycaemic control, dyslipidaemia, hypertension). A supervised exercise and motivation program gives significantly better improvement in MWD and quality of life (QOL) than an advice only program. This should include walking on a treadmill or track to near maximal pain for at least 30 min, with a minimum of three sessions per week for at least 6 months. The advantage of supervision in an exercise program has been questioned in a systematic review (Wind *EJVES* 2007).

Although walking seems to be the best form of exercise, any form of exercise seems to help. Walking with Nordic poles has, for example, been shown to improve walking distance (Oakley *EJVES* 2008 and Spafford BJS 2014). Upper limb exercise (arm cranking) was also shown to be beneficial (Saxton JVS 2011).

The greatest benefit for exercise seems to be in non smokers. But, there is no clear survival benefit. In a randomised study of angioplasty vs. exercise, angioplasty increased the ABPI at 3, 6 and 9 months compared to exercise but the CD, although initially improved, later they were similar.
Patients with IC who get weekly physical activity beyond light intensity have lower mortality than sedentary counterparts (Gardner AW *JVS* 2008).

A meta-analysis of randomised and non randomised trials (Gardner *JAMA* 1995) showed a 180% increase in CD and 130% increase in MWD. Another meta-analysis (Bulmer *Sports Med* 2004) showed an 80% increase in CD and 120% increase in MWD.

Exercise increases plasma IL-6, decreases FGF-2 and increases expression of VEGF-AmRNA in calf muscle biopsies (Palmer-Kazen *EJVES* 2009). This evidence of inflammation in claudicants may explain the arteriogenesis and angiogenesis that accounts for symptom improvement in some patients. Hypoxia is also a potent stimulant of angiogenesis. Hypoxia up-regulates HIF-1 alpha which stimulates transcription of the VEGF gene.

Supervised exercise also improves physical function and balance (Mockford *BJS* 2013 (from Hull)).

At the 2014 Charring Cross International Symposium, a debate on the motion that supervised exercise, smoking cessation and best medical management should precede intervention was won by 71% to 29%.

In a randomised trial, home based walking exercise increased the walking distance (McDermott JAMA 2013).

Cochrane review 2005 – limited evidence suggests that exercise can be helpful.
Cochrane review 2007 – supervised exercise therapy, when compared to unsupervised exercise has not been shown to have clinical relevance.

Drugs.
Naftidrofuryl (Praxilene) 200mg tds.
A $5HT_2$ antagonist which enhances skeletal muscle ATP production. A meta analysis (De Backer *BMJ* 2009) showed that naftidrofuryl increased the CD when compared to placebo. This may be due to peripheral vasodilatation due to inhibition of 5-hydroxytryptamine 2 receptors or to reduce platelet aggregation. It has also been shown to reduce angina.

Pentoxifylline (Trental)400mg tds
This is a methylxanthine derivative which reduceses blood viscocity by decreasing platelet aggregation, fibrinogen, leukocyte activation and adhesion and possibly increases red cell deformity. A randomised trial showed a 20% increase in the CD when compared to placebo. Those with an ABPI of more than 0.5 did better than those with an ABPI of less than 0.5. However, more recent studies have show little benefit when compared to placebo. Pentoxifylline may also be useful in reducing reperfusion injury and in treatment of severe Raynauds.

Cilostazol (100mg twice daily).
This is a modified quinolinone which acts via type III phosphodiesterase inhibition, thus increasing cAMP in vessel walls and platelets, causing vasodilatation and reduced platelet aggregation. It also has beneficial effects on lipids, raising HDL. It is contraindicated in those with heart failure – increased mortality. The commonest side effects are headache (30%), diarrhoea, dizziness and palpitations. CD and MWD are increased by 58% compared to 9.8% with placebo at 12 weeks. In a study of placebo vs. pentoxifylline vs. cilostazol, no difference was found between the first two but those on cilostazol could walk further. Cilostazol also inhibits intimal hyperplasia, restores

endothelial function following balloon injury and increases VEGF mediated collateral vessel formation. $T_{½}$ is 10.5 hours and primary route of elimination is urinary.

Cochrane review 2014 – Cilostazol has been shown to be of benefit in improving walking distance.

The Pharmaceutical Benefit Advisory Committee in July 2009 rejected the Australian distribuiters submission for PBS listing on the basis of uncertain clinical benefit, uncertain cost effectiveness and uncertain utilisation estimates.

Carnitine.
Carnitine augments the entry of pyruvate into the citric acid cycle, increasing production of ATP. It also enhances oxidation of long chain fatty acids and decreases lactate levels. It results in a 26% increase in CD when compared to placebo.

Prostaglandins.
These are vasodilators and inhibitors of platelet aggregation. Beraprost is an orally active PGI_2 analog. Side effects include flushing, headaches.
Intravenous PGE1 has significant benefit over placebo but is not very practical.

Beta blockers.
These were previously thought to have an unfavorable effect on MWD but meta-analysis shows that symptoms of IC are no worse with β blockers.

Rifalazil.
An antibiotic active against Chlamydia pneumoniae. PROVIDENCE-1 – a prospective randomised double blind study in patients (n = 297) with high IgG titres against Chlamydia. After 6 months, MWD had increased by 20% in treatment group and 16% in placebo group i.e. no significant difference.

Ramipril (ACEIIC BJS 2013).
A randomised trail of 10mg ramipril vs placebo. Small numbers – 14 got ramipril and 19 placebo. Maximum walking distance improved by 106% in those on ramipril after 24 weeks but QOL was unchanged. This effect may be due to maintained collateral blood flow through inhibition of angiotensin ii, a potent vasoconstrictor. May also reduce breakdown of bradykinin causing vasodilatation or may simulate angiogenesis.
Side effects include abnormal dreams.

Others.
Verapamil – a calcium channel blocker.
Statins – atorvastatin increases walking distance (4S study). See medical management chapter.
Effect of Simvastatin (40mg/day) on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. Am J Med 2003 114: 359 - 364

	Baseline		6 months	
	Simvastatin	Placebo	Simvastatin	Placebo
Pain free walking (m)	72 +/- 13	74 +/- 15	190 +/- 38	100 +/- 34
Total walking (m)	96 +/- 18	93 +/- 13	230 +/- 35	104 +/- 29

GTN – shown in a small (but fantastic) randomised study to be beneficial (Walker *JVS*).
Vit C – prevents endothelial dysfunction in claudicants.

Vit E – Cochrane review 2005 – no benefit.
L – arginine – can improve claudication distance.
Anticoagulants – Cochrane review 2005 – no benefit.
Buflomedil – Cochrane review 2005 – there is limited evidence which suggests increased CD and MWD.
Omega-3 fatty acids – Cochrane review 2005 – no benefit.
Fish oil – this is a good source of polyunsaturated fatty acids.
Garlic – no evidence of benefit.
Subcutaneous carbon dioxide insufflations – no benefit
Chelation therapy with EDTA – no benefit.
Caffeine – in a randomised study showed that it increased MWD by 26.6% but reduced postural stability (Momsen *BJS* 2010).
Dark chocolate – In a randomised study (Loffredo Journal of American Heart Association 2014), dark (40g) but not milk chocolate improved MWD.

In a systematic review and meta-analysis of drug therapy for improved walking distance in intermittent claudication (Momsen *EJVES* 2009), of 43 trials, vasodilators and phosphodiesterase inhibitors showed significant improvement over placebo but the advantages were modest (MWD improved by 50m). Statins were the most effective with improved MWD by 160m.

Other interventions.
Weight loss can improve insulin sensitivity, increase HDL-C and improve CD. A brief psychological intervention can reduce perceived walking pain, increase daily walking and reduce the demand for intervention (Cunningham *ESVS Amsterdam* 2010).

Intermittent pneumatic compression (IPC).
IPC of the foot resulted in improved CD and improved post exercise ABPI up to 1 year after treatment. Improved MWD and ABPI was confirmed in a small randomised study (unsupervised exercise vs. supervised exercise vs. IPC (ESVS Abstract 2004)).

Endovascular intervention.
Approximately 40% of patients with IC have lesions suitable for angioplasty. The risk of amputation with angioplasty is 0.3%. Restenosis occurs in 20%. 60% chance of clinical success at 3 years. The Edinburgh study of angioplasty vs. exercise advice alone showed an initial improvement in CD and QOL in the angioplasty group but at two years there was no difference. Thus short term benefit only. The Oxford study compared angioplasty to supervised exercise. After 6 months, CD was better in exercise group. The results are not improved by stents. About 10% of claudicants with failed balloon angioplasty are clinically worse.
In a randomised trial from Oxford (Perkins EJVS 1996), exercise training gave greater improvement in claudication and maximum walking distance than angioplasty.

Oslo Balloon angioplasty vs. concervative treatment study (OBACT)(Nylander EJVES 2007).
Of 826 patients recruited to the study, only 56 went on to be randomised. All those randomised had an angiogram. There were no angioplasty complications! After 2 years, those who had angioplasty had significantly better ABPI's. The CD and MWD were improved in both groups but significantly more so in the angioplasty group after 2 years. QOL was also improved in the angioplasty group.

In a randomised study reported by Lee et al (VSSGBI meeting 2007) comparing angioplasty for femoropopliteal lesions, a supervised exercise program (SEP) and angioplasty plus exercise program, all groups had significant improvements in walking distance and QOL.

Table 2. Results of randomised study by Lee.

	SEP 51 patients	PTA 57 patients	SEP plus PTA 49 patients
Improved	63%	67	82
No change	27%	23	14
Worse	10%	10	4

MIMIC (Greenhalgh EJVES 2008).

A randomised trial of mild to moderate claudication comparing BMT plus exercise program and BMT, plus exercise plus angioplasty. 1401 patients considered for inclusion, 127 randomised. Study stopped early due to funding issues.

Table 3. Results of MIMIC trial.

	Femoropopliteal		Aortoiliac	
	Control n = 45	PTA n = 48	Control n = 15	PTA n = 19
ACD (m) at randomisation	126	133	126	114
AWD at 6 months	167	202	178 [a]	316 [a]
AWD at 24 months	155 [b]	245 [b]	168 [d]	354 [d]
ABPI at randomisation	0.69	0.66	0.66	0.68
ABPI at 24 months	0.72 [c]	0.83 [c]	0.74 [e]	0.9 [e]
Failed PTA		11 patients		2 patients

Significant results marked with letters.

No stents were used in the SFA. 5 stents were used in the iliac trial. There were very few PTA complications.

So ACD was not significantly improved at 1 year but was improved (by 38%) at 2 years. However, the QOL scores were no different between the groups.

CLEVER (Claudication: exercise versus endoluminal revascularisation) (Murphy Circulation 2011 and 2012).

Suggested that in patients on standard therapy, adding a supervised treadmill exercise program improved walking ability significantly better than stenting. Patients on either additional therapy improved walking ability better than standard therapy alone, which is home walking and cilostazol.

CLEVER enrolled 111 peripheral arterial disease (PAD) patients from 29 centers in the United States. The patients' average age was 64 years, 61% were male, and 80% were Caucasian. More than 50% of the patients smoked, and approximately 25% had diabetes. The investigators randomized patients to home walking plus cilostazol or to the same approach plus one of two other interventions: supervised treadmill exercise or placement of a stent to reduce narrowing in the iliac artery. At 6 months after enrollment, patients in the supervised exercise program significantly increased their treadmill walking time, as did those who received stents. In contrast, patients who only exercised at home showed little improvement. The average walking time in each group improved by 5.8 minutes (supervised exercise plus cilostazol), 3.7 minutes (stents plus cilostazol), and 1.2 minutes (home exercise plus cilostazol). "The evidence shows that those who receive the usual medical care do not enjoy a substantial improvement in their symptoms at all," commented Dr. Murphy. "It is important to note that both the supervised exercise and stent treatments provided substantially more benefit than usual home-based medical care, and both are proven to be effective treatments. I think that both of these therapies offer substantial advantages over the usual care." Patients in both the supervised exercise and stent groups scored better on a variety of quality-of-life measurements. However, patients in the stent group described a better quality of life compared to

both the supervised- or home-exercise programs. The reasons for the dissociation between treadmill walking and quality-of-life improvements are not clear. Exercise treatment improved leg function and symptoms, but not blood flow to the leg.

Randomised clinical trial of angioplasty, supervised exercise and combination treatment (Mazari BJS 2012).
These patients had femoro popliteal disease and included 178 patients. PTA and SEP were equally effective in improving clinical outcomes. PTA plus SEP produced a more sustained clinical improvement.

Comparing Exercise Therapy with Angioplasty for Claudication (CETAC) trial (Spronk Radiology 2009) and Fakhry BJS 2013).
Supervised exercise and endovascular treatment are equivalent after 12 months. In the longer term, SET and ER were equally effective in improving functional performance and QOL. There was however a higher reintervention rate in the ER group. After median follow up of 7 years, 21% of patients had died, there being nio difference between the SET and ER groups. Of the survivers, there was no difference in claudication distance between the groups. There were two minor amputaions in the SET group and 3 major amputations in the ER group.

Cochrane review 2005 – endovascular stents for intermittent claudication. Not enough evidence to support using stents over angioplasty alone.
Cochrane review 2005 – angioplasty vs. non surgical management for intermittent claudication. Angioplasty relieves the effects of claudication in the short term but there are doubts about the long term effects.

CETAC trial (BJS 2013).
A single centre randomised trail of endovascular treatment vs. supervised exercise as initial treatment for intermittent claudication. 75 assigned to SET and 76 to ER. Ater median follow up of 7 years, 17 SET patients and 15 ER patients had died. There was no difference in ABPI, MWD, QOL after 7 years between the two groups. Seven years after randomisation, the proportion of patients who needed secondary intervention was higher in the SET (53%) vs ER (27%). There wre 2 minor amputations in the SET group and 3 major amputations in the ER group.

Subintimal angioplasty for IC.
Technical success rate 87%. Most failures are due to problems with re-entry. 5 year assisted primary patency 64%. (EJVES 2004)

External iliac stenting for intermittent claudication (Maurel Annals of Vascular Surgery 2009).
In this report of 70 EIA stenosis being stentined for moderate to sever claudication using nitinol self expanding stents e.g. Luminex (Bard) or balloon expandable stents for tight or calcified lesions. Post procedure all patients had LMWH for 5 dyas and long term dualantiplatelet therapy. There were 2 EIA perfortaions, both treated with a covered stent. Primary patency at one year was 97%, at two years 89% and at three years 83%. They felt that stenting the EIA for claudication was acceptable.

ERASE (Endovascular revascularisation and supervised exercise) RCT (Fakhry JAMA 2015).
A randomised study of supervised exercise vs endovasculat treatment plus supervised exercise in the Netherlands in 212 patients with 100 – 500m MWD.
Results:

Table 2. Functional Performance Measures

Functional Performance Measures	Mean (99% CI)			
	Supervised Exercise (n = 106)	Endovascular Revascularization Plus Supervised Exercise (n = 106)	Between-Group Difference	*P* Value[a]
Maximum walking distance, m				
At baseline	285 (244 to 326)	264 (228 to 300)		
1 mo	438 (282 to 595)[b]	1004 (835 to 1174)[b]	566 (358 to 774)	<.001
6 mo	851 (683 to 1018)[b]	1260 (1076 to 1444)[b]	409 (183 to 636)	<.001
12 mo	955 (786 to 1124)[b]	1237 (1058 to 1418)[b]	282 (60 to 505)	.001
Pain-free walking distance, m				
At baseline	135 (113 to 157)	117 (96 to 138)		
1 mo	181 (23 to 339)[b]	724 (561 to 886)[b]	543 (340 to 744)	<.001
6 mo	542 (378 to 707)[b]	1071 (900 to 1243)[b]	529 (315 to 743)	<.001
12 mo	712 (549 to 876)[b]	1120 (948 to 1293)[b]	408 (195 to 622)	<.001
Ankle brachial index at rest[c]				
At baseline	0.68 (0.64 to 0.72)	0.71 (0.67 to 0.76)		
1 mo	−0.02 (−0.07 to 0.02)[b]	0.19 (0.15 to 0.23)[b]	0.21 (0.15 to 0.27)	<.001
6 mo	0.04 (−0.01 to 0.09)[b]	0.16 (0.11 to 0.20)[b]	0.12 (0.05 to 0.17)	<.001
12 mo	0.03 (−0.02 to 0.08)[b]	0.16 (0.11 to 0.21)[b]	0.13 (0.06 to 0.19)	<.001
Ankle brachial index after exercise[c]				
At baseline	0.40 (0.34 to 0.46)	0.43 (0.38 to 0.48)		
1 mo	0.03 (−0.02 to 0.09)[b]	0.36 (0.30 to 0.42)[b]	0.33 (0.25 to 0.40)	<.001
6 mo	0.12 (0.06 to 0.18)[b]	0.33 (0.27 to 0.39)[b]	0.21 (0.13 to 0.29)	<.001
12 mo	0.11 (0.05 to 0.18)[b]	0.33 (0.27 to 0.40)[b]	0.22 (0.13 to 0.31)	<.001

Quality of life was also signficantly improved in those with combined treatment. The probleems with this study is the shot follow up – only 12 months, and the lack of financial analysis – does the additional cost of endovascular treatment justify the addition 280m walking distance?

Bypass surgery.

There is little evidence of the effectiveness from randomised trails. There were no clear differences between bypass surgery and angioplasty. In the Vascunet registry, the incidence of death or amputation following lower limb bypass for claudication was 1% (Lees ESVS Abstracts Athens 2011).

Therapeutic angiogenesis.

In the phase II double blind placebo controlled study of Del-1 (VLTS-589) for IC (Grossman PM AHJ 2007), the aim was to investigate the safety and efficacy of a plasmid expressing developmentally regulated endothelial cell locus 1 (Del-1) in conjunction with poloxamer 188 (VLTS-589, a non viral, plasmid based therapeutic) vs. poloxamer 188 alone in patients with moderate to sever IC. Del-1 is a member of the family of angiomatrix proteins that are transiently expressed during vasculogenesis that induce a potent angiogenic response. Del-1 stimulates up regulation of the integrins αυβ5 and αυβ3 and triggers angiogenesis indirectly by initiating ligation of the integrins αυβ5 which in turn increases transcription factor Hox-3 and the expression of αυβ3. This process results in the activation of host cellular responses compatible with an angiogenic phenotype. The drug is given by intramuscular injection. There were no differences in the results of study drug vs. placebo.

In the TRAFFIC study, a single dose of the angiogenic protein recombinant fibroblast growth factor produced significant 90 benefit in claudicants.

What do I do in practise?

When patients are first seen a good history is obtained and examination performed including ABPI. Medical management is optimised – stop smoking, antiplatelet, statin, blood pressure control, ACE inhibitor and exercise advise. Patients are referred to community physiotherapy for an exercise program. The patient is then reviewed 4 months later. If there is deterioration in symptoms or symptoms limit mobility significantly, intervention (angioplasty) is offered provided they have been compliant with BMT.

Plantar fasciitis.

Classic symptom is sever heel or foot pain on the first step in the morning or after rest. Usually brought on by trauma or repetitive strain causing a tear at the origin of the planatar fascia. Has been called heel spur syndrome but may not be associated with a spur. May also be associated with Achilles tendon tightness.

Treatment.

1. Local stretching before weight bearing. Achilles tendon stretching has been tried but better to stretch the plantar fascia by pulling the toes up for 10 sec 10 times (Ben DiGiovanni *Journal of Bone and joint surgery* 2003 and 2006).

Local steroid injection. Can cause fat pad atrophy.