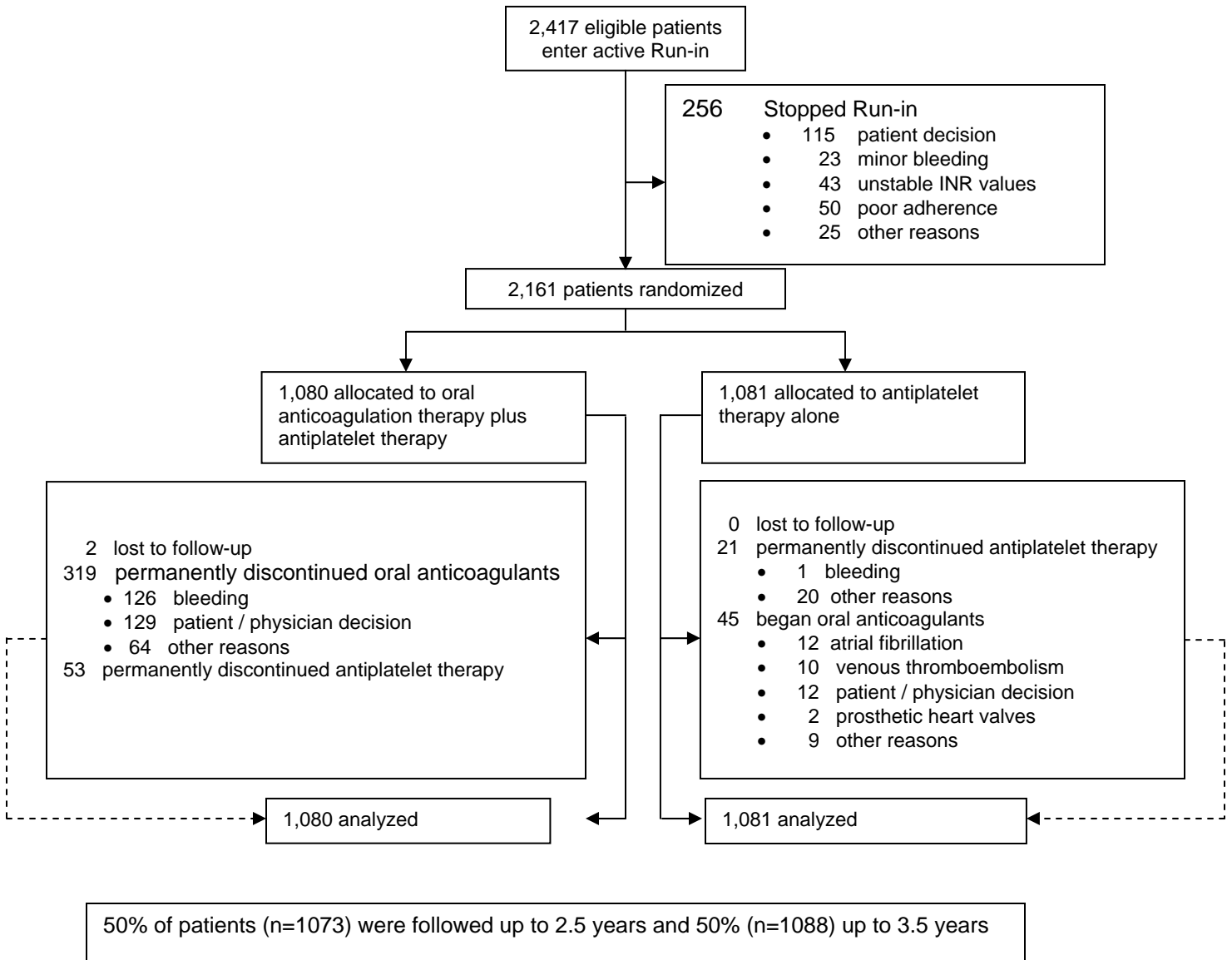


Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007;357:217-27.

On-Line Supplementary Material:
Patient Enrollment and Follow-up



Supplementary Tables for On-line Use:

Below we present information we collected during the trial on 1) Medications prescribed 2) Advice provided to patients, and 3) Surgical procedures. As indicated by the Tables below, overall there are no substantial differences in treatment provided or advice given between the treatment groups.

Drug Use by Treatment Group at Baseline, 1 year, 2 year, Final Visit

		Baseline	1 Year	2 year	Final Visit
Statin (%)	OAC/AP	42.8	52.5	59.0	67.2
	AP	45.2	54.1	59.0	70.4
ACE Inhibitors (%)	OAC/AP	50.5	54.7	57.3	62.8
	AP	50.3	54.3	57.9	63.8
Beta Blockers (%)	OAC/AP	31.8	34.5	39.2	40.8
	AP	32.1	33.9	37.7	44.1
Pentoxifylline (%)	OAC/AP	25.1	26.1	22.7	19.4
	AP	26.5	28.0	24.9	21.5

Percentage of patients who Received Risk Factor/Lifestyle Advice at clinic visits:

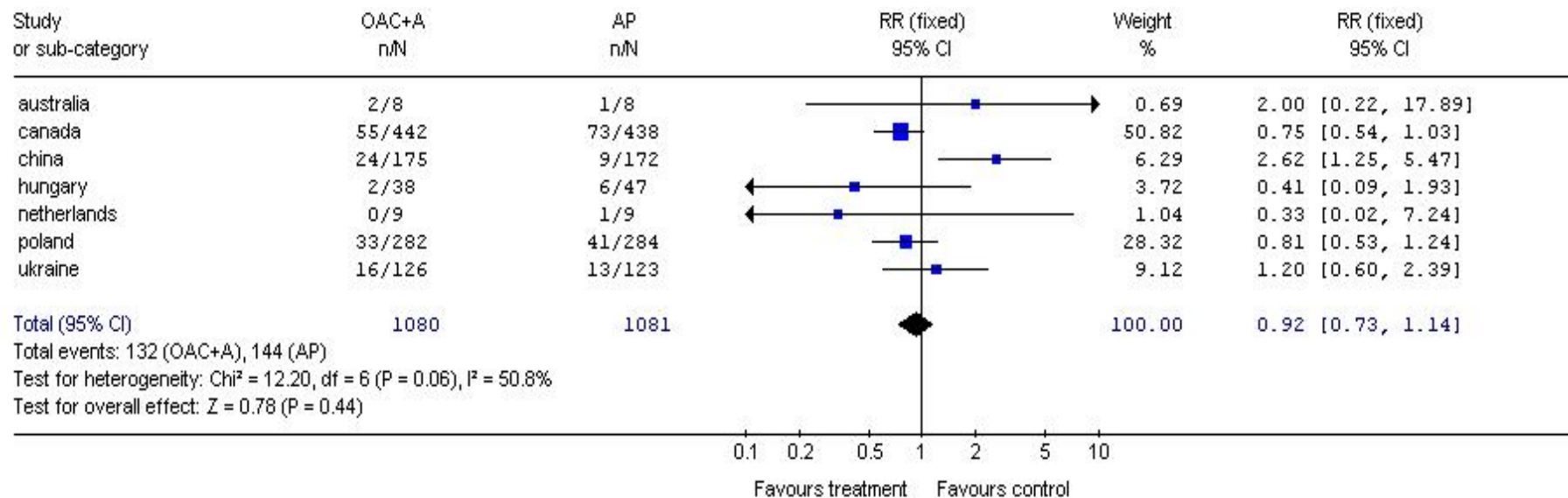
	Baseline		12 months	
	OAC/AP n=1080	AP N=1081	OAC/AP	AP
Smoking Cessation (%)	52.6	49.9	45.9	46.0
Optimal glucose control (%)	43.2	43.5	41.2	42.3
Disease specific dietary plan (%)	84.5	83.6	81.9	82.9
Avoidance of excessive alcohol (%)	66.5	64.3	65.1	61.8
Regular exercise (%)	88.6	89.4	89.4	90.1
Maintenance of normal blood pressure (%)	88.0	87.8	87.9	87.9
Adherence to medication prescribed by physicians (%)	94.1	94.0	92.6	93.0

Surgical Interventions performed in WAVE by Treatment group

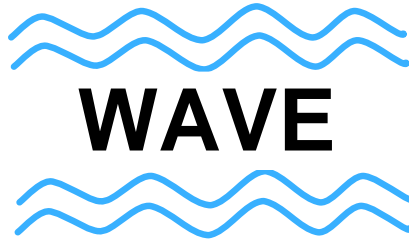
	OAC/AP N=1080	AP N=1081	P value
Peripheral revascularization	36 (3.3)	40 (3.7)	0.64
Limb Amputation	8 (0.7)	12 (1.1)	0.37
CABG	9 (0.8)	16 (1.5)	0.16

CABG: Coronary Artery Bypass Graft Surgery

Supplementary On-Line
Comparison of Treatment Effect for Co-Primary 1 by Country



This exploratory subgroup analysis by country shows that subjects randomized from some countries showed relative risks that favoured antiplatelet therapy alone, including Australia, Ukraine, and China, whereas the other countries favoured the combination therapy. The overall test for heterogeneity of the treatment effect by country is of borderline statistical significance ($P=0.06$).



Warfarin and Antiplatelet Vascular Evaluation

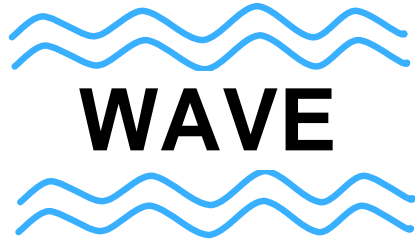
PROTOCOL

**A Phase III Randomized Trial of Warfarin Plus Antiplatelet Therapy versus
Antiplatelet Therapy Alone in Patients with Peripheral Vascular Disease**

**STUDY COORDINATING CENTRE:
Canadian Cardiovascular Collaboration (CCC) Project Office**

**HGH-McMaster Clinic – Population Health Section
Preventive Cardiology and Therapeutics Research Program
237 Barton Street East
Hamilton, Ontario CANADA L8L 2X2**

**SPONSORS:
MEDICAL RESEARCH COUNCIL OF CANADA
HEART AND STROKE FOUNDATION OF ONTARIO**



Warfarin and Antiplatelet Vascular Evaluation

A Phase III Randomized Trial of Warfarin Plus Antiplatelet Therapy versus Antiplatelet Therapy Alone in Patients with Peripheral Vascular Disease

The following is a table presenting the countries participating in the WAVE Study and the oral anticoagulant being used in that country:

<i>COUNTRY</i>	<i>ORAL ANTICOAGULANT USED</i>
Australia	Warfarin
Canada	Warfarin
Hungary	Acenocoumarol
Poland	Acenocoumarol

TABLE OF CONTENTS

1.0	STUDY SUMMARY	6
	Figure 1. PVD TRIAL - FLOW DIAGRAM.....	7
2.0	OVERVIEW	8
3.0	RATIONALE	8
	3.1 INTRODUCTION	8
	3.2 NATURAL HISTORY OF PATIENTS WITH PERIPHERAL ATHEROSCLEROSIS	8
	3.3 RISK OF CARDIOVASCULAR MORBIDITY AND MORTALITY	9
	3.4 IDENTIFYING HIGH-RISK PVD PATIENTS	9
	3.5 ANTITHROMBOTIC THERAPY IN PATIENTS WITH PVD	10
	TABLE 1: TRIALS OF WARFARIN IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE	12
	3.6 RATIONALE FOR LONG-TERM PROPHYLAXIS WITH MODERATE INTENSITY WARFARIN PLUS ANTIPLATELET THERAPY IN PVD PATIENTS.....	12
	FIGURE 2. HIGH, LOW AND MODERATE INTENSITY WARFARIN.....	14
	3.7 SAFETY OF COMBINED MODERATE INTENSITY WARFARIN AND ANTIPLATELET THERAPY IN PATIENTS WITH ARTERIAL DISEASE.....	15
	3.8 IS THE WARFARIN QUESTION STILL RELEVANT IN THE CONTEXT OF CURRENT TREATMENTS?.....	16
4.0	STUDY OBJECTIVES	17
5.0	STUDY POPULATION	17
	5.1 INCLUSION CRITERIA	17
	5.2 EXCLUSION CRITERIA	18
	TABLE 2: REASONS TO EXCLUDE ELIGIBLE PATIENTS	19
6.0	DESIGN AND METHODS.....	19
	6.1 STUDY OUTCOMES.....	19
	TABLE 3: DEFINITIONS OF STUDY OUTCOMES	20
	6.2 ENTRY INTO THE STUDY	21
	6.3 METHOD OF TREATMENT ALLOCATION:	21
	6.4 RISK FACTOR ASSESMENT:	21
	6.5 FOLLOW-UP SCHEDULE AND PROCEDURES	22
7.0	DRUG ADMINISTRATION AND MONITORING.....	22
	7.1 MONITORING OF TREATMENTS	23
8.0	ADHERENCE.....	23
	8.1 ACCEPTABLE REASONS FOR <u>TEMPORARILY</u> INTERRUPTING WARFARIN*	23
	8.2 ACCEPTABLE REASONS FOR <u>PERMANENTLY</u> DISCONTINUING WARFARIN*	24
9.0	STATISTICAL CONSIDERATIONS.....	24
	9.1 STUDY SIZE.....	24
	TABLE 4: SAMPLE SIZE REQUIREMENTS (PER GROUP).....	25
	9.2 STATISTICAL ANALYSIS	26
10.	STUDY MONITORING	27
11.0	ADJUDICATION.....	27
12.0	DATA COLLECTION.....	28

13.0 SUBSTUDIES	28
14.0 OWNERSHIP OF DATA AND PUBLICATION POLICY	28
15.0 PROPOSED TIMETABLE	29
16.0 STUDY ORGANIZATION AND ADMINISTRATION	29
17.0 REFERENCES	31

APPENDIXES:

APPENDIX A: Warfarin Dosage Nomogram.....	35
APPENDIX B: Acenocoumarol Dosage Nomogram	36
APPENDIX C: Guidelines for the Temporary Interruption of Warfarin in Patients Undergoing Surgery or Other Invasive Procedures	37
APPENDIX D: Management of Bleeding in PVD Study Patients	39
APPENDIX E: Study Organization	41
APPENDIX F: Blood Collection Substudy	46
APPENDIX G: DNA Package	48
APPENDIX H: Patient Information Sheet and Consent Form	51
APPENDIX I: Inclusion Criteria Change	54

1.0 STUDY SUMMARY

Eligibility: Patients with established peripheral vascular disease (PVD) between the ages of 35 and 85 years who have i. Intermittent claudication with objective evidence of PVD (e.g. ABI < 0.90), or ii. Ischemic rest pain, or iii. Ischemic non-healing ulcers or focal gangrene, or iv. Amputation for vascular causes, or v. Previous peripheral vascular revascularization (angioplasty or bypass surgery), or vi. Blue toe syndrome, or vii. Other significant peripheral arterial disease (e.g. carotid stenosis).

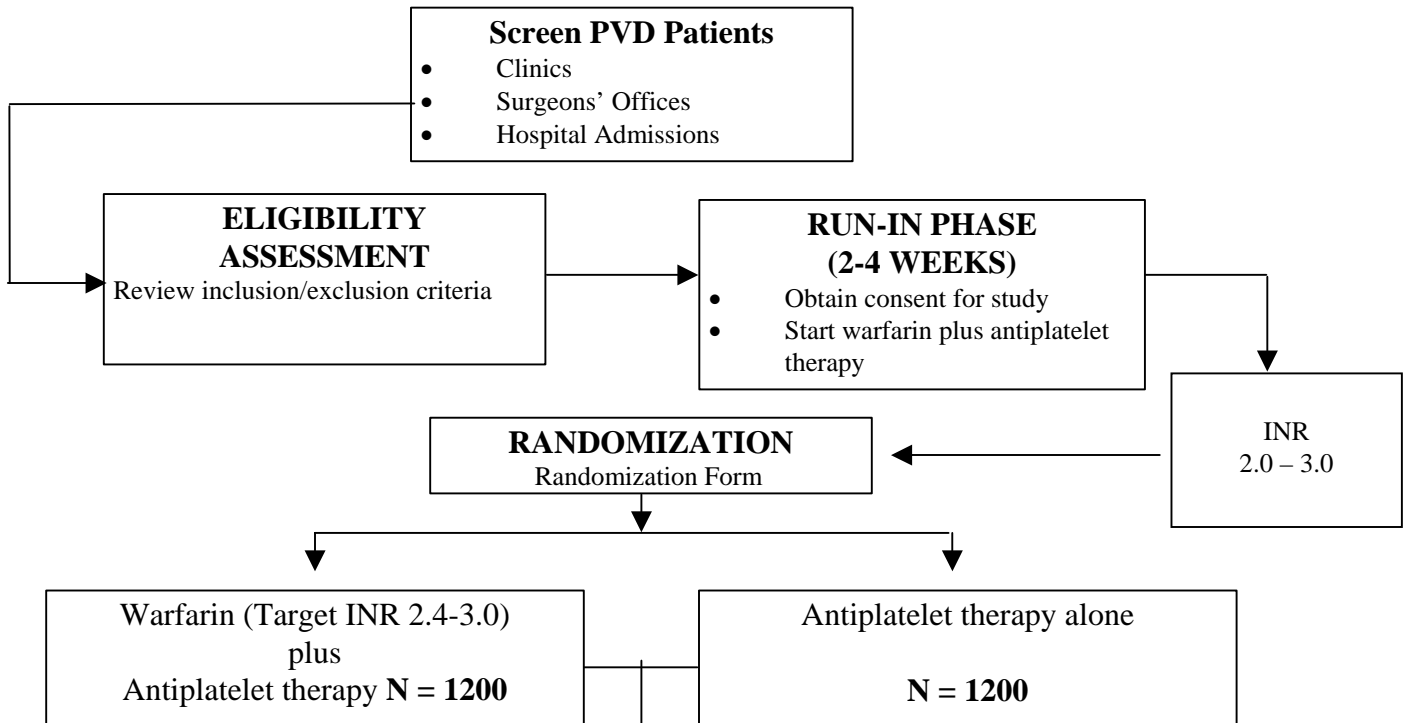
Intervention: Run-in period for 2-4 weeks where all eligible patients take warfarin and antiplatelet therapy. If an INR between 2.0-3.0 is achieved, the patient will be randomized and will either receive moderate intensity warfarin (target international normalized ratio [INR] range 2.4-3) plus antiplatelet therapy or antiplatelet therapy alone.

Study Outcomes: Co-primary outcomes are defined: A. Composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke, and B. Composite of CV death, MI, stroke, or severe ischemia requiring reperfusion/reconstruction of the coronary or peripheral arterial circulation. Safety outcomes include life-threatening, moderate bleeding, and minor bleeding

Sample Size: 2,400 patients with PVD, randomized equally to warfarin and antiplatelet therapy or antiplatelet therapy alone. All patients must stay on the allocated therapy for 2.5 years. Adherence to warfarin must be greater than 90% to maintain study power, and no more than 10% of patients in the control group are expected to receive warfarin.

Follow-up Schedule: Patients will require clinic visits at Day 35, and at 3, 9, 15, 21, 27, and 30 months after entry into the study. Telephone follow-up will occur at 6, 12, 18, and 24 months after entry. For patients on warfarin, INRs will be measured monthly, or more frequently if required. For patients who stop warfarin therapy prematurely, every attempt will be made to have them restart it.

FIGURE 1. PVD TRIAL - FLOW DIAGRAM



Follow-up Assessment:

INR check at 1 and 2 months	35 DAYS
INR check at 3, 4, 5 months	3 MONTHS
INR check at 6, 7, 8 months	6 MONTHS ^
INR check at 9, 10, 11 months	9 MONTHS
INR check at 12, 13, 14 months	12 MONTHS ^
INR check at 15, 16, 17 months	15 MONTHS
INR check at 18, 19, 20 months	18 MONTHS ^
INR check at 21, 22, 23 months	21 MONTHS
INR check at 24, 25, 26 months	24 MONTHS ^
INR check at 27, 28, 29 months	27 MONTHS
INR check at 30 months	30 MONTHS

^OPTION OF TELEPHONE FOLLOW-UP

2.0 OVERVIEW

Despite the use of aspirin, patients with peripheral vascular disease (PVD) have high rates of cardiovascular (CV) events such as myocardial infarction (MI), strokes and revascularization procedures. This is a large, multicentre, randomized clinical trial in high-risk PVD patients to evaluate the additional benefit of moderate intensity warfarin (target INR of 2.4-3.0) to antiplatelet therapy compared to antiplatelet therapy alone in reducing serious cardiovascular events. Special features of the study design include i. Inclusion of subjects at high risk of vascular events. ii. Large size, so that moderate, but important effects on clinically relevant outcomes may be reliably detected or excluded. iii. Efficient study design. iv. Simplicity in study design as only key baseline information, and simple follow up forms for outcome measures will be recorded in all subjects. v. Wide eligibility criteria so the result of the trial will be generalizable to a broad, yet high-risk population, and vi. Central blinded adjudication for all primary and secondary events reported by centres.

3.0 RATIONALE

3.1 INTRODUCTION

Atherosclerosis is the underlying cause of PVD of the lower extremities, and leads to intermittent claudication, leg ulceration and gangrene. More importantly, symptomatic PVD is an ominous sign that widespread atherosclerosis is present and patients with this condition suffer a threefold increase in myocardial infarction (MI), stroke, and CV death¹⁻⁴. These CV events are a consequence of rupture of an atherosclerotic plaque, which leads to platelet activation and thrombin generation, thrombus formation and occlusion of a critical blood vessel. Antiplatelet therapy has been clearly demonstrated to reduce major CV events. It is also reasonable to expect that this process may be further attenuated by the addition of an anti-thrombin agent (such as warfarin) in combination with antiplatelet agents. **We propose to evaluate the effect of the combination of warfarin and antiplatelet therapy compared with antiplatelet therapy alone in reducing CV events over the long-term in patients with PVD.**

3.2 NATURAL HISTORY OF PATIENTS WITH PERIPHERAL ATHEROSCLEROSIS

Atherosclerosis of the arteries of the lower extremity is the most common form of PVD. Progressive narrowing of these arteries reduces blood flow to the lower limb during exercise or rest, and typically produces symptoms of intermittent claudication. Epidemiological studies indicate that up to 5% of men and 2.5% of women \geq 60 years of age have symptoms of intermittent claudication^{3,5}. The prevalence is at least three times higher when non-invasive tests are used to determine arterial insufficiency in both symptomatic and asymptomatic individuals. However, the symptoms of PVD of the lower extremities progress rather slowly over time and, after 5 to 10 years, over 70% of patients report either no change or improvement in their leg symptoms. Approximately 15 to 20% of patients with intermittent claudication will eventually develop critical leg ischemia that endangers the viability of the lower extremity and requires surgical revascularization or limb amputation^{6,7}. Of this group, 26% of patients have progressive

vascular disease and undergo at least one repeat ipsilateral revascularization procedure⁸. Therefore, although intermittent claudication is debilitating for patients, **most** patients do not have progressive leg symptoms and only 20% will require surgical intervention.

3.3 RISK OF CARDIOVASCULAR MORBIDITY AND MORTALITY

Even more important than the lower extremity sequelae of PVD is the systemic effect of atherosclerosis in the coronary and cerebrovascular arterial beds, as patients with PVD suffer a significantly increased risk of CV death, MI, and stroke. Therefore, while the majority of patients with intermittent claudication will never develop progressive symptoms of their legs requiring revascularization or amputation, their mortality rate is two to three times higher than that of age and sex-matched controls³. In one cohort of 5,738 men in Finland, the risk of death was increased 3-fold when intermittent claudication was present. However once adjusted for the presence of coronary heart disease (CHD), intermittent claudication did not remain a significant predictor of future mortality. This adds to the evidence that CHD is the major cause of death in patients with intermittent claudication¹. In one study the all-cause mortality 5 and 15 years after the diagnosis of lower extremity PVD was 30% and 70%, respectively, compared with 10% and 30% in the appropriate control groups^{8,9}. The 5-year mortality rate is even greater (40%) in those patients with concomitant symptomatic coronary artery or cerebrovascular disease⁷. ***Taking these data together, 75% of patients with lower extremity arterial disease will die of a coronary or cerebrovascular event over a 15-year period***¹⁰. In addition, the risk of CV morbidity is also increased, as 20% of patients with intermittent claudication will suffer a nonfatal CV event (e.g. MI or stroke) over a 5-year period⁷. Furthermore, patients with PVD have a significantly higher CV event rate compared to patients with other manifestations of vascular disease. In the Canadian-based Heart Outcomes Prevention Evaluation (HOPE) trial cohort, patients with PVD at entry (n=1,329) had a 2.7 fold increase (95% CI: 2.4-3.2) in CV death, MI, stroke, leg amputation and peripheral bypass surgery at two years compared with patients with other vascular disease at entry (n=8,211) (21.8% vs 9.2%, P<0.0001)¹¹. Therefore, given the high rate of CV morbidity and mortality, in addition to the leg sequelae in patients with PVD, identifying effective therapies to reduce these conditions is crucial¹².

3.4 IDENTIFYING HIGH-RISK PVD PATIENTS

Patients with intermittent claudication with an ankle-brachial index (ABI) <0.9, or previous vascular reconstructions have high annual rates of serious CV events and constitute a high-risk population.

i. *Patients with Intermittent Claudication and Low ABI's:* The ABI is the ratio of systolic ankle pressure and systolic brachial pressure and is a simple non-invasive test that can be used to risk stratify patients. **As the ABI decreases, the risk of CV morbidity and mortality increases.** Population-based studies in Belgium, Sweden, Scotland, United States and Canada have demonstrated a two to five fold increase in the relative risk of fatal and non-fatal CV events in people with a low ABI¹³⁻¹⁸.

ii. Patients with Previous Vascular Reconstruction: Patients who have undergone a previous peripheral vascular reconstruction are also at high-risk of suffering from future recurrent peripheral and CV events. **In the HOPE trial cohort (n=1,329) patients with a previous history of peripheral vascular surgery or intermittent claudication with an ABI < 0.9 at entry, the 2 year incidence of death, MI, stroke and peripheral artery intervention (revascularization surgery and amputation) was 22%¹¹.**

3.5 ANTITHROMBOTIC THERAPY IN PATIENTS WITH PVD

Given the central role of platelet activation and thrombin generation in causing occlusive thrombi of the coronary, cerebrovascular and peripheral arterial circulation, long-term antiplatelet and antithrombin therapy should be considered in the setting of high-risk primary or secondary prevention of PVD.

i. Antiplatelet therapy reduces peripheral artery occlusion: Long-term antiplatelet therapy modifies the natural history of lower extremity PVD. Individual trials testing the effect of antiplatelet therapy to prevent vascular occlusion have for the most part been small and have produced conflicting results¹⁹⁻²². However, the effectiveness of antiplatelet therapy in preventing arterial occlusion patients with peripheral vein grafts is apparent from an overview of clinical trials conducted by the Antiplatelet Trialist' Collaboration (APTC)²³. Combining data from more than 11 randomized clinical trials and 2,000 patients, a 30% reduction in risk of graft occlusion during 19 months of follow-up was observed (P<0.00001). These results confirm the benefits of anti-platelet therapy in patients with claudication and peripheral grafts.

ii. Antiplatelet therapy reduces cardiovascular events in patients with PVD: A more compelling rationale to administer antiplatelet therapy to patients with PVD is to prevent death and disability from stroke and MI. The original meta-analysis conducted by the APTC of 31 randomized trials involving more than 29,000 patients with vascular disease, convincingly showed that long-term aspirin therapy significantly reduced overall vascular mortality as well as nonfatal stroke and MI²³. Since the original overview, the CAPRIE trial, a large international randomized trial which compared clopidogrel (a thienopyridine compound) with aspirin in 19,185 patients, including over 6,300 patients with PVD was conducted²⁴. A significant relative risk reduction in recurrent CV events of 8.7% with clopidogrel over aspirin was observed. The greatest benefit was achieved in patients with PVD, who had a 23.8% (95% CI: 8.9-36.2%) relative risk reduction in stroke, MI and vascular death²⁴. Since this trial, the APTC overview was updated, included 184 randomized trials of antiplatelet therapy involving more than 140,000 patients²⁵ and confirmed that among high-risk patients, antiplatelet therapy is protective and reduces nonfatal MI by one third, nonfatal stroke by about one third, and death from all vascular causes by about one sixth. Specific subgroup analyses from 39 trials involving 9,000 patients with intermittent claudication, infrainguinal arterial reconstructions, and peripheral angioplasty demonstrated a significant 21% (2P<0.009) reduction in vascular death, MI or stroke in patients with PVD treated with antiplatelet therapy (6.3%, 273/4361) compared to control (7.5%, 329/4362).

iii. Oral Anticoagulant Therapy: Coumarin derivatives prevent thrombin generation by reducing the concentrations of Factor II and the other Vitamin K dependent factors (Factor VII, IX, and X). The results of studies of oral anticoagulants (in the absence of antiplatelet therapy) in patients with PVD have been conflicting. Kretschmer et al conducted a randomized open study of 116 patients undergoing lower limb vein graft surgery and compared warfarin therapy to control²⁶⁻²⁷. A 37% reduction in peripheral artery occlusion (18% vs 29%, P<0.18) in the warfarin group was observed, along with an unexpectedly large 52% reduction in mortality (16.6% vs 34%, P<0.023) in patients treated with warfarin after 5 years of follow up. Following this, De Smit et al randomized 300 patients with varying degrees of PVD to warfarin or placebo and observed a 69% reduction in death, MI, stroke and PVD after 5 years of follow up²⁸. However, another trial in which 130 patients undergoing either vein or synthetic infrainguinal grafting who received intravenous heparin postoperatively and were randomized to warfarin (INR 2-3) or standard therapy, no difference in graft patency or survival was observed, and warfarin therapy was associated with a 5% incidence of serious preoperative bleeding²⁹ (Table 1). **Therefore, despite the promising results of some earlier trials, because of the conflicting results of later trials, the increasing acceptance of antiplatelet therapy, and the extra efforts involved with using oral anticoagulants, warfarin has not been widely adopted for the treatment of patients with PVD.**

iv. Oral anticoagulants and antiplatelet therapy combined: The effect of warfarin, in combination with aspirin has been studied in three more recent randomized controlled trials in patients undergoing infrainguinal vein bypass grafts. Unfortunately, the results of these trials are conflicting and do not clarify the role of warfarin in patients with PVD³⁰⁻³². Johnson et al conducted an open multicentre clinical trial of 458 veterans undergoing elective infrainguinal vein bypass grafting and randomized patients to warfarin (target INR 1.5-2.8) plus aspirin or aspirin alone. No difference in patency at 4 years of warfarin therapy was observed (74%) compared with the aspirin group (77%). However, the results of this trial are limited because 30% of patients randomized to warfarin stopped taking their medication, or had INR values below the therapeutic range at the time of graft failure. Sarac et al randomized 56 patients at high-risk of graft failure who were undergoing infrainguinal bypass to receive initial therapy with IV heparin followed by the combination of moderate intensity warfarin (target INR 2.0-3.0) and aspirin (325 mg/day) versus aspirin alone. The primary patency rate at three years was significantly greater in the warfarin and aspirin group (3 year patency 78% with combination therapy versus 59% with aspirin alone; P=0.04). Warfarin therapy was associated with an increased incidence of peri-operative hematoma (35% versus 3.7%; P=0.004), although this was not associated with an increase in transfusion requirements. No difference in survival after five years of follow-up was observed in this small study³¹ (Table 2). The ADMIT trial (Arterial Disease Multiple Intervention Trial) Pilot study was conducted to evaluate the feasibility of recruiting patients with PVD into a 2x2x2 double blind randomized pilot trial (n=486) which evaluated lipid lowering with nicotinic acid versus placebo, antioxidant therapy (beta-carotene, vitamin E and C) versus placebo, and low dose warfarin versus placebo (in the presence of aspirin) to target an INR of 1.8 (range 1.5 to 2.0)³². Recruitment for this trial finished in 1994, but the results of this study have not yet been published. *Therefore, although the trials in which warfarin plus aspirin therapy was compared with aspirin therapy alone produced mixed results, they were small, focused on peripheral artery patency after vascular reconstruction, and were*

not designed to assess the potential benefit of warfarin plus antiplatelet therapy in reducing CV outcomes, an outcome cluster that has tremendous clinical importance.

TABLE 1: TRIALS OF WARFARIN IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Trial	Population	Intervention	Events	Risk Reduction
Kretschmer 1988	Infrainguinal vein graft surgery	Warfarin vs Control	Mortality: 10/60 (16.7%) 20/59 (34%)	52% ↓ in mortality at 5 years & (37% ↓ in graft occlusion)
Arfvidsson 1990	Primary infrainguinal reconstruction	Warfarin vs Control	Graft Failure: 14/61 (23%) 14/55 (25%)	No difference in graft failure at 1 year
DeSmit 1992	Chronic peripheral arterial disease	Warfarin vs Placebo	Death,MI, Stroke, Graft failure: 14/155 (9%) 42/145 (29%)	69% ↓ death, MI, stroke, graft failure at 5 years
Johnson 1998	Elective vein bypass grafts	Warfarin & ASA vs ASA	Graft Failure: 59/229 (26%) 53/229 (23%)	No difference in graft failure at 4 years
Sarac 1998	High-risk for graft failure	Warfarin & ASA vs ASA	Graft Failure: 10/37 (26%) 13/27 (49%)	67% ↓ in graft failure at 3 years

Note: All of these trials have been small (n<500) and have focused primarily upon peripheral graft patency.

3.6 RATIONALE FOR LONG-TERM PROPHYLAXIS WITH MODERATE INTENSITY WARFARIN PLUS ANTIPLATELET THERAPY IN PVD PATIENTS

Warfarin is widely used as an oral anticoagulant for the prophylaxis and treatment of arterial thromboembolic disease. The goal in treating patients with warfarin is to target the anticoagulant intensity defined by the INR, which maximizes efficacy and minimizes bleeding.

High Intensity Warfarin: The majority of studies in which warfarin was tested in patients after MI used high intensity warfarin (INR 2.8-4.8) in the absence of antiplatelet therapy. Several randomized controlled trials³²⁻³⁴ and a recent meta-analysis³⁵ including over 10,000 patients following MI have demonstrated a significant reduction in mortality (by 20%), reinfarction (by 45%) and stroke (by 20%) with long term anticoagulant therapy after MI (all P<0.001) (Figure 2a). None of these trials used antiplatelet drugs routinely as the majority of these trials were

conducted before aspirin was demonstrated to be effective. However, since these trials were conducted, the use of antiplatelet therapy, but not warfarin, has become routine following MI.

Low Intensity Warfarin: After aspirin was being increasingly used to prevent recurrent ischemic events in patients with vascular disease, and in an attempt to minimize bleeding complications, the efficacy of **low intensity warfarin** (INR=1.5) in combination with aspirin was tested. **No additional benefit** in reducing recurrent vascular events (MI, stroke, vascular death) is apparent. In a meta-analysis of over 8,000 patients including data from the CARS³⁶ and POST-CABG³⁷ trials, no differences in the combined outcome of death, MI, and stroke between warfarin and aspirin vs. aspirin alone were observed³⁵ (Figure 2b).

Moderate Intensity Warfarin: *There is accumulating evidence that moderate intensity warfarin (INR 2.0-3.0) in patients with atrial fibrillation, prosthetic valves and unstable angina is effective and safe.* Three randomized controlled trials have demonstrated the benefits of moderate intensity warfarin (INR:1.5-4.5) in the prevention of thromboembolic events and stroke in patients with atrial fibrillation³⁸⁻⁴⁰. A clinical trial in patients with homograft valves demonstrated that use of moderate intensity of warfarin (INR 2.0-3.0) compared with higher intensity of warfarin (INR 3.0-4.0) results in equal efficacy but fewer bleeding episodes⁴¹. Furthermore, in a trial comparing warfarin plus aspirin versus warfarin (INR 3.0-4.5) alone in patients with mechanical valves, low dose aspirin added to warfarin significantly reduced total mortality, vascular mortality, and stroke⁴². Although the addition of aspirin to warfarin increased the risk of minor bleeding, no significant difference in major bleeds occurred between the groups and, overall, the benefit of aspirin outweighed the risk⁴¹. In addition, in two smaller trials of patients with unstable angina, the combination of moderate intensity warfarin plus aspirin compared with aspirin alone resulted in a 30% risk reduction in CV death, MI, and refractory angina⁴³⁻⁴⁴ (Figure 2c). *Therefore, the available data indicate a strong rationale for testing the efficacy of long term moderate intensity of warfarin (target INR between 2-3) in addition to antiplatelet therapy to prevent major ischemic events (vascular death, MI, stroke and limb-threatening ischemia requiring an intervention (amputation, revascularization surgery) in patients with symptomatic PVD.*

FIGURE 2. HIGH, LOW AND MODERATE INTENSITY WARFARIN

Figure 2(a)

**HIGH INTENSITY INR 2.8-4.8 (No Aspirin)
n=9,527**

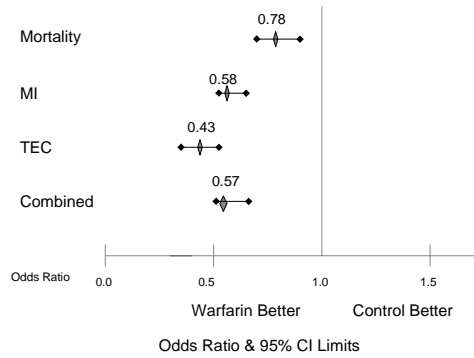


Figure 2(b)

**LOW INTENSITY: INR 1.5 (With Aspirin)
n=8,455**

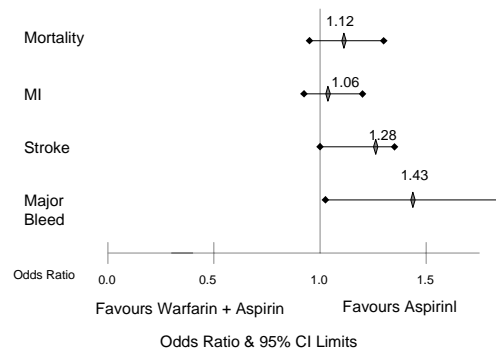
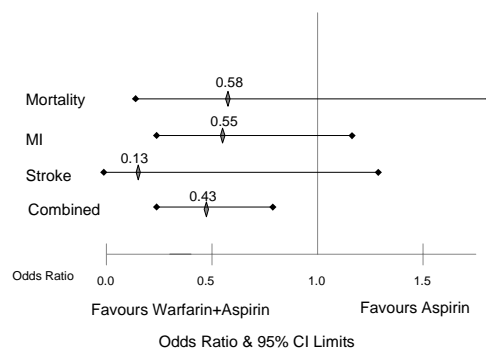


Figure 2(c)

**MODERATE INTENSITY: INR 2-3 (With Aspirin)
n=480**



3.7 SAFETY OF COMBINED MODERATE INTENSITY WARFARIN AND ANTIPLATELET THERAPY IN PATIENTS WITH ARTERIAL DISEASE

The goal of anticoagulant therapy with warfarin is to identify the lowest level of anticoagulation (by INR value) at which the antithrombotic effect is maximized, and the bleeding events are minimized. The risk of bleeding in patients who receive oral anticoagulants is directly related to:

i. Intensity of Anticoagulation: Data from the post-MI, atrial fibrillation and mechanical valve population suggest that high intensity warfarin therapy is associated with higher rates of bleeding, without clear gains in efficacy compared with moderate intensity regimens^{45,46}. In a prospective assessment of bleeding rates in 2,745 outpatients treated with oral anticoagulants who were followed for an average of 267 days, the INR range of 2.0 to 2.9 was associated with the lowest bleeding rates [4.8% (54/1116)] and clinical events compared with higher intensity ranges. Patients with INR values between 3.0 and 4.4 had a 2-fold increase, and patients with INR values between 4.5 and 6.9 had an 8-fold increase in bleeding events compared with the moderate intensity group. Overall, the rate of fatal, major, and minor bleeding in this cohort was low: 0.25%, 1.1% and 6.2% per year, respectively⁴⁷. Taking this information together with the results of clinical trials involving patients with atrial fibrillation who were treated with long-term anticoagulants^{48,49}, moderate intensity warfarin therapy (target INR 2.0-3.0) is associated with an annual risk of major bleeding of approximately 1.7% per year, and fatal bleeding of 0.2% per year⁴⁸. The hazard of long-term warfarin therapy is balanced by its potential to reduce the high rate of major CV events (i.e. 10-12% per year) which is expected in patients with symptomatic PVD.

ii. Clinical factors: Clinical factors allow stratification of patients into low, moderate, and high-risk of bleeding on warfarin therapy. Risk factors include advancing age, the presence of serious co-morbidity (i.e. renal failure), history of stroke, and history of gastrointestinal bleeding⁵⁰. **Therefore patients > 85 years, with a recent history of stroke or peptic ulcer disease will be excluded from entry into this trial.**

iii. Duration of anticoagulant therapy: The cumulative risk of bleeding increases with the duration of anticoagulant therapy. Data from patients with venous thrombosis demonstrate that the annual rate of major bleeding events is about 2% per year⁴⁸. Data from the OASIS-2 trial of patients with unstable angina who were treated with warfarin indicate that the annual rate of major bleeding is 3.3%, 1.2% of which were life-threatening (defined as requiring ≥ 4 units of blood product transfusion, requiring surgery, or significantly disabling). This risk can be minimized with careful monitoring of warfarin therapy as one third of all bleeding complications on warfarin occur in the first 3 months after initiation of treatment [RR=1.75 (1.27-2.44)]⁴⁹. In patient populations in whom the risk of the thrombotic recurrence decreases over time, consideration of the duration of warfarin therapy given the changing risk-benefit ratio is needed. **However, in patients with symptomatic PVD the rate of death, MI, and stroke remains extraordinarily high; therefore, the benefit of preventing these events using long-term antithrombotic therapy clearly outweighs the risk of major hemorrhage.**

iv. Concomitant antiplatelet therapy: Concomitant antiplatelet therapy in patients being treated with warfarin may be associated with a greater risk of bleeding than with either therapy

alone. However, the results of recent large randomized clinical trials of combination moderate intensity anticoagulants and antiplatelet therapy do not demonstrate a significant increase in life-threatening bleeding rates compared with patients on antiplatelet therapy alone. In a meta-analysis which included 3,146 patients who received moderate intensity warfarin the absolute rate of major bleeding in the moderate intensity warfarin and aspirin patients was 3.3% (8/240) versus 1.7% (4/240) in patients on aspirin alone in patients followed for less than one year; the relative increase in major bleeding was 1.88 (95% CI: 0.59-6.00)³⁵. **Taken together there is accumulating evidence based on a modest number of patients that moderate intensity warfarin plus antiplatelet therapy compared with antiplatelet therapy alone is efficacious and relatively safe when adherence to therapy is maintained, patients are carefully monitored, and circumstances that increase the risk of bleeding are avoided.**

3.8 IS THE WARFARIN QUESTION STILL RELEVANT IN THE CONTEXT OF CURRENT TREATMENTS?

- I. Oral glycoprotein IIb/IIIa inhibitors appeared theoretically promising, yet to date the trial results have been disappointing and numerous questions regarding these agents (e.g. optimal dose and method of monitoring) remain unresolved. Recently, three large Phase III trials (10,000 patients in OPUS/TIMI-16⁵¹, 7,500 in EXCITE⁵¹, and over 9,000 in SYMPHONY⁵² testing these agents in patients with arterial disease were stopped because of a lack of efficacy. Furthermore, in the OPUS study there was a significant excess in mortality in the active arm.
- II. Combination of antiplatelet agents such as thienopyridines (e.g. ticlopidine and clopidogrel) which inhibit ADP induced platelet aggregation and aspirin which inhibits the cyclo-oxygenase pathway also appear promising. However, the efficacy and safety profile of this combination in patients with CVD (apart from the arterial stent population), has not yet been established, and should not preclude a rigorous evaluation of alternate strategies such as warfarin (an established and familiar therapy) plus aspirin.
- III. Warfarin has been widely used in the prevention of thrombotic events for the past forty years. Further, warfarin is commonly used in patients with venous thrombosis and several arterial diseases (e.g. atrial fibrillation and mechanical valves). The INR, which is used to monitor warfarin, is a valid, reliable, and universally-used test. An overview of trials in patients with arterial disease to date suggests there is great potential for the combination of warfarin and aspirin to significantly reduce CV death, MI, and stroke. Although this benefit is balanced by the potential hazard of major bleeding, this hazard is largely outweighed by the overwhelming effectiveness of warfarin and aspirin, and should not preclude its full evaluation. If this trial provides convincing evidence supporting the value of warfarin and if the benefits outweigh the risks by a clinically important margin, then warfarin in combination with antiplatelet therapy is likely to become widely accepted for this indication.

4.0 STUDY OBJECTIVES

The primary objective of this study is to determine whether moderate intensity warfarin (target INR range 2.4-3.0) in combination with antiplatelet therapy is superior to antiplatelet therapy alone in preventing:

- a. cardiovascular death, MI, or stroke, and
- b. cardiovascular death, MI, stroke, or severe ischemia of the coronary or peripheral arterial circulation leading to an intervention, in patients with PVD over the long-term (2.5 years).

Secondary objectives include determining the effect of combined warfarin and antiplatelet therapy to reduce the composite outcome of: a) CV death, MI, stroke, or revascularization of the coronary or peripheral arterial circulation, b) CV death, MI, stroke, amputation, revascularization and severe coronary ischemia with ECG changes; c) death, MI, TIA, stroke, amputation, coronary or peripheral revascularization (including carotid endarterectomy), and severe coronary ischemia with ECG changes.

Other objectives include a comparison of the safety profile of warfarin plus antiplatelet therapy and antiplatelet therapy alone on life-threatening, moderate and minor bleeding.

5.0 STUDY POPULATION

5.1 INCLUSION CRITERIA

Men and women with established PVD who are at high-risk for development of occlusive vascular disease are eligible for the trial. Eligible patients include those between the age of 35 and 85 years and at least one of the following:

- i. intermittent claudication with objective evidence of PVD (i.e. ankle-brachial index of < 0.9, duplex scanning or angiographic evidence of arterial occlusion or stenosis > 50%, absent arterial pulses of the symptomatic limb with ankle-brachial index < 0.9*)
- ii. ischemic rest pain of the lower limbs
- iii. ischemic non-healing ulcers or focal gangrene
- iv. previous limb amputations (minor and major) because of vascular insufficiency
- v. previous arterial surgery or angioplasty for vascular insufficiency of the lower limbs
- vi. blue toe syndrome
- vii. other significant peripheral arterial disease i. Carotid artery disease: a). symptomatic: (hemispheric transient ischemic attacks, amaurosis fugax, or strokes older than 6 months) with objective evidence of carotid stenosis or previous carotid endarterectomy, or b). asymptomatic: with objective evidence [duplex scanning or angiography] of carotid stenosis >50%), ii. subclavian artery occlusive disease (angiographic evidence or unmeasurable brachial pressure in one of the two upper limbs)

- * Diabetics without palpable pulses and ankle-brachial index > 0.9 should be assessed by a vascular surgeon before being included

5.2 EXCLUSION CRITERIA

Temporary

Potential subjects will be temporarily excluded if they need to undergo:

- i.** vascular diagnostic (angiography) or interventional procedures (arterial bypass graft surgery or angioplasty), or
- ii.** limb amputation for vascular insufficiency

All patients should be reassessed for entry into the study after their intervention (s)

Permanent

Potential subjects will be excluded with any of the following (Table 2) :

- i.** active bleeding or high-risk for bleeding
- ii.** clear indication for long-term warfarin use (i.e. atrial fibrillation)
- iii.** previous allergy or intolerance to warfarin
- iv.** stroke in the last 6 months
- v.** renal failure requiring dialysis
- vi.** known significant abdominal aortic or cerebral aneurysm
- vii.** peripheral arterial aneurysms (iliac or femoral) without evidence of lower limb ischemia
- viii.** significant liver disease (i.e. cirrhosis)
- ix.** cancer with an expected life expectancy < 6 months
- x.** anticipated non-adherence to warfarin
- xi.** excessive alcohol use
- xii.** pregnancy or planning to become pregnant
- xiii.** failure to provide informed consent

TABLE 2: REASONS TO EXCLUDE ELIGIBLE PATIENTS

Reason	Description
Active Bleeding or High-Risk for Bleeding	<ul style="list-style-type: none"> • GI hemorrhage requiring transfusion • Endoscopic diagnosis of peptic ulcer disease / ulcerative esophagitis < 1 year • Coagulopathy • Anemia (hemoglobin < 90 g/L) • Thrombocytopenia (platelets < 100 x 10⁹/L) • Intracranial Hemorrhage • Recurrent Falls • Daily use of NSAIDS for ≥3 months (existing or planned)
Stroke	<ul style="list-style-type: none"> • Any stroke within the previous 6 months
Renal Insufficiency Requiring Dialysis	
Aneurysms	<ul style="list-style-type: none"> • Abdominal Aortic aneurysm known to be significant e.g. > 4 cm • Iliac or femoral aneurysm without evidence of lower limb ischemia • Any Cerebral Aneurysm
Anticipated Non-Adherence to Warfarin	<ul style="list-style-type: none"> • Poor adherence to current medications, or irregular attendance at office visits
Excessive Alcohol Use	<ul style="list-style-type: none"> • Regular or erratic heavy drinking (>10-15 drinks per week)
Previous allergy to warfarin	<ul style="list-style-type: none"> • Warfarin skin necrosis
Indication for long-term warfarin use	<ul style="list-style-type: none"> • e.g. Atrial Fibrillation
Failure to give informed consent	
Severe Hepatic Insufficiency	<ul style="list-style-type: none"> • Cirrhosis
Life Expectancy < 6 months	<ul style="list-style-type: none"> • Terminal Cancer

6.0 DESIGN AND METHODS

This study is a multicentre, randomized, open trial of warfarin plus antiplatelet therapy versus antiplatelet therapy alone in patients with PVD.

6.1 STUDY OUTCOMES

Primary Outcome:

The co-primary outcomes are A. The composite of cardiovascular death, first occurrence of MI, or stroke and B. The composite of cardiovascular death, first occurrence of MI, stroke, or severe

ischemia requiring urgent intervention of the coronary (PTCA, CABG) or peripheral artery circulation (thrombolytic therapy, angioplasty, bypass surgery, limb amputation.)

Secondary Outcomes:

Secondary outcomes include i. CV death, MI, stroke, amputation, revascularization of the coronary or peripheral arteries, or admission to hospital for unstable angina with ECG changes, ii. CV death, MI, stroke, TIA, amputation or revascularization of the coronary, carotid, or leg arteries, and iii. all cause death, MI, stroke, amputation or revascularization of the coronary or peripheral arteries (Table 3)

Safety Outcomes:

Life-threatening, moderate, and minor bleeding. (Table 3)

TABLE 3: DEFINITIONS OF STUDY OUTCOMES

Outcome	Definition
Death	Subdivided as cardiovascular and non-cardiovascular. All deaths with a clear cardiovascular cause including haemorrhagic or unknown cause will be classified as cardiovascular. Only deaths due to a documented non-cardiovascular cause (e.g. cancer) will be classified as non-cardiovascular.
MI (2 of 3 criteria)	<ul style="list-style-type: none"> • Typical ischemic chest pain, elevation of creatine kinase (CK) enzyme or its MB fraction or troponin values, new ECG changes which include new persistent ST/T changes, new BBB or new Q-waves in at least 2 consecutive leads
Severe Coronary Ischemia leading to an intervention	<ul style="list-style-type: none"> • Unstable angina with ECG changes requiring hospitalization which leads to coronary revascularization (PTCA, CABG)(or transfer for revascularization) during the hospitalization
Revascularization of Coronary Arteries	<ul style="list-style-type: none"> • PTCA: Percutaneous Transluminal Coronary Angioplasty • CABG: Coronary Artery Bypass Graft Surgery
Severe Limb Ischemia leading to an intervention	<ul style="list-style-type: none"> • Severe ischemia of the lower extremity which is deemed to threaten the viability of the limb, and is associated with continuing ischemic pain, and neurologic deficit, or inadequate skin capillary circulation, or inaudible arterial flow signals by Doppler of the pedal arteries <u>AND</u> which leads to hospitalization for an intervention such as <u>thrombolytic therapy, angioplasty, bypass surgery or amputation.</u>
Reperfusion/Reconstruction of Peripheral Arteries	<ul style="list-style-type: none"> • Catheter directed thrombolytic therapy of a peripheral artery • Percutaneous transluminal angioplasty of the iliac or femoral arteries (or their main branches) • Surgical revascularization of the aorta or infrainguinal arteries

Outcome	Definition
Amputation	<ul style="list-style-type: none"> Amputation of the limb secondary to vascular insufficiency – subdivided into Major (proximal to the transmetatarsal level) and Minor (distal to the transmetatarsal level)
Stroke	<ul style="list-style-type: none"> New focal neurologic deficit thought to be vascular in origin lasting greater than 24 hours. Confirmation with CT scan/MRI is recommended but not mandatory. Strokes will be further classified as ischemic, hemorrhagic, or uncertain
TIA	<ul style="list-style-type: none"> Transient Ischemic Attack: New Onset Focal neurological deficit that resolves within 24 hours
Unstable Angina with ECG changes	<ul style="list-style-type: none"> An episode of angina lasting greater than 15 minutes which is refractory to the patients usual medications which leads to hospital admission <u>and</u> is associated with ECG changes consistent with coronary ischemia.
Life-Threatening Bleeding	<ul style="list-style-type: none"> Fatal or intra-cranial bleeding, or bleeding requiring surgical intervention or transfusion of at least 4 units of blood or plasma expanders.
Moderate and Minor Bleeding	<ul style="list-style-type: none"> Bleeding which requires ≤ 3 units of blood or blood products will be classified as moderate. All other bleeding not requiring transfusion (but leading to the temporary or permanent cessation of warfarin) will be classified as minor.

6.2 ENTRY INTO THE STUDY

Consenting patients will attend a clinic visit, during which the study will be explained by the nurse and centre investigator, the consent form will be signed, baseline blood work taken and all patients will enter the 2-4 week Run-In period during which they will take warfarin and antiplatelet therapy. An INR of between 2.0-3.0 will be targeted. During this period, the patient's INR should be checked a minimum of 3 times. When the patient's INR is stable at 2.0-3.0, and the patient has experienced no serious side effects, he/she will be eligible for randomization into the study. If the patient has not achieved a stable INR of 2.0-3.0 within 4 weeks, he/she will not be eligible to participate in this study.

6.3 METHOD OF TREATMENT ALLOCATION:

Randomization will be performed by a toll-free telephone call to a central, 24-hour automated randomization service located at the Project Office in Hamilton. After eligibility data have been provided over the telephone, patients will be randomized in equal proportions to receive either warfarin plus antiplatelet therapy or antiplatelet therapy alone. Patients will be considered randomized as soon as the treatment allocation is given over the telephone.

For further details please see Manual of Operations

6.4 RISK FACTOR ASSESSMENT:

Given the high-risk nature of the PVD population, the importance of healthy lifestyle practices

need to be emphasized. In all patients a “Lifestyle Assessment” will be conducted at baseline, at the 1 year follow-up, and at the final study visit. Key risk factors for vascular disease (e.g. smoking), as well as important lifestyle practices (e.g. weight control) will be reviewed. All patients will receive a “Prevention Pamphlet” which outlines each modifiable risk factor for PVD, and will include advice regarding risk factor prevention strategies. All patients will receive a summary of their risk factor profile over the course of the study at the end of their trial follow-up.

6.5 FOLLOW-UP SCHEDULE AND PROCEDURES

Patients will be enrolled into the study over 18 months from approximately 18 regional centres in Canada and Poland. The primary follow-up period will occur after each patient has completed 2.5 years (30 months) of follow-up. Follow-up assessments to the clinic will occur at 35 days, 3, 9, 15, 21, 27, and 30 months for all patients. Additional follow-up assessments (telephone or clinic) will occur at 6, 12, 18, and 24 months (Figure 1). Information to be collected at each assessment will include event information, other hospitalizations, and compliance with the assigned treatment regimen. INR measurements must be performed monthly in all patients on warfarin or more frequently if required.

7.0 DRUG ADMINISTRATION AND MONITORING

During the Run-In, warfarin should be initiated with a starting dose of 5 mg/day for the first 3 days. (Note: In Poland Acenocoumarol will be used at a starting dose of 4 mg/day) This approach usually results in patients achieving an anti-thrombotic effect and an INR within the therapeutic range of 2.0 to 3.0 within 4 or 5 days⁵³. However this initiation approach may be varied in selected patients who are deemed to require lower doses (e.g. elderly.). For those patients randomized into the study, treatment will continue for 2.5 years.

Warfarin Patients: All patients randomized to receive warfarin must also take antiplatelet therapy (most commonly aspirin at a recommended dose of 81 mg/day). For in-hospital patients (recent post peripheral vascular intervention, or AMI) the recommended time of initiating the Run-in period is at the time of hospital discharge. This time is chosen to minimize the risk of perioperative bleeding, and to avoid counting early peripheral artery re-occlusion as a primary outcome event, given that early thrombotic re-occlusion is likely to be due to technical factors and warfarin therapy started after surgery is not likely to prevent these events. A suggested maintenance dose nomogram is found Appendix A.

Antiplatelet Therapy Alone: Antiplatelet therapy should be taken daily. Acceptable antiplatelet agents include aspirin (recommended dose 81 mg to 325 mg/day), ticlopidine, or clopidogrel.

7.1 MONITORING OF TREATMENTS

Warfarin will be monitored by INR values and dose adjustment instructions will be made by telephone by the centre nurse in conjunction with the centre investigator. In most patients, the INR will be measured at baseline, after the third 5 mg dose of warfarin, then 2 times in the following week until the therapeutic range has been achieved. The goal is to achieve an INR of 2 to 3 within two weeks. Following randomization, INR values will be obtained at 35 days, at 2 months and each month thereafter until follow up is complete. In patients with an unstable INR, or who are taking drugs that modify the INR (Manual of Operations), more frequent INRs are recommended at the discretion of the study physician.

8.0 ADHERENCE

Adherence is critical to maintain study power. Our target compliance with warfarin is 90% over 2.5 years in each centre.

If a patient is non-adherent or a centre investigator is considering warfarin discontinuation, consultation with the Project Office in Hamilton is strongly recommended. The Project Office will closely monitor the withdrawal rates throughout the trial, and will provide reminders to centres to restart warfarin where appropriate (the study nurse will closely monitor patients who undergo interventional procedures and we will urge that therapy is restarted afterward).

8.1 ACCEPTABLE REASONS FOR TEMPORARILY INTERRUPTING WARFARIN*

- bleeding – moderate or minor
- diagnostic procedure involving an arterial puncture
- surgery including tooth extraction
- stroke
- excessive INR values (i.e.. > 3.5)
- need for intravenous or subcutaneous antithrombotic therapy (e.g. unfractionated or low molecular weight heparin)

*General guidelines for: i.) pre-procedural discontinuation of warfarin and for restarting warfarin after a temporary interruption are provided in Appendix B, and ii.) the management of bleeding or excessive INR values in the absence of bleeding are provided in Appendix C. Discussion with the project office staff regarding these issues is encouraged.

8.2 ACCEPTABLE REASONS FOR PERMANENTLY DISCONTINUING WARFARIN*

- life-threatening bleeding (excluding post-surgical bleeding)
- moderate bleeding requiring transfusion
- recurrent minor bleeding
- primary hemorrhagic stroke
- warfarin skin necrosis
- high-risk for falls (e.g. after amputation)

*Please note that permanent discontinuation of warfarin requires discussion with the Project Office physician.

9.0 STATISTICAL CONSIDERATIONS

9.1 STUDY SIZE

- i. **Estimated control event rate:** Data from the APTC overview, in which more than 9,000 patients with PVD were analyzed, and data from 1,329 HOPE trial patients recruited from Canada (who matched our inclusion criteria) indicate that the 2 year event rate (CV death, MI, stroke) in patients receiving antiplatelet therapy is approximately 12%²⁵. Based on data from the HOPE trial, we anticipate the control event rate (for first occurrence and non-overlapping events) for the **Composite A:** cardiovascular death, non-fatal MI, or non-fatal stroke to be 13.8% (Table 4), and for **Composite B:** the rate of cardiovascular death, first occurrence of MI, stroke, or severe ischemia requiring urgent reperfusion/reconstruction of the coronary (PTCA, CABG) or peripheral artery circulation (thrombolytic therapy, angioplasty, bypass surgery or amputation) to be 24.1% over 2.5 years.
- ii. **Expected risk reduction with combined warfarin and antiplatelet therapy compared with antiplatelet therapy alone:** Previous trials using high intensity warfarin (INR 2.8-4.8) vs. control, and moderate intensity warfarin (INR 2-3) plus aspirin vs. aspirin, have *observed* between a 30 and 35% relative risk reduction in favor of warfarin³⁵. However this observed estimate of the treatment effect includes all patients who did not adhere to warfarin, and is therefore an underestimate of the “*real*” or *theoretical* relative risk reduction with warfarin which likely ranges from between 35 to 40%.
- iii. **Non-adherence to warfarin:** A review of open trials in which moderate intensity warfarin was used and adherence to warfarin was monitored closely, indicates that an adherence rate with warfarin of over 90% can be achieved^{38,39,54,55}. Given that the majority of patients come off warfarin therapy early in the course of therapy, we anticipate a non-adherence rate of approximately 10% with warfarin over 2.5 years of follow-up. However we

considered the effect on study power if up to a 15% non-adherence rate occurred. Furthermore, given the high-risk population included in the trial, it is reasonable to expect that up to 5% of patients in the control group will develop a medical indication which necessitates warfarin therapy (e.g. atrial fibrillation, venous thrombosis) over the course of the 2.5 year follow-up. Therefore, we considered the effect on sample size of a non-adherence rate of 10 to 15% with warfarin and a 5% use of warfarin by control group patients (Table 4).

By using a sample of 2,400 patients and equal allocation, considering a control event rate of 24.1% for Composite B, we will have over 90% power to detect a 30% real relative risk reduction with warfarin. This allows for a non-adherence rate with warfarin of up to 15%, and use of warfarin in the control group of 5% (observed risk reduction of 25%). With this sample size, for Composite A (Control rate=13.8%), we will have 80% power to detect a 35% real relative risk reduction with warfarin. This allows for a non-adherence rate of up to 15%, and use of warfarin in the control group of 5% (observed risk reduction 28.7%) (Table 4).

TABLE 4: SAMPLE SIZE REQUIREMENTS (PER GROUP)
(two-sided alpha=0.029)

Composite A:

Original Control Event Rate = 13.8%			
RRR	NA Power	10%	15%
25%	80%	2327	2685
	90%	3053	3521
30%	80%	1564	1762
	90%	2052	2311
35%	80%	1115	1235
	90%	1462	1620

Composite B:

Original Control Event Rate = 24.1%			
RRR	NA	10%	15%
	Power		
25%	80%	1180	1331
	90%	1547	1745
30%	80%	808	925
	90%	1059	1213
35%	80%	582	639
	90%	762	838

RRR = Real Risk Reduction

NA = Non-Adherence in the active group; for each calculation we have assumed that 5.0% of patients in the control group will receive open label warfarin

9.2 STATISTICAL ANALYSIS

The aims of this study are to determine the efficacy and safety of warfarin plus antiplatelet therapy versus antiplatelet therapy alone in patients with PVD.

The **primary analysis** will compare treatment groups on the first occurrence of an event in the co-primary outcomes of **Composite A:** CV death, MI, or stroke, and **Composite B:** CV death, MI, stroke, or severe ischemia requiring urgent intervention of the coronary (PTCA, CABG) or peripheral artery circulation (thrombolytic therapy, angioplasty, bypass surgery, amputation) during 2.5 years using a log-rank statistic (2 sided α)⁵⁶, and based on an intention to treat. Assuming non-independence between Composite A, and B, and given that Composite A represents approximately 55% of events in Composite B, significance will be declared for both Composite A and B at $P < 0.029$, providing a total type I error rate for both co-primary outcomes of less than 0.05.

Secondary analyses will compare the primary outcome clusters plus coronary and carotid reperfusion/revascularization and unstable angina requiring hospital admission. In addition the rates of bleeding subdivided by type i.e. life-threatening, moderate, and minor will be compared between treatment groups. The primary statistical analysis will be conducted as an intention-to-treat analysis. Survival curves will be estimated using the Kaplan-Meier procedure and will be compared using log-rank tests⁵⁶. Treatment effects and their 95% confidence intervals will be estimated using Cox regression. A secondary analysis using Cox regression will be used to adjust for any imbalances in baseline characteristics between the treatment groups. Exploratory subgroup analyses (e.g. centres with compliance and below the median, previous vascular reconstruction, diabetes, gender, current smokers versus non-smokers, therapeutic patients on warfarin versus control, patients on statins versus not on statins) will be done by stratified analysis, including tests for interactions (e.g. interaction between treatment and diagnosis of diabetes at baseline) in the Cox model⁵⁷.

10. STUDY MONITORING

An independent Data and Safety Monitoring Board (DSMB) will be established to monitor the progress of all aspects of the study and to ensure that the study meets the highest standards of ethics and patient safety. Two formal interim analyses are planned, after the first 1/3 (800), and after 2/3 (1,600) patients have been followed for 2.5 years. For efficacy, the combined endpoint of CV death, MI, or stroke will be monitored using a modified Haybittle-Peto rule⁵⁷ of 4 standard deviations in the first half of the study (before 50% of patients' 2.5-year data are available) and 3 standard deviations in the second half. The boundary will have to be exceeded on at least two consecutive time points three months apart. Given the extremeness of the monitoring boundary practically no adjustment for the Type I error in the final analysis will be required. The occurrence of life-threatening bleeds (including intracranial bleeds), moderate, and minor bleeds will also be reviewed by the DSMB. Safety data will be monitored every 6 months, or more frequently if requested by the DSMB. Although, no formal boundaries for safety monitoring will be defined, clear and consistent evidence of net harm with no beneficial effect must be apparent prior to termination of the study. Given the extensive previous experience with warfarin the main potential for adverse events is related to life-threatening bleeding. No adverse effects on the primary or secondary outcome are likely. Therefore no formal guidelines for monitoring of the efficacy outcome (CV death, MI, stroke, severe coronary or peripheral ischemia requiring intervention) for harm are proposed. Nevertheless, should an unexpected situation arise (e.g. a substantial excess in intracranial bleeds with no benefit on any other endpoint), the independent DSMB will be in a position to make the appropriate informed judgement. The recommendation of the DSMB to stop the trial would be based on the pattern of the treatment effect of warfarin across all endpoints, and include an assessment of the overall benefit/risk ratio. In addition, the DSMB will take into account all available data from other relevant studies to guide their decisions (e.g. a 2 SD excess of the primary endpoint and life-threatening bleeding with the active agent may constitute grounds to terminate the study).

11.0 ADJUDICATION

All primary and secondary endpoints including death classified by cause, MI, stroke, limb-threatening ischemia requiring an intervention, unstable angina, TIA revascularization procedures, amputation, and moderate or life-threatening bleeding will be adjudicated, utilizing standard definitions, by a central committee of clinicians blind to the treatment allocation. (Table 3, and Adjudication Manual). For each primary and secondary event reported by a centre, all relevant case report forms, discharge summaries, ECGs, and laboratory reports will be collated and blinded (i.e. removal of INR values or references to warfarin in physician's notes) at the Project Office, and sent to an independent adjudicator. Disagreements between the centre report and the first adjudicator will require resolution by a second independent adjudicator.

12.0 DATA COLLECTION

Data management is performed using DataFax software. Case Report Forms (CRFs) will be received centrally by FAX via toll free lines and read into a validation database using optical character recognition. At the Project Office, each CRF is validated two separate times by at least two different people before entry into the study database (i.e. before it is declared “clean”). Within-form and between-form data checks are performed weekly; problems requiring local resolution are noted on Quality Control (QC) reports which are faxed weekly to investigators. This system allows us to keep up with data entry and verification on a weekly basis.

13.0 SUBSTUDIES

In our efforts to learn more about patients with PVD, and their prognostic markers, collection of a baseline blood sample from consecutive trial patients with central processing and analysis is planned. (Appendix E) However, only committed centers who are equipped to draw, process and store blood samples will be included. Funding for analysis of these samples will require supplementary funding sources. All other substudies of the trial require prior approval from the Steering Committee, which will determine if the question is of high scientific value, and will not interfere with the conduct of the overall trial. Substudy funding will generally be the responsibility of the investigator proposing the additional data collection.

14.0 OWNERSHIP OF DATA AND PUBLICATION POLICY

The main database for the trial which includes the results of blood analysis will be kept centrally at the Project Office. All data collected from the trial are collectively owned by the collaborating investigators, and decisions regarding its use for presentations, publications, and decisions regarding authorship will be made by the Steering Committee. The Steering Committee will be guided by the principles outlined in the Vancouver Guidelines for authorship⁵⁸. In general the main authors of the primary papers will be the PI, chair of the Steering Committee and one lead investigator from each of the top 10 centres, and key coordinating centre staff on behalf of the whole study. All whole-hearted collaborators will be recognized as part of the study group. The secondary papers will be allocated to any of the members of the Steering Committee or other active investigators based upon their contribution to the study through a process of consensus.

15.0 PROPOSED TIMETABLE

Phase I (September 1, 1999 - December 31, 1999)

During Phase I, all centres should obtain their institution's Institutional Review Board (IRB) Approval. This has been achieved in Hamilton and we will assist other centres in preparing their IRB applications. Additional goals of Phase I include:

- i. Development of Case Report Forms (CRF's)
- ii. Development of a comprehensive Manual of Operations
- iii. Development of study aids
- iv. Conduct a training workshop for study centres

Phase II - Recruitment (January 1, 2000 – June 30, 2001)

Recruitment begins, and will continue until the target sample size has been recruited. It is anticipated that this will be achieved over an 18 month period. We anticipate that **60% of total sample will be recruited in the first 12 months of Phase 2 followed by the remaining 40% in the ensuing 6 months.**

Phase III – Follow-Up (July 1, 2001 – Jan. 2004)

All patients will remain on treatment for 2.5 years. The last patient follow-up is anticipated to occur in early January 2004.

Phase IV – Close-Out and Analysis (Jan 2004 – Sept, 2004)

The close out period for the study will be 6 months for scheduling final patient visits, obtaining data, completion of missing data, and confirmation and classification of events. Data analysis and publication will require another 3 months of project office efforts.

16.0 STUDY ORGANIZATION AND ADMINISTRATION

Steering Committee: The Steering Committee will be composed of the Steering Committee Chairperson, the Principal Investigator (PI), key representatives from the Project Office, and key representatives from each region who are deemed to have clinical and methodological expertise. The committee has overall responsibility for producing and conducting a scientifically sound design and ensuring accurate reporting of the study. They must address and resolve all scientific issues regarding the conduct of the trial. The committee will meet at least twice per year. All Substudies must be approved by the Steering Committee. In addition, all decisions regarding the use of study data for public presentation, and publication including issues of authorship must be approved by the Steering Committee.

Adjudication Committee: The Events adjudication Committee will be responsible for validating all reported primary and secondary outcomes. The Events adjudication process will be coordinated by the Project Office in Hamilton. Adjudicators will be trained using test cases performed to ensure consistency of the application of study definitions. Reported events must be adjudicated by at least one committee member. Disagreements between an adjudicator and a centres report will be reviewed according to a pre-defined algorithm which must be agreed to by the Adjudication Committee.

Operations Committee: The Operations committee, composed of key project office staff and two Principal investigators from outside Hamilton, is responsible for ensuring that study execution and management is of the highest quality. Specifically the Operations Committee will monitor recruitment, compliance, and adjudication and address the day to day issues arising from the trial. This committee will meet by telephone on a monthly or bimonthly basis, and each meeting will be documented with minutes.

Data Safety Monitoring Board: The DSMB is primarily responsible to regularly review the safety data and serious adverse events, review a formal interim analysis of the efficacy data, and provide feedback to the Steering Committee. In addition the DSMB will respond to special requests from IRB's, provide recommendation for protocol amendments, and verify the final analysis of the study performed by the DSMB associated statistician.

17.0 REFERENCES

1. Rennin A, Takkunen H, Aromaa A. Prevalence of intermittent claudication and its effect on mortality. *Acta Medica Scandinavia* 1982; 211:256
2. Weitz J, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: A critical review. *Circulation* 1996; 94:3049
3. Criqui MH, Fronck A, Barrett-Conner E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985; 71:510-515.
4. Newman AB, Siscovick D, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the cardiovascular health study. *Circulation* 1993; 88:837-845.
5. Dagenais G, Maurice S, Robitaille N, Gingras S, Lupien P. Intermittent claudication in Quebec men from 1974-1986: the Quebec Cardiovascular Study. *Clinical Investigations in Medicine* 1991;14:93-100.
6. Jelnes R, Gaardsting O, Hougaard JK, Baekgaard N, Tonnesen KH, Schroeder T. Fate in intermittent claudication: outcome and risk factors. *Br Med J* 1986; 293:1137-1140.
7. Dormandy J. Peripheral vascular disease. *Med North Am* 1994; 353-360.
8. Farkouh ME, Rihal CS, Gersh BJ, Rooke TW, Hallett JWJr, O'Fallon WM, et al. Influence of coronary heart disease on morbidity and mortality after lower extremity revascularization surgery: a population based study in Olmsted County, Minnesota. *J Am Coll Cardiology* 1994; 24:1290-1296.
9. Dormandy J, Mahir M, Ascady G, Balsano F, De Leeuw P, Blomberg P, et al. Fate of the patient with chronic leg ischemia: a review article. *J Cardiovasc Surg (Torino)* 1989; 30:50-57.
10. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication. *J Am Geriatr Soc.* 1985; 33:13-18.
11. Heart Outcomes Protection Evaluation (HOPE Trial) Personal Communication S. Yusuf (Principal Investigator).
12. Clagett GP. Antithrombotic therapy for lower extremity bypass. *Journal of Vascular Surgery* 1992; 15:873-875.
13. Fowkes FGR, Price JF, Leng GC. Targeting subclinical atherosclerosis. *BMJ* 1998; 316:
14. Ogren M, Hedblad B, Isacson S-O, Janzon L, Jungquist G, Lindell S-E. Non-invasively detected carotid stenosis and ischaemic heart disease in men with leg arteriosclerosis. *The Lancet* 1993; 342:1138-1141.
15. Howell MA, Colgan MP, Seeger RW, Ramsey DE, Sumner DS. Relationship of severity of lower limb peripheral vascular disease to mortality and morbidity:A six-year follow up study. *Journal of Vascular Surgery* 1989; 9:691-697.
16. Sikkink CJ, van Asten WN, van't Hof MA, van Langen H, van der Vliet JA. Decreased ankle/brachial indices in relation to morbidity and mortality in patients with peripheral arterial disease. *Vasc Med* 1997; 2:169-173. (Abstract).
17. Leng GC, Fowkes FGR, Lee AJ, Dunbar J, Housley.E., Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ* 1996; 313:1440-1444.

18. Antiplatelet Trialist' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994; 308:159-168.
19. Green RM, Roedersheimer R, DeWeese JA. Effects of aspirin and dipyridamole on expanded polytetrafluoroethylene graft patency. *Surgery* 1982; 92:1016-1026.
20. Goldman M, Hall C, Dykes J, Hawker RJ, McDonnell M. Does indium-platelet deposition predict patency in prosthetic arterial grafts? *Br.J.Surg* 1983; 70:635-638.
21. McCollum C, Alexander C, Kenchington G, Franks PJ, Greenhalgh R. Antiplatelet drugs in femoropopliteal vein bypasses: A multicenter trial. *Journal of Vascular Surgery* 1991; 13:150-162.
22. Kohler TR, Kaufman JL, Kacoyanis G, Clowes A, Donaldson MC, Kelly E, et al. Effect of aspirin and dipyridamole on the patency of lower extremity bypass grafts. *Surgery* 1984; 96:462-466.
23. Antiplatelet Trialist' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; 308:81-106.
24. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348:1329-1339.
25. Antiplatelet Trialist' Collaboration. The Aspirin Papers. *British Medical Journal* 1997;
26. Kretschmer GJ, Herbst F, Prager M, Sautner T, Wenzl E, Berlakovich GA, et al. A decade of oral anticoagulant treatment to maintain autologous vein grafts for femoropopliteal atherosclerosis. *Arch Surg* 1992; 127:1112-1115.
27. Kretschmer G, Schemper M, Ehringer H, Wenzl E, Polterauer P, Marçosi L. Influence of postoperative anticoagulant treatment on patient survival after femoropopliteal vein bypass surgery. *The Lancet* 1988; April 9:797-799.
28. de Smit P, van Urk H. Dutch oral anticoagulation trial. *ACA* 19 A.D.;
29. Arfvidsson B, Lundgren F, Drott C, Schersten T, Lundholm K. Influence of Coumarin Treatment on patency and limb salvage after peripheral arterial reconstructive surgery. *American Heart Journal*. 159, 556-560. 1990
30. Johnson WC. Does Oral anticoagulation improve patency of vein bypasses? A prospective randomized study. 1997; *Proceedings from the 51st SVS/ISCVS*:44
31. Sarac TP, Huber TS, Back MR, Ozaki CK, Carlton LM, Flynn TC, et al. Warfarin improves the outcome of infrainguinal vein bypass grafting at high-risk for failure. *J Vascular Surgery* 1998, Sept 28(3):446-457
32. Egan D, Garg R, Wilt T et al. Rationale and design of the arterial disease multiple intervention trial (ADMIT) pilot study. *Am J Cardiol* (In Press)
33. Anonymous. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) research group. *Lancet* 1994; 343:499-503.
34. Smith P, Arnesen H, Home I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1990;323:147-152.
35. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999;282:2058-2067.
36. CARS Investigators. Coumadin Aspirin Reinfarction Trial. *Lancet* 1997; 350:389-396.

37. Post Coronary Bypass Graft Trial Investigators. The effect of aggressive lowering of low density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary artery bypass grafts. *New Engl J Med* 1997; 336:
38. Stroke prevention in atrial fibrillation study. Final results. *Circulation* 1991; 84:527-539.
39. Singer DE, Hughes RA, Gress DR, Sheehan MA et al. The effect of aspirin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The BAATAF study. *Am Heart J* 1992;124:1567-73.
40. Ezekowitz MD, Bridgers SL, James KE, Cardliner NH, et al. Warfarin in the prevention of stroke associated with non-rheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study. Final Results. *Circulation* 1991;84:527-39.
41. Turpie AG, Gunstensen J, Hirsh J, Nelson H, Gent M. Randomised comparison of two intensities of oral anticoagulant therapy after tissue heart valve replacment. *Lancet* 1988; 1:1242-1245
42. Turpie AG, Gent M, Laupacis A, Latour Y, Gunstensen J, Basile F, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement [see comments]. *New England.Journal.of.Medicine* 1993; 329:524-529.
43. Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wiecezorek I, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. *Circulation* 1994; 89:81-88.
44. Anand SS, Yusuf S, Pogue J, Weitz J, Flather M. Long-Term Anticoagulant Therapy in Patients with Unstable Angina or Suspected Non-Q wave MI: Organization to Assess Strategies for Ischemic Syndromes (OASIS) Pilot Study Results. *Circulation* 1998;98:1064-1070.
45. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. [Review]. *Chest* 1995; 108:Suppl):276S-290S.
46. Hirsh J, Dalen JE, Deykin D, Poller L, Bussey H. Oral anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. [Review]. *Chest* 1995; 108:Suppl):231S-246S.
47. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, et al. Bleeding complications of oral anticoagulant treatment:an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; 348:423-428.
48. Schulman S, Granqvist S, Holmstrom M, Carlsson A, Lindmarker P, Nicol P, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *New England Journal of Medicine* 1997; 336:393-398.
49. Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 2: Oral anticoagulants. American Heart Association [published erratum appears in *Circulation* 1995 Jan 15;91(2):A55-A56]. *Circulation* 1994; 89:1469-1480.
50. Levine M, Hirsh J. Hemorrhagic complications of anticoagulant therapy. *Seminars in Thrombosis and Hemostasis* 1986.;12:39-57.
51. Ferguson JJ. Highlights of the 48th scientific session of the American College of cardiology. *Circulation* 1999; 100: 570-575.
52. Topol EJ. Excite Trial, presented at hotline session, European Society of Cardiology Meeting, Barcelona, 1999.

53. Harrison L, Johnston M, Massicote P, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Annals of Internal Medicine* 1997; 126:133-136.
54. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin in high-risk patients with atrial fibrillation: stroke prevention in atrial fibrillation III randomised clinical trial. *The Lancet* 1996; 348:633-638.
55. SPAF Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: SPAF ii Study. *Lancet* 1994; 343:687-91
56. Kalbfleish JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. 1980; New York, John Wiley and Sons Inc.
57. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *British Journal of Radiology* 1971; 44:793-797
58. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Ann Intern Med* 1997; 126: 34-47.
59. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. *N Engl J Med* 1997; 336: 1506-1511.

APPENDIX A: Warfarin Dosage Nomogram

Warfarin Dosage Adjustment Algorithm

INR	Warfarin Dose Adjustment*	Current Daily Dose (mg)				
		2.5	5.0	7.5	10.0	12.5
		Adjusted Daily Dose (mg)				
1.0-2.0	Increase x 2 days	5.0	7.5	10.0	12.5	15.0
2.0-3.0	No change	—	—	—	—	—
3.0-6.0	Decrease x 2 days	1.25	2.5	5.0	7.5	10.0
6.0-10.0 [†]	Decrease x 2 days	0	1.25	2.5	5.0	7.5
10.0-18.0 [§]	Decrease x 2 days	0	0	0	0	2.5
>18.0 [§]	Discontinue warfarin and consider hospitalization/reversal of anticoagulation					

[†] Consider oral vitamin K, 2.5–5 mg

[§] Oral vitamin K, 2.5–5 mg

* Allow 2 days after dosage change for clotting factor equilibration. Repeat INR 2 days after increasing or decreasing warfarin dosage and use new guide to management. After increase or decrease of dose for two days, go to new higher (or lower) dosage level (e.g., if 5.0 qd, alternate 5.0/7.5; if alternate 2.5/5.0, increase to 5.0 qd).

APPENDIX B: Acenocoumarol Dosage Nomogram

Acenocoumarol Dosage Adjustment Algorithm- Poland

INR	Dose Adjustment*	Current Daily Dose							
		1	2	3	4	5	6	7	8
1.0-2.0	Increase x 2 days	2	4	4	6	6	8	8	10
2.0-3.0	No change	-	-	-	-	-	-	-	-
3.0-6.0	Decrease x 2 days	0	1	2	2	3	4	4	6
6.0-10.0 †	Decrease x 2 days	0	0	1	1	2	2	2	2
10.0-18.0 §	Decrease x 2 days	0	0	0	0	0	0	0	0
> 18.0 §	Discontinue and consider hospitalization								

† consider oral vitamin K, 2.5-5 mg

§ Oral vitamin K, 2.5-5 mg

* Allow 2 days after dosage change for clotting factor equilibration. Repeat INR 2 days after increasing or decreasing warfarin dosage and use new guide to management. After increase or decrease of dose for two days, go to new higher (or lower) dosage level (e.g., if 5.0 qd, alternate 5.0/7.5; if alternate 2.5/5.0, increase to 5.0 qd)

APPENDIX C: Guidelines for the Temporary Interruption of Warfarin in Patients Undergoing Surgery or Other Invasive Procedures

The goal of these guidelines are i. to facilitate efficient management of study patients randomized to warfarin therapy who require temporary discontinuation, ii. to minimize any potential for bleeding, and iii. to maximize long-term adherence to warfarin by ensuring that patients resume warfarin therapy after completion of the intervention.

An algorithm for the management of study patients in the peri-operative setting is provided below.

Important factors to consider when temporarily discontinuing warfarin:

(See Kearon C and Hirsh J. Management of anticoagulation before and after elective surgery. *N Engl J Med* 1997⁵⁹ for a more detailed discussion)

1) The long half-life of warfarin

The anticoagulant effect of warfarin takes several days to wear off after warfarin therapy is discontinued. In study patients with an INR in the therapeutic range (2.0-3.0), warfarin should be **withheld for a total of 5 doses prior to surgery**. In patients with an INR above the target therapeutic range, warfarin may need to be withheld for a longer period of time (see algorithm).

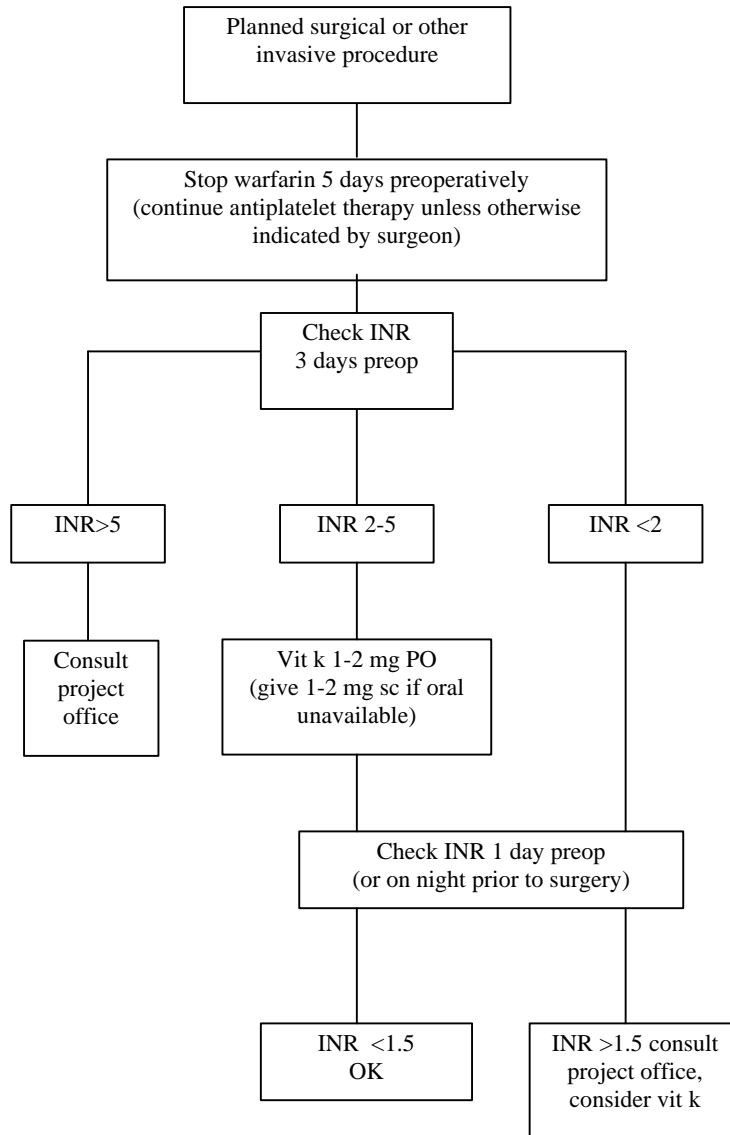
2) The risk of thrombotic complications when warfarin therapy is interrupted:

In general, the risk of thrombosis needs to be individually assessed in patients. However, in study patients who do not have a separate co-existing indication for warfarin therapy (e.g. some patients already taking warfarin may develop atrial fibrillation), the risk of a peri-operative arterial (atherothrombotic) event is low, and peri-operative heparin therapy is not indicated.

3) The risk of bleeding from the surgical site:

Although there is an increased risk of bleeding from the operative site with the peri-operative use of therapeutic doses of heparin, extensive experience with the use of post-operative warfarin confirms that bleeding is uncommon when warfarin is started after major surgery. The prothrombin time does not start to increase until 12-24 hours after recommencement of warfarin, and it takes about 3 days for the INR to reach 2.0. **Therefore, if the patient is stable and no additional invasive procedures are planned, warfarin therapy can be restarted on the night after surgery.**

Peri-operative management of warfarin: algorithm



**Resume regular dose of warfarin therapy (and antiplatelet therapy)
as soon as possible after the procedure**

APPENDIX D: Management of Bleeding in PVD Study Patients

1. Major and life-threatening Bleeding

In all patients who have major or life-threatening bleeding, the haematology/coagulation service of the institution should be consulted and the following measures should be taken immediately:

- Stop warfarin, antiplatelet therapy, and any other antithrombotic therapy
 - Establish adequate large bore IV access
 - Begin volume expansion
 - Draw blood for CBC, Coagulation profile including INR, blood group / antibody screen and request urgent cross-matching of 2 or more units of packed cells
 - Transfuse packed cells according to clinical condition
Consider **Frozen Plasma** and/or intravenous **vitamin K**

Determine site of bleeding

If vascular access site..... Apply manual pressure

If Gastrointestinal bleeding:..... Consult Gastroenterology/General Surgery

If Intracranial bleeding suspected..... CT Scan of head

*If Retroperitoneal bleeding suspected.....*CT scan of abdomen

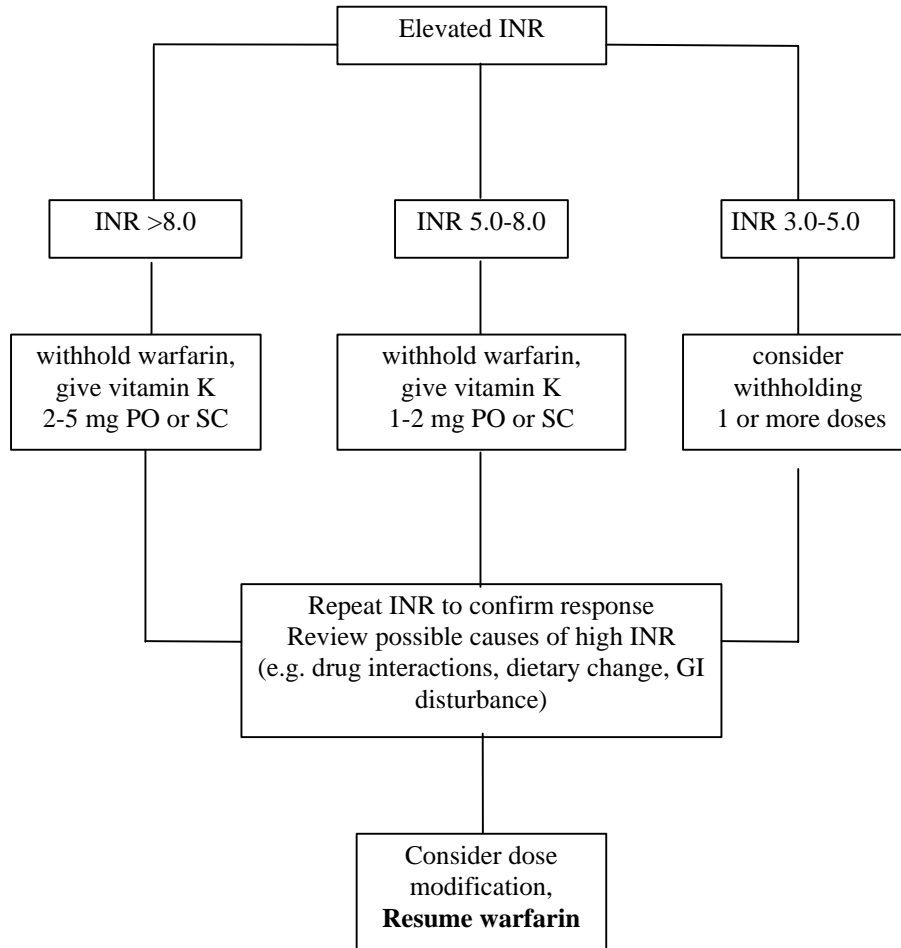
<p>Warfarin should be permanently discontinued in patients who develop major or life-threatening bleeding in the absence of surgical or other trauma</p>

2. Minor Bleeding

Minor bleeding (e.g. oozing from puncture sites, bruising around puncture sites) may occur during warfarin therapy and is not unexpected. If minor bleeding is causing discomfort or is considered clinically worrying, warfarin therapy may be temporarily withheld at the discretion of the investigator. If temporary discontinuation of warfarin is considered necessary, the INR should be checked to exclude excessive warfarin anticoagulation (INR >3.0).

3. High INR in the Absence of Bleeding

An elevated INR (INR>3.0) in the absence of bleeding can generally be managed by a dose reduction or temporary discontinuation of warfarin. In cases where the INR is elevated above 5.0, a small dose of oral (or SC) vitamin K may be considered. Most patients will begin to respond to vitamin K within 24 hours.



Note: SC/IV preparations of Vit K may be given orally e.g. for solutions with concentration of 10 mg Vit K/1 mL – to give 1 mg oral Vit K, draw up 0.1 mL of this solution with an insulin syringe, mix with a small amount of juice in a medicine cup, and administer to patient.

APPENDIX E: Study Organization

1. Steering Committee:

Principal Investigator:	Sonia Anand
Chair of Steering Committee:	Salim Yusuf
Project Office Physician	John Eikelboom
Pharmaceutical Coordinator:	Jeff Thompson
Study Coordinator:	Patty Montague
Regional Representatives	Andrejz Budaj, Claudio Cina, Hui Lee, Stephane Sauve, Bob Magissano, Richard Davies, Randy Guzman, George Hajjar, Gilbert Gosselin, Denis Gossard, Bruce Sussex, Richard Crowell

2. Participating Centres:

Investigator	Dr. Richard Crowell
Study Nurse	Cheryl Forbes
	Queen Elizabeth-II HSC
	New Halifax Infirmary, Room 2108
	Halifax, Nova Scotia B3K 6A3
	Tel: 902-473-3940
	Fax: 902-473-2434
	Email: richard.crowell@is.dal.ca

Investigator	Dr. Claudio Cina
Study Nurse	Alison Magi and Linda Frenette
	304 Victoria Avenue North
	Hamilton, Ontario L8L 5G4
	Tel: 905-777-5321
	Fax: 905-777-1508
	Email: cinacs@fhs.mcmaster.ca

Investigator	Dr. Denis Gossard
Study Nurse	Chantal Briand
	Hopital Maisonneuve-Rosemont
	Recherche Clinique Cardiologie-5e etage
	5415 Boul. De L'Assomption
	Montreal, Quebec H1T 2M4
	Tel: 514-252-3400 ext. 4466
	Fax: 514-254-7455
	Email: dgossard@internet.hmr.qc.caext.

Investigator
Study Nurse

Dr. Gilbert Gosselin
Monique Brouillette
Institut de Cardiologie de Montreal
Centre de recherche
500 rue Belanger est
Montreal, Quebec H1T 1C8
Tel: 514-376-3330 ext. 3629
Fax: 514-593-2573
Email:

Investigator
Study Nurse

Dr. Richard Davies
To be named
University of Ottawa Heart Institute
40 Ruskin Avenue
Ottawa, Ontario K1Y 4E9
Tel: 613-761-4729
Fax: 613-724-6234
Email: rfdavies@heartinst.on.ca

Investigator
Study Nurse

Dr. Georges Hajjar
Sylvie Poloni
Ottawa Civic Hospital
Civic Parkdale Clinic, Suite 630
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9
Tel: 613-761-4766
Fax: 613-761-5362
Email: ghajjar@ottawahospital.on.ca

Investigator
Study Nurse

Dr. Hui Nien Lee
Karen Barban, Sue McLean
The Group Health Centre
240 McNabb Street
Sault Ste. Marie, Ontario P6B 1Y5
Tel: 705-759-1234
Fax: 705-946-5241
Email: huilee@sympatico.ca

Investigator
Study Nurse

Dr. Sante Fratesi
Karen Barban and Sue McLean
325-955 Queen St. E.
Sault Ste. Marie, Ontario P6A 2C3
Tel: 705-942-6960
Fax: 705-942-8896
Email: samfratesi@sympatico.ca

Investigator
Study Nurse

Dr. Bruce Sussex
Marie Burry, Sharon Newman
The General Hospital
Dept. of Cardiology Research
University of Newfoundland
Health Sciences Complex, Rm. 2309
300 Prince Philip Drive
St. John's, Newfoundland A1B 3V6
Tel: 709-737-7337
Fax: 709-737-3396
Email:

Investigator
Study Nurse

Dr. Stéphane Sauvé
Dara Cole
Sudbury Regional Hospital
St. Joseph Health Centre
700 Paris Street
Sudbury, Ontario P3E 3B5
Tel: 705-674-3181 x7011
Fax: 705-675-4738
Email: saus@neilnet.com

Investigator
Study Nurse

Dr. John Fenton
Dara Cole
262 Caswell Drive
Sudbury, Ontario P3E 2N8
Tel: 705-522-4611
Fax: c/o 705-675-4738
Email:

Investigator
Study Nurse

Dr. Barry B. Rubin
To be named
The Toronto Hospital
EC5 302A - 200 Elizabeth Street
Toronto, Ontario M5G 2C4
Tel: 416-340-3645
Fax: 416-340-5029
Email: brubin@torhosp.toronto.on.ca

Investigator
Study Nurse

Dr. Andrew Morris
Wendy Weighell
St. Boniface General Hospital
409 Tache Avenue, C3197
Winnipeg, Manitoba R2H 2A6
Tel: 204-233-8563
Fax: 204-233-7154

Email: amorris@mail.sbgh.mb.ca

Investigator
Study Nurse

Dr. Randy Guzman
Wendy Weighell
St. Boniface General Hospital
Z3051-409 Tache Ave.
Winnipeg, MB
Tel: 204-237-2570
Fax: 204-237-3429
Email: rguzman@gwmail.sbgm.mb.ca

Investigator
Study Nurse

Dr. Robert Maggisano/ Dr. John Blakely
to be advised
Sunnybrook HSC
H185-2075 Bayview Ave.
Toronto, Ontario
Tel: 416-480-4737
Fax: 416-480-5815
Email:

3. Adjudication:

Co-Chairs: Dr. Bruce Sussex, Dr. Stephane Sauve
Members: *Dr. Claudio Cina, Dr. Randy Guzman, Dr. Beata
Klosjewicz-Wasek*

4. Operations Committee:

Members: Sonia Anand, Salim Yusuf, John Eikelboom, Patty Montague, Andrezj
Budaj, Hui Lee, Gilbert Gosselin

5. Data Safety and Monitoring Committee:

Chair: Dr. Gilles Dagenias
Members: Dr. Jeffrey Ginsberg, Wayne Taylor, Dr. Andrew Hill

6. Project Office:

Sonia Anand, Salim Yusuf, John Eikelboom, Patty
Montague, Carrie Cuvay, Rose Mayhew, Kathy
Picken

7. Biostatistics:

Janice Pogue, Qilong Yi

8. Pharmacy Contact

Jeff Thompson, Hamilton Health Sciences
Corporation, General Hospital Division

9. Administration

Beena Cracknell, Rose Mayhew

10. Coaguchek Contacts

Hubert Czerwinski, Jack Robertson, Bettina Steiner

11. Sponsors

The Medical Research Council of Canada
The Heart and Stroke Foundation of Ontario
Roche Diagnostics (Support in kind)

APPENDIX F: Blood Collection Substudy

In our efforts to learn more about patients with PVD, and their prognostic markers, a baseline blood sample (20 mL) will be collected from consecutive trial patients. However, only committed centres who are equipped to draw, process and store blood samples will be included. Central storage and analysis is planned. Funding for analysis of these samples will require supplementary funding sources.

In those centres that decide to participate, a 20 mL blood sample will be collected from all patients participating in the study. This sample will be collected at the Randomization visit, before the first dose of drug is given. Specific details of the blood collection procedures will be described in the Manual of Operations.

The following factors are of interest and the methods by which each will be assayed are listed:

Laboratory Test	Method
PAI-1	Chromogenic Assay kit for PAI-1: Spectrolyse/PL PAI-1 is a two-stage indirect enzymatic assay.
Lp(a)	Quantitative determination performed by automated immunoprecipitin analysis.
Fibrinogen	Clauss method
Complete blood count:	Automated cell counter.
HBA1c	765 Glycomat determination uses low pressure cation exchange chromatography in conjunction with gradient elution to separate human hemoglobin subtypes
Insulin	¹²⁵ I-labeled insulin competes with the subjects insulin for sites on the insulin specific antibody immobilized to the wall of a polypropylene tube. The antibody fraction is isolated by decanting the supernatant, the gamma counts being inversely related to the amount of insulin present.
Glucose	Glucose oxidation is catalyzed by glucose oxidase to form hydrogen peroxide and gluconate. Oxidative coupling catalyzed by peroxidase in the presence of chromogens produces a dye, measured by reflected light.
Cholesterol	Cholesterol esters in the presence of cholesterol ester hydrolase and cholesterol oxidase form cholesterol and hydrogen peroxidase, in proportion to the original cholesterol concentration.
HDL-C	Precipitated with dextran sulphate and a calcium salt, then measured the same as cholesterol.
Triglycerides	Hydrolyzed by lipase to glycerol and fatty acids. Glycerol is phosphorylated by glucose kinase, and is oxidized forming hydrogen peroxide which is measured by production of a dye at 540 nanometres (nm).
Homocysteine	High-Performance liquid chromatography

In addition, the buffy coat, containing DNA, will be removed and stored from each participant. As storage and use of genetic material is of concern to some, we have developed a “DNA Information Package.” (Appendix F) This package contains an IRB Information Sheet, for the Ethics Review Board at each institution, and a Patient Information Sheet, to be given to the patient at the time of informed consent. It also contains a suggested Consent Form to be used at those institutions participating in this substudy.

The following is the current list of candidate genes:

PHENOTYPE	GENOTYPE
Body Mass Index Abdominal Obesity	FABP2 codon 54, AGT codon 174
Elevated Fasting Glucose Insulin Resistance	FABP2 codon 54, PON 2 codon 148
Plasma total cholesterol Plasma LDL-L Plasma Apo B Plasma Triglycerides	APOE isotype, PON 1 codon 192 APOE isotype, APOC 3, PON1 codon 192 APOC3 promoter, FABP2 codon 54 PON 1 codon 192, M+DNA
Plasma HDL – C Plasma Apo A-1 Plasma Lp(a)	HL promoter, APOC3 promoter, PON1 codon 192 F7 codon 353
Activated Protein C Resistance	F5 Leiden
Systolic BP Diastolic BP	ACE, AGT promoter, AGT, AGTR1
Homocysteine	MTHFR position 677

Note: The list of candidate genes is constantly expanding. However, the volume of buffy coat collected from each participant will allow us to accommodate new candidate genes as they are discovered.

APPENDIX G: DNA Package

1. IRB Information Sheet

Addressing Ethical Concerns in the Collection, Storage and Processing of Genetic Material (DNA) in the PVD Trial Substudy

Study Rationale: We propose to determine the prevalence of conventional (already discovered) and emerging (to be discovered) alleles linked to the development of atherosclerosis, or its risk factors. The development of atherosclerosis is not a monogenetic condition (i.e. unlike cystic fibrosis), but is likely the result of polygenic genetic variants and unique environmental interactions. Therefore the development of atherosclerosis and eventually cardiovascular disease is the result of multiple genes and environmental factor interactions. In addition, the identification of deleterious genetic alleles may only indicate a predisposition to atherosclerosis given that other non-genetic factors also influence its development. Furthermore, the genetic data collected in the PVD Trial will be used to derive population estimates of allele prevalence, and will not identify individual variants.

Given the potential sensitivities of human genetic material analysis, and the historical misuse of genetic material by certain investigators, a number of ethical issues need to be addressed to consenting participants in epidemiologic studies in which DNA is analyzed.

1. The most important aspect in engaging in such research is that the genetic researcher and scientific investigators must seek free and informed consent from all individuals who contribute their DNA material for this scientific endeavor. A comprehensive Consent form including all of these issues will be created for each participant along with a patient information sheet.
2. All laboratory data collected from the epidemiologic component will be anonymized such that individual identifiers will be stripped from the database, preventing the determination of a unique individual's genetic results. Anonymization ensures the confidentiality and protection of privacy of all participants in the epidemiologic component.
3. All blood samples (after transport) will be stored at the study's Core laboratory located at the Project Office at the Hamilton General Hospital in Hamilton, Ontario, Canada in liquid nitrogen. While the study is ongoing, and during data cleaning, the blood samples will be linked by an identification number to the case record forms in the main database (i.e. an individual's initials, and DOB). **However no analysis of genetic material will occur before the clinical trial has been completed and the database has been declared clean.** Once the database is declared clean, a copy of the database will be made and merged with the genetic specimens. All unique identifying numbers (i.e. patient initials) will be deleted from this database. This database will be supervised by the Principle Investigators of the study and will be kept in a separate physical location from the main database in our genetic research laboratory to avoid any link between this database and the clinical centres. Therefore the privacy of individual participants in this study is maintained
4. Because the database will be anonymized there is no direct implications to the families and

biological relatives of participants in the study. As well, the issues around confidentiality of results, loss of benefits, and other harms such as an employers or insurers using this data have been obviated. No data collected by the Project Office will ever be used for any gene alteration therapy, or commercial purposes.

5. All laboratory samples will be stored for 25 years.
6. Subjects may choose to withdraw from the clinical trial or the blood collection component if this request is made before the database has been declared clean, i.e., while the study is ongoing. With this formal request, the laboratory samples of the subject will be destroyed. However, given that the data will be anonymized at the completion of the study, requests to withdraw individual samples after 4 years will not be possible.
7. The access to the laboratory data including the genetic material will be limited to the Principle Investigators at the Project Office.

The above statements present the essential features of reasonable disclosure in the contents of DNA banking in the setting of epidemiologic studies. These major categories of content reflect the types of questions that all investigators participating in the study can and should anticipate from subjects participating in the epidemiologic component. Full disclosure of these details allows informed participation in research.

2. Patient Information Sheet- Storage of Genetic Material

Commonly asked questions by subjects participating in studies in which genetic material is collected.

Q: Will information about my DNA get into the wrong hands?

A: Your DNA will be stored and shipped to the central laboratory located at the Hamilton General Hospital, McMaster University in Hamilton, Ontario, Canada. Here it will be stored in liquid nitrogen for a minimum of 4 years (while the study is being completed) and a maximum of 25 years before it will be analyzed. This facility is secure, and it is restricted to laboratory personnel only. Prior to the analysis of the DNA all individual identifiers will be stripped from the main database. Following this the DNA will be transferred to our genetic research laboratory at a separate physical location. Therefore we will not be able to link your personal DNA results to you. Rather all DNA analysis will be performed on a group basis (i.e., by province or by ethnic group). Therefore, because the data is anonymized, your results will not be available to you, your physicians, your family members, or any other individual.

Q: Can I withdraw my personal involvement (my banked sample) from this research project at any time?

A: After participation in the study and up until the time the database is anonymized (at the completion of the study) you may request that your personal DNA samples be destroyed if you would like to withdraw from the study. This request can be made to your local centre who will then request that your samples be withdrawn from the study from the central laboratory. After the time of anonymization, no linking between individual samples and yourself can be made, therefore this process will not be possible.

Q: How long do you plan to keep my DNA?

A: All DNA samples will be banked for 25 years. At the present time we know of a number of genes related to the causes of heart disease. However over the next few years new tests may emerge, therefore we plan to keep all samples for up to 25 years.

Q: If you find out something important about me from my DNA will you tell me?

A: No DNA analysis will be performed prior to the anonymization of the database. Therefore, individual results will not be available to any participants in the study. The objective of this study is to determine group differences of genetic abnormalities and not individual variations.

Q: Will other people in the future have access to my DNA sample?

A: All DNA samples will be kept under close supervision at the core laboratory in Hamilton. For the next 4 years no analysis of the DNA will be performed. After the database has been made anonymous, the Principle Investigators of the study will be allowed to analyze the DNA samples, however no link between yourself and the DNA will be possible at this time

Q: Will other scientists do other experiments with my DNA for other purposes?

A: The only researchers who will have access to the banked samples of DNA will be the Principle Investigators of the study. The DNA samples will not be used for any other purposes such as commercial use, or gene alteration.

APPENDIX H: PATIENT INFORMATION SHEET AND CONSENT FORM

This information/form can be customized to meet each study centre's needs, and should be copied onto appropriate letterhead for each



Warfarin and Antiplatelet Vascular Evaluation

LETTER OF INFORMATION FOR PATIENTS

A study of: Combined warfarin and antiplatelet therapy versus antiplatelet therapy alone in patients with peripheral vascular disease

You suffer from blocked arteries in your legs, known as **peripheral vascular disease (PVD)**.

The purpose of this letter is to give you details about a study to discover new treatments PVD in which you are invited to participate. After you read this letter carefully, you will be asked to sign a statement indicating that you understand the nature of the study, and that you voluntarily consent to participate.

Purpose of the Study

People with PVD are at increased risk of complications which include further blockages of blood vessels in the legs (leg pain), in the heart (resulting in a heart attack) and the brain (resulting in a stroke). It is routine practice to treat people with PVD with antiplatelet drugs like aspirin to reduce the risk of these complications. However, although antiplatelet therapy is proven to be an effective treatment, it prevents less than half of these complications.

The purpose of this study is to evaluate whether the addition of warfarin (a blood-thinning medication) to an antiplatelet therapy like aspirin is better than antiplatelet therapy alone (i.e. usual treatment) for the prevention of leg surgery, heart attacks, stroke and death in people PVD. 2,400 people from across Canada and Poland with PVD will be invited to participate in the study.

Conduct of the Study

Participation in this study is voluntary. Both the warfarin and the antiplatelet therapy are in tablet form that you would take once daily. All participants will receive warfarin and antiplatelet

therapy for the run-in or start-up phase of the first 2 to 4 weeks of the study. During this period, participants will require monitoring of the blood levels of warfarin until the desired blood level of warfarin is achieved. This will involve a minimum of three finger-prick blood tests (requiring a drop of blood from your fingertip).

After the run-in phase, if you choose to continue to participate in this study, one blood sample will be drawn, consisting of three tubes for a total volume of 20 mL (less than 2 tablespoons of blood). This sample will be used to measure blood counts, cholesterol, clotting factors, and, genetic markers related to PVD, and other cardiovascular risk factors. Your only discomfort would be related to the needle prick for drawing the blood, and the most common adverse effect is bruising around the vein from where the blood sample is drawn. (For blood collection version only.)

When you start the study, you will be assigned (on a random basis using a method that is similar to tossing a coin) to receive warfarin plus antiplatelet therapy or antiplatelet therapy alone, for a period of 2 1/2 years. Both you and your doctor will know

exactly which medication you will be taking. Physical measurements such as blood pressure, height and weight will also be taken. You can choose to withdraw from the study at anytime. If you do not agree to participate, you will receive standard medical care as directed by your physician.

Study participants who use warfarin and antiplatelet therapy will continue to require regular (once per month) monitoring of the blood levels of warfarin. You can have these tests done at the WAVE clinic or at a laboratory close to your home so you do not have to come into hospital for all of them. A physician and nurse will review your blood results and advise if changes in the dose are required. Persons who are allocated to receive antiplatelet therapy alone will not require any extra blood tests.

You will be required to attend a follow-up visit at the hospital after one month, and then will follow-up at the hospital or receive a phone call every 3 months until the end of the study.

Treatment Benefit

The benefits of being involved in this study are that in addition to receiving close medical supervision throughout the study, you will greatly help us to answer important medical questions on the prevention of serious for people with PVD. Many other people, including you, may benefit in the future from this study.

Risks Associated with this Study

Warfarin has been widely used in medicine over the past 30 years and its effects and side effects are very well known. The major potential side-effect of warfarin is bleeding due to an excessive level of warfarin in the blood. In order to prevent this you will need to have regular blood tests with adjustments in the dose of warfarin if the level in the blood is too high or too low. **If bleeding does occur, you will receive prompt medical attention to determine if you require treatment. If you are**

unable to reach your local study team, 24-hour help is available by calling the co-ordination centre in Hamilton at 1-800-xxx-xxxx.

Your Health is our Primary Concern

We will be monitoring the study very closely. If there are any unexpected findings before the study is scheduled to finish (for example if people receiving warfarin are clearly better off or clearly worse off), we will inform you of these results, and recommend changes to your treatment if necessary.

Confidentiality

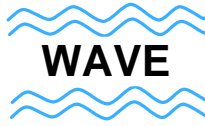
All information collected from you for this study will be kept strictly confidential. You will be able to withdraw from the study at any time and for any reason without affecting the quality of your medical care and with no penalty or loss of benefit. Only your physician, his/her research staff, the study co-ordinating centre (Canadian Cardiovascular Collaboration Project Office, Hamilton, Canada) will have access to your study records. You will be identified on study records by a number and/or your initials. **At no time will you or your individual results be identified in any published medical report.**

Researchers and Sponsors

Funding for this study is provided by the Medical Research Council of Canada, and the Heart and Stroke Foundation of Ontario

THIS INFORMATION TO BE CUSTOMIZED FOR EACH STUDY CENTRE

You may telephone the study co-ordinator, (Patty Montague at Hamilton General Hospital at 905-527-4322 ext. 44547) if you have any problems or questions regarding your participation in the study. Alternatively you may contact the local investigator (Dr. Sonia Anand at 527 4322 ext. 44557) if you have any general questions regarding the study.



Warfarin and Antiplatelet Vascular Evaluation

CONSENT FORM FOR PATIENTS

Combined warfarin and antiplatelet therapy versus antiplatelet therapy alone in patients with peripheral vascular disease

I agree to participate in the WAVE study, evaluating combined warfarin and antiplatelet therapy versus antiplatelet therapy alone in patients with peripheral vascular disease.

I have read the Letter of Information for Patients and I understand the purpose and conduct of the study.

I voluntarily consent to participate in this study and I understand that I can withdraw from it at any time and for any reason. I will not be required to pay anything for the study drugs, nor for any visits or tests done. I will not be denied any treatment that my doctor believes that I require.

I acknowledge that the results of this study may or may not be of direct benefit to my medical management.

I understand that there are some possible side effects or risks related to this study. These are detailed in the Patient Information Brochure, which I have read.

I understand that my blood sample may be stored for up to 25 years at Project Office in Hamilton, Ontario, and that it will be used for medical testing only, and will not be used for gene alteration therapy, or commercial purposes. (For blood collection version only.)

I understand that the information gained from this study will be used for medical statistical purposes only, and while it may be published, I will not be identified and my personal results will remain confidential.

I understand that I will be invited to provide my health insurance number and social insurance number, for future statistical follow-up. I may refuse to provide this information, and it will not prevent me from participating in the study

By signing this form I acknowledge that I have read and understand all the information pertaining to this study. I also acknowledge that I have received a copy of this consent for my own files.

Patient's Signature

Patient's name (block letters)

Date

Witness' Signature

Witness' Name (block letters)

Date

Appendix I: Protocol Amendments

WAVE Protocol Amendment – October 28, 2000

RE: PROJECT NO. 00-57

The following are amendments made to the WAVE protocol as per the decisions made at the October 28, 2000 WAVE Investigator's Meeting:

1. Patients with vascular disease and evidence of asymptomatic PAD (i.e. an $ABI < 0.90$) will be eligible for entry into WAVE. It is anticipated that approximately 800, of the planned 2,400 sample, will be recruited from this source.
2. Patients who are on Cox-II inhibitors will be eligible for entry into WAVE. Only patients who are on non-selective Cox inhibitors, on a regular basis, will be excluded.
3. The overall event rate of the trial will be monitored at the point when the first patient has reached 1 year follow-up. If the event rate is found to be lower than anticipated, the Steering Committee would like to increase the length of follow-up of all WAVE patients from 2.5 years to 3 years. This decision will be made in conjunction with the Data Safety and Monitoring Board (DSMB).