JUSSI MIKKELSSON

Glycoprotein IIIa $PL^{A1/A2}$ Polymorphism as a Risk Factor for Coronary Thrombosis and Sudden Cardiac Death

University of Tampere
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ACADEMIC DISSERTATION

To be presented, with the permission of
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Medical School of the University of Tampere,
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University of Tampere
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To Kaisu

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II Mikkelsson J, Perola M, Kauppila LI, Laippala P, Savolainen V, Pajarinen J, Penttilä A, Karhunen PJ. GP IIIa Pl^A polymorphism in the progression of abdominal aortic atherosclerosis. Atherosclerosis 1999;147:55-60.

III Mikkelsson J, Perola M, Laippala P, Penttilä A, Karhunen PJ. Glycoprotein IIIa $Pl^{A1/A2}$ polymorphism and sudden cardiac death. J Am Coll Cardiol 2000; 36:1317-23.

IV Mikkelsson J, Perola M, Penttilä A, Goldschmidt-Clermont PJ, Karhunen PJ. The GPIIIa (beta3 integrin) Pl^A polymorphism in the early development of coronary atherosclerosis. Atherosclerosis; in press.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AMI	acute myocardial infarction
BMI	body mass index
BRS	baroreflex sensitivity
CAD	coronary artery disease
CI	confidence interval
EF	ejection fraction
GP	glycoprotein
HDL	high-density lipoprotein
HRV	heart rate variability
HSDS	Helsinki sudden death study
LAD	left anterior descending coronary artery
Lcx	left circumflex coronary artery
LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
MI	myocardial infarction
MTHFR	methylenetetrahydrofolate reductase
NBT	nitro blue tetrazolium
OR	odds ratio
PAI-1	plasminogen activator inhibitor-1
PHS	Physicians' health study
RCA	right coronary artery
SCD	sudden cardiac death
SD	standard deviation
TF	tissue factor
T-PA	tissue-plasminogen activator
UAP	unstable angina pectoris
VF	ventricular fibrillation
VSMC	vascular smooth muscle cell
VT	ventricular tachycardia

INTRODUCTION

Of mortality in the western world, from 30 to 40 % is due to complications of atherosclerosis, namely coronary artery disease (CAD), stroke and gangrene of the peripheries, with CAD being by far the most common of these conditions (Hoyert *et al.* 1999). Sudden cardiac death (SCD) is today the most common manifestation of CAD in early middle age and accounts for approximately 50% of the estimated annual cardiovascular deaths (Rissanen *et al.* 1975a, Kannel and Thomas 1982, Virmani *et al.* 1995, Traven *et al.* 1996, Mehta *et al.* 1997, Sexton *et al.* 1997, Zipes and Wellens 1998). Although individuals with diagnosed CAD, and especially those with congestive heart failure (CHF), are at an especially high risk for SCD, almost half of SCD events occur in individuals without a history of cardiac disease (Figure 1) (Epstein *et al.* 1989, Sexton *et al.* 1997, Zipes and Wellens 1998, Airaksinen 1999).

One of the main problems in SCD is that knowledge on predisposing factors is scanty. At present, there are very few parameters that would give a clue of the future risk of SCD in an asymptomatic individual. The previously asymptomatic individuals who suffer SCD are the key to the problem in the prevention of events. Risk stratification and preventive methods are available for patients with diagnosed CAD and especially those with CHF who are known to be at a high risk of dying suddenly. E.g. beta-blockers should be administered to every patient with diagnosed CAD (Hjemdahl *et al.* 1996, Freemantle *et al.* 1999, Hjalmarson 1999), and especially to patients with CHF (Teerlink and Massie 1999), and implantable cardiofibrillatory device to patients with aborted sudden death (resuscitated patients) not related to ischemia or myocardial infarction (MI) and those showing sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) in electrophysiologic testing (Buxton *et al.* 1999, Cappato 1999). However, in half of the SCD victims preventive measures could not have been taken, as these asymptomatic individuals remain unrecognized by the medical community. The majority of these individuals would not have had a positive exercise test had they been tested antemortem. Because all individuals with traditional risk factors of CAD and MI cannot be targeted with effective primary prevention (beta-blockers, amidarone or cardiofibrillatory devices) and almost none of these risk factors can be used to identify individuals who are at an especially increased risk of SCD, markers of SCD risk are needed, for both asymptomatic and symptomatic individuals (Epstein *et al.* 1989, Myerburg *et al.* 1997).

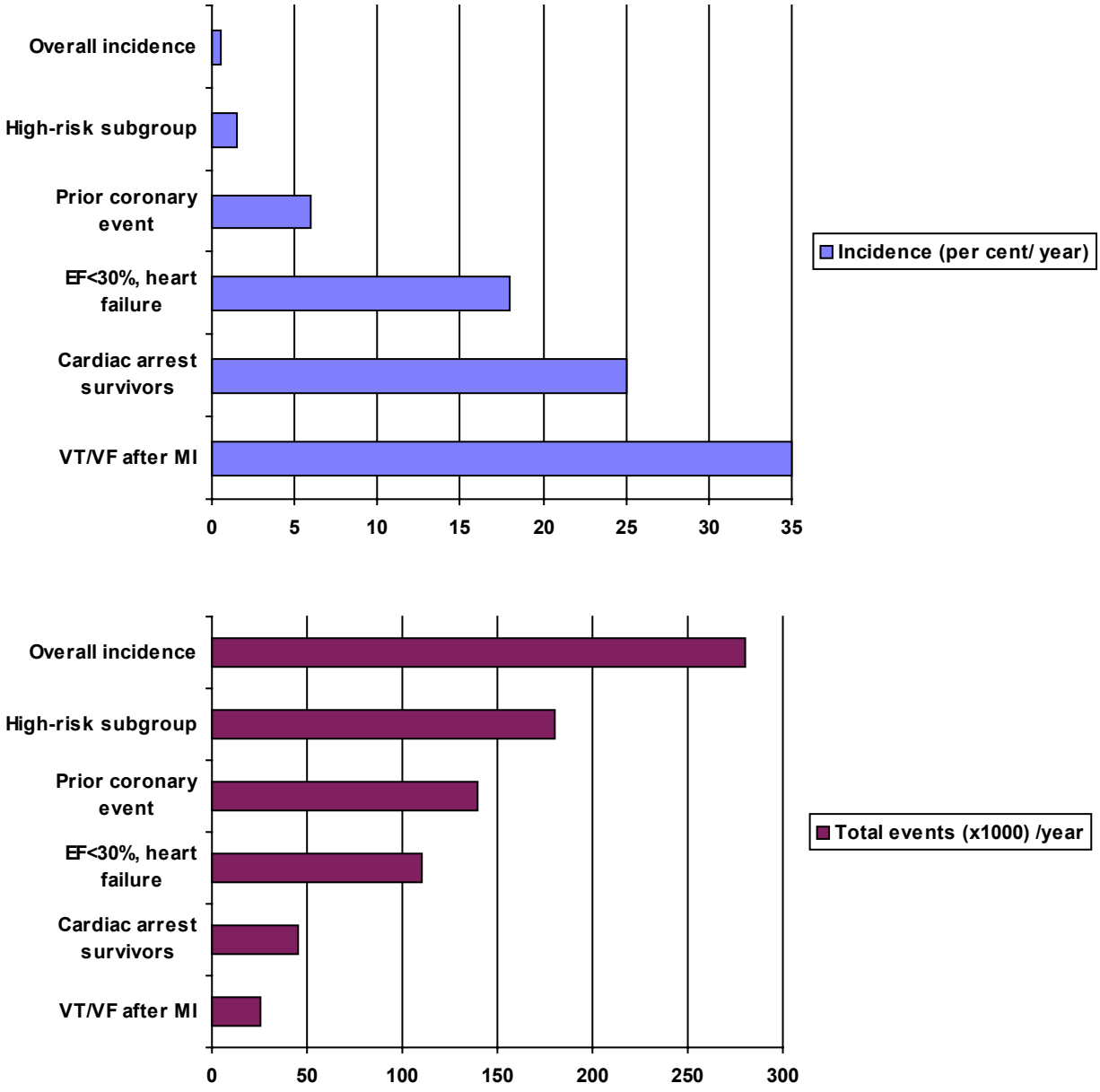
Naturally, because most SCD are caused by CAD, the risk factors of SCD are very much the same as those of CAD itself, namely hypertension, diabetes, hypercholesterolemia, low high-density lipoprotein (HDL), smoking and family history (Kannel and Thomas 1982). However, smoking and family history of SCD have been found to independently predict the risk of SCD (Sexton *et al.* 1997). Smoking can be intervened, although with limited success, but family history as a risk factor has not been well characterized yet.

First of all, the risk factor known as positive family history of premature CAD/SCD is by definition one first-degree relative with diagnosed CAD (or in the case of sudden death, SCD) *before* the age of 55 in male and 65 in female relatives. The strength of the risk increases with increasing number of affected first-degree relatives (Hunt *et al.* 1986, Colditz *et al.* 1991). All individuals with positive family history, due to Mendelian inheritance, may not be at an increased risk of SCD. It is thus important to try to characterize individual protein/gene markers associated with the increased risk of SCD.

SCD without preceeding CAD symptoms in the young (under 60) is very often (over half of the cases) due to acute coronary thrombosis. This justifies the search for markers of thrombogenicity, both acquired and inherited. However, other mechanisms of death are also involved, as the pathologic substrate in part of the SCD victims is an old infarct scar and/or extensive coronary disease. The proportion of such individuals increases with increasing age (Davies *et al.* 1989, Virmani *et al.* 1995, Mehta *et al.* 1997, Virmani *et al.* 1998). Risk factors for SCD in these individuals may be more closely associated with the electrical instability and/or regional hyperinnervation within the myocardium (Hartikainen *et al.* 1996, Zipes and Wellens 1998, Cao *et al.* 2000a and 2000b). This thesis focuses on one possible inherited thrombogenic marker of SCD.

Figure 1. Sudden death incidence and total events in various population pools. (Reproduced with permission from the article by Myerburg et al. (1992))

VT/VF after MI are those in whom such arrhythmias develop spontaneously or in electrophysiologic testing after the acute phase of MI. Cardiac arrest survivors are those who are resuscitated out-of-hospital or in the emergency room. EF<30% are individuals in whom the ejection fraction of the left ventricle is severely reduced (to <30%), this group contains several subgroups which are not presented separately. Prior coronary event consists of unstable angina pectoris or MI. High-risk subgroup are men with several risk factors for coronary disease. Overall incidence is the whole population of a community.



REVIEW OF THE LITERATURE

1.The importance of platelet aggregation and thrombus formation in acute myocardial infarction

Coronary thrombosis was suggested to be the pathognomic feature in acute myocardial infarction (AMI) already in the beginning of the 20th century. In the 1950s and 1960s experimental evidence of successful fibrinolytic treatment of myocardial infarction began to mount up. However, severe doubts on the importance of coronary thrombosis in MI patients surfaced from a couple of 1970s autopsy studies (Roberts and Buja 1972). Surprisingly, these studies changed the view of the cardiologic community on the importance of coronary thrombosis in MI (Pyorala *et al.* 1977). Thrombosis was even regarded as a secondary phenomenon to otherwise slowed down circulation (Erhardt *et al.* 1973). After important angiographic studies on MI patients during the first hours of the event (De Wood *et al.* 1980) and a large number of studies on the fibrinolytic treatment of MI (FTT Collaborative Group 1994), the role of coronary thrombosis in acute impending Q-wave myocardial infarction has become universally accepted and thrombolysis has become the therapy-of-choice in the treatment of MI patients. The most recent research on MI treatment now focuses on the combination of fibrinolytic and antithrombotic therapy (e.g. GUSTO-IV AMI), which further illustrates the central role of thrombosis in the pathogenesis of acute MI.

2.Sudden cardiac death due to coronary artery disease

SCD by clinical definition is an unexpected natural death occuring within one hour from the onset of symptoms in a person without a prior fatal condition (Zipes and Wellens 1998). World Health Organisation has defined SCD as death occuring within 24 hours of the onset of symptoms (Virmani *et al.* 1995). Slightly more than 50% of out-of-hospital cardiac deaths take place within the first hour from the beginning of symptoms (Friedman *et al.* 1973, Friedman *et al.* 1975, Rissanen *et al.* 1975a, Goldstein *et al.* 1986, Leach *et al.* 1995). SCD is the most common manifestation of CAD and it accounts for approximately 50% of the estimated annual cardiovascular deaths (Mehta *et al.* 1997, Zipes and Wellens 1998). Almost half of these events occur in subjects without a history of cardiac disease (Haghfelt 1980, Epstein *et al.* 1989, Sexton *et al.* 1997, Airaksinen 1999).

SCD and especially sudden unexpected cardiac death is by far the most common manifestation of CAD in early middle age and its relative incidence decreases with increasing age (Rissanen *et al.* 1975a, Haghfelt 1980, Kannel and Thomas 1982, Gillum 1989, Virmani *et al.* 1995, Traven *et al.* 1996, Sexton *et al.* 1997), as the underlying coronary stenoses are more severe and collaterals present in older age (Epstein *et al.* 1989). SCD in individuals over 35 years is predominantly due to CAD (Virmani *et al.* 1995). This review focuses in sudden cardiac death due to CAD.

2.1 Autopsy findings in cases of out-of-hospital cardiac death

AMI and/or fatal thrombosis is found in 20 to 50% of victims of out-of-hospital cardiac death. An old infarct scar is present in 40 to 70% of cases. Severe CAD is the only existing pathology in 10 to 15% of cases. From 20 to 30% of individuals who are resuscitated from VF develop transmural MI and another 20% show evidence of non-transmural infarctation (Liberthson *et al.* 1974, Friedman *et al.* 1975, Rissanen *et al.* 1975a, 1975b, Lie and Titus 1975, Goldstein *et al.* 1981, Davies *et al.* 1989, Roberts *et al.* 1990, Farb *et al.* 1995, Grubb *et al.* 1995, Leach *et al.* 1995, Spaulding *et al.* 1997, Zipes and Wellens 1998).

The findings at autopsy are related to the time from the beginning of the symptoms of the terminal episode to the actual death as well as to the mechanism of death:

Those who die instantly or within 15 to 20 minutes from the beginning of symptoms (often nausea, dyspnea or only syncope) often present with an old infarct scar and/or extensive coronary disease in the absence of an acute lesion at the autopsy although an organising thrombus may be present (Friedman *et al.* 1973, Baba *et al.* 1975, Kuller *et al.* 1975, Goldstein *et al.* 1986, Davies 1992, Leach *et al. 1995*). The mechanism of death is most likely either a re-entrant VT which turns into VF (85%) or asystole/bradycardia due to sinus depression (15%) (Bayes de Luna *et al.* 1989, Kragel *et al.* 1991, Stevenson 1995, Mehta *et al.* 1997, Zipes and Wellens 1998).

Those who die in the matter of hours after the beginning of symptoms (very often chest pain or indigestion) often have an acute lesion and thrombosis (Friedman *et al.* 1973, Davies 1992). Individuals surviving longer than 3.5 hours from the beginning of symptoms almost always have an acute lesion at the autopsy. Thrombosis is, however, also found in many individuals who die in the matter of minutes, but the frequency of thrombosis at autopsy increases with increasing duration of symptoms (Leach *et al.* 1995). The mechanism of death usually is VF, which has been suggested to be mediated by ischemia as well as platelet microemboli to the intramyocardial vessels (Haerem *et al.* 1972, Davies *et al.* 1986, Hammon and Oates 1986, Bayes de Luna *et al.* 1989, Davies 1992, Fuster *et al.* 1992b, Mehta *et al.* 1997, Erbel and Heusch 1999, Rentrop 2000).

There are naturally also many individuals who have had a previous MI and have presented with a new acute lesion. These individuals are susceptible to sudden death via both of the-above mechanisms.

Individuals with only an acute lesion at the autopsy often have less severe coronary disease and are on average younger compared to those without an acute lesion (Davies *et al.* 1989, Burke *et al.* 1997, Virmani *et al.* 1998, Farb *et al.* 1999). In early middle age, out-of-hospital cardiac death is very often associated with acute MI and/or coronary thrombosis, whereas the incidence of thrombosis decreases and the prevalence of extensive coronary disease increases with increasing age in victims of out-of-hospital cardiac death (Leach *et al.* 1995, Virmani *et al.* 1995, Mehta *et al.* 1997).

The above differences in the basic pathology of cardiac death explain differences in the frequency of acute thrombi and MIs between studies of sudden out-of-hospital deaths, as some of the studies have clearly used the one-hour definition of sudden cardiac death and have thus excluded many cases with acute lesions, whereas other studies have included all sudden out-of-hospital deaths.

2.2 Risk factors of sudden cardiac death

The risk factors of sudden cardiac death in middle age are essentially the same as those of its substrate, atherosclerosis and CAD, namely elevated total cholesterol, decreased high-density lipoprotein (HDL), male sex, cigarette smoking, elevated blood pressure and diabetes (Kannel and Thomas 1982, Solberg and Strong 1983, Castelli 1996, Balkau *et al.* 1999, Jousilahti *et al.* 1999). Only few factors have been found to particularly increase the risk of dying suddenly from CAD.The strongest is cigarette smoking (Friedman *et al.* 1975, Wilhelmsen 1988, Cupples *et al.* 1992, Wannamethee *et al.* 1995, Escobedo and Zack 1996, Escobedo and Caspersen 1997, Sexton *et al.* 1997).

Cigarette smoking predisposes to plaque ruptures/erosions (Farb *et al.* 1996, Burke *et al.* 1997, Farb *et al.* 1999) and it elevates the plasma fibrinogen levels (Kannel *et al.* 1987a). Cigarette smoking is the most prominent risk factor in young patients with transmural MI (Glover *et al.* 1982, Hoit *et al.* 1986, Barbash *et al.* 1995, Parish *et al.* 1995, Ciruzzi *et al.* 1997, Moccetti *et al.* 1997, Choudhury and Marsh 1999) as well as young victims of SCD (Friedman *et al.* 1975, Wannamethee *et al.* 1995, Escobedo and Zack 1996, Escobedo and Caspersen 1997, Sexton *et al.* 1997), especially those without previous CAD diagnosis (McKenna *et al.* 1980, Escobedo and Zack 1996, Escobedo and Caspersen 1997). The magnitude of risk strongly correlates with the daily amount of smoked cigarettes.

Hypertension is often associated with the development of extensive coronary disease, decreased heart rate variability (HRV) and SCD in the absence of an acute lesion (Farrell *et al.* 1991, Schwartz *et al.* 1992, Huikuri 1995, Huikuri *et al.* 1996 , Burke *et al.* 1996, Mehta *et al.* 1997, Virmani *et al.* 1998). Elevated *cholesterol*, elevated cholesterol/HDL ratio and decreased HDL levels are associated with an increased risk of plaque ruptures and SCD with an acute lesion (Friedman *et al.* 1975, Virmani *et al.* 1998, Burke *et al.* 1999a, Farb *et al.* 1999).

Patients with *small ejection fraction (EF), left ventricular hypertrophy (LVH), ventricular arrhythmias and conduction defects* are also at an increased risk of SCD in the absence of an acute lesion (Schatzkin *et al.* 1984, Farrell *et al.* 1991, Cupples *et al.* 1992, Zipes and Wellens 1998).

Heavy alcohol consumption and binge drinking are associated with an increased incidence of SCD, with the underlying pathology being CAD in the great majority of cases (Wannamethee and Shaper 1992, Kauhanen *et al.* 1997, Chenet *et al.* 1998). The mechanism is in part related to feedback-aggregability of platelets (Renaud and Ruf 1996) but also to a hyperadrenergic state during alcohol withdrawal (Kupari and Koskinen 1998). This is likely to be a contributing factor to the weekly variation of SCD with increased incidence on Saturdays, Sundays and especially Mondays (Chenet *et al.* 1998, Evans *et al.* 2000). Moderate consumption has, however, been found to be protective against SCD due to CAD (Albert *et al.* 1999, de Vreede-Swagemakers *et al.* 1999).

Psychological factors are also important for the Monday peak of SCD (Chenet *et al.* 1998, Evans *et al.* 2000), as mechanisms related to stress from work and early wake-up are likely to contribute as triggers. Recent drastic life changes leading to sadness, frustration and anger have also been found to predispose to SCD (Rahe *et al.* 1974, Lown 1987) through effects of catecholamines on HRV, blood pressure and hemostasis (Krantz *et al.* 2000).

Family history has been found to be a strong independent predictor of MI at early middle-age (Rissanen 1979, Glover *et al.* 1982, Hoit *et al.* 1986, Barbash *et al.* 1995, Jousilahti *et al.* 1996, Ciruzzi *et al.* 1997, Moccetti *et al.* 1997, Balkau *et al.* 1999, Choudhury *et al.* 1999, Hippe *et al.* 1999). The magnitude of the risk associated with positive family history of MI at early middle-age increases steeply with increasing number of affected first-degree relatives (Hunt *et al.* 1986, Colditz *et al.* 1991) Family history of primary cardiac arrest and/or SCD has also been found to be a risk factor for SCD (Barrett-Connor and Khaw 1984, , Sexton *et al.* 1997, Friedlander *et al.* 1998, Jouven *et al.* 1999, Balkau *et al.* 1999) and important in predicting mortality from CAD (Marenberg *et al.* 1994). Exact genetic factors that have been studied are returned to later in this review.

3. Coronary thrombosis in myocardial infarction

Acute occlusive thrombosis is found in 80 to 95% of cases of transmural MI at the autopsy and by angiography of clinical patients whereas occlusive thrombosis is found in 20 to 25% of cases of non-transmural MI. Hemodynamically significant collaterals have prevented the full thickness of the myocardium from becoming ischemic in non-transmural MI with total occlusion. Compared to the fibrin-rich thrombus of transmural MI, a platelet-rich mural thrombus is found in almost half of the cases of non-transmural MI in clinical patients. In clinical patients with unstable angina pectoris (UAP), the evolvement into MI is often associated with the development of an enlarging platelet-aggregate at the apex of the culprit lesion. (Schwartz and Gerrity 1975, Davies *et al.* 1976, De Wood *et al.* 1980, Hansen 1982, Schaper 1982, De Wood *et al.* 1983, Freifeld *et al.* 1983, Ambrose *et al.* 1988, Andersen *et al.* 1989, Epstein *et al.* 1989, Kragel *et al.* 1991, Fuster *et al.* 1992b, Mizuno *et al.* 1992, Wilensky *et al.* 1993, Keen *et al.* 1994, Hussain *et al.* 1995, Mann *et al.* 1998, Nesto *et al.* 1998, Tousoulis *et al.* 1998, Abela *et al.* 1999, Arbustini *et al.* 1999a, Fuster 1999a, 1999b, Rentrop 2000)

Men with Q-wave MI are usually younger than men with UAP who eventually develop non-Q-wave MIs (Murphy and Connell 1992, Roy and Mukherjee 1993). They also more often have only one severely diseased vessel and no previous CAD diagnosis as opposed to men with non-Q-wave MI who usually have at least a two-vessel disease and previous symptomatic angina pectoris (Murphy and Connell 1992). In Q-wave MI there is almost always (85-90%) an acutely occluded vessel with a fibrin-rich coronary thrombus in it and the full thickness of the myocardium is infarcted because of the lack of collateral vessels (De Wood *et al.* 1980, Hansen 1982, Kragel *et al.* 1991, Dacanay *et al.* 1994). In men with non-Q-wave MI, a totally occluded vessel is identified in only 25% of cases and the thrombotic material in the culprit lesion (present in up to 50% of cases) is mainly composed of platelets (white thrombus) (Freifeld *et al.* 1983, Mizuno *et al.* 1992, Keen *et al.* 1994, Hussain *et al.* 1995).

The underlying pathology in acute thrombosis is a rupture of a lipid-rich plaque in 60 to 80% of cases and erosion of a fibrous lesion in the rest of the cases (Leach *et al.* 1995, Farb *et al.* 1996, Arbustini *et al.* 1999b, Falk 1999). Patients with plaque erosion are on average younger than those with plaque ruptures (Farb *et al.* 1996, Burke *et al.* 1997). A plaque rupture is more likely to occur during strenuous physical activity or mental stress whereas the erosion of a proteoglycan-rich lesion usually takes place at rest (Burke *et al.* 1997, 1999a). A rupture of the fibrous cap of a plaque with a lipid-rich core usually takes place at the shoulder region of the plaque and is due to hemodynamic shear-stress, mechanical pressure or inflammatory components, the most vulnerable plaques being those with the thinnest fibrous caps and the largest fatty core (Fuster *et al.* 1992a, 1992b, Liao 1998).

3.1 Thrombosis in acute myocardial infarction at autopsy and in clinical studies--explanations for a controversy

The opinion of the cardiologic community has in recent years been increasingly supportive of the role of thrombosis as the key event in the development of MI (Fuster 1999a, 1999b). However, in numerous cases of SCD with AMI, thrombosis is not found. The most likely explanations are the fact that in cases of transmural AMI, even at autopsy, a macroscopic fibrin-rich thrombus is present, whereas in non-transmural/subendocardial AMI macroscopic thrombi are usually (80-90%) absent at autopsy (current study series, see Table 1), but platelet material as well as fibrin can be found in the culprit lesion in several cases, if detailed microscopy or staining are carried out. This corresponds to the presence of platelet-rich thrombi in clinical studies of non-Q-wave MI patients. In addition, micro-emboli in the intramyocardial vessels may contribute to the development of subendocardial AMI. The thrombotic involvement in cases with subendocardial AMI is often missed at autopsy as microscopic analysis and stainings of culprit lesions without macroscopic thrombi as well as studies on intramyocardial vessels are not a part of a routine autopsy. (Schwartz and Gerrity 1975, Stehbens 1985, Davies *et al.* 1986, 1989, Farb *et al.* 1995, Virmani *et al.* 1995, Farb *et al.* 1996, Erbel *et al.* 1999)

TABLE 1. Distribution of coronary thrombosis in men with transmural or non-transmural AMI in the current study series.

AMI TYPE	THROMBUS PRESENT	THROMBUS ABSENT
TRANSMURAL	34 (89.5%)	4 (10.5%)
NON-TRANSMURAL	5 (10.9%)	41 (89.1%)

3.2 Molecular biology of platelet aggregation and thrombus formation

The rupture of a plaque exposes tissue factor (TF) and other plaque components to the flowing blood. TF is a powerful activator of the coagulation cascade and results in the formation of thrombin which, in turn, is the most powerful activator of platelet glycoprotein (GP)IIb/IIIa receptors. The receptors go through a conformational change, which increases their affinity to fibrinogen. Thrombin also forms fibrin from fibrinogen. Although other GP receptors are also involved in binding to the exposed plaque components, binding of GPIIb/IIIa to fibrinogen is the final common pathway in the formation of a stable and often occlusive thrombus (Fuster *et al.* 1992a, 1992b, Cotran *et al.* 1994, Rosenfeld and Gralnick 1997, Badimon JJ *et al.* 1999).
In clinically silent cases of plaque rupture, when the systemic and local thrombotic state is sufficiently subdued, the forming thrombus may be limited in size or spontaneously lysed enough to prevent myocardial injury (Ong *et al.* 1983, Pichard *et al.* 1983, Falk 1999, Fuster 1999b, Weissberg 1999, Rentrop 2000).

A superficial erosion of a plaque often exposes collagen, which is the ligand of GPIa/IIa and GPIb-V-IX complex. GPIa/IIa is a collagen receptor in itself and GPIb-V-IX binds to collagen via von Willebrand factor. These GPs contribute to the mural platelet-rich thrombus in most cases of UAP and non-Q-wave MI. Also the high shear-stress of severely stenotic lesions makes platelets adhere to culprit lesions via GPIb complex and GPIa/IIa. This is the most usual mechanism of slow progression of severe CAD (Fuster *et al.* 1992a, 1992b, Cotran *et al.* 1994, Mailhac *et al.* 1994, Savage *et al.* 1996, Rosenfeld and Gralnick 1997, Ruggeri *et al.* 1999, Santoro 1999). This adhesion of platelets also causes vascular smooth muscle cell (VSMC) proliferation and subsequent fibrous tissue generation, which contributes to the organisation of the platelet-rich thrombus (Fuster *et al.* 1992a, 1992b ,Ross 1999).

The thrombotic state following rupture of a plaque is endogenously regulated by the balance/imbalance between tissue plasminogen activator (T-PA) and plasminogen activator inhibitor-1 (PAI-1). Other possible determinants of the size and stability of the thrombus involve other proteins of the coagulation cascade such as thrombin, thrombomodulin, fibrinogen or factor VII as well as systemic epinephrine levels.(Kannel *et al.* 1987b, Ridker *et al.* 1993, Cotran *et al.* 1994, Iacoviello *et al.* 1996, Wiman 1996, Scarabin *et al.* 1998, Van der Bom *et al.* 1998, Falk 1999, Redondo *et al.* 1999)

Platelets also contribute to the progression of elevated/complicated coronary lesions by adhering to damaged endothelium after minor ruptures and fissures to the coronary plaque. By re-organisation and fibrous tissue generation, promoted e.g. by platelet-derived growth factors, the coronary lesion grows more stenotic. Evidence of this has been found in studies showing layers of platelet materia of different ages in culprit coronary lesions (Fuster *et al.* 1992a and 1992b). Intimal hyperplasia also results from insults against the endothelium. Smooth muscle hyperplastic responses and fibrous tissue generation are mediated by several receptors in the endothelium and vSMC, such as the GPIIIa as part of the vitronectin receptor. The expression of GPIIIa is increased after injuries to the endothelium and is significantly elevated in atherosclerotic versus non-diseased arteries (Brown *et al.* 1994, Hoshiga *et al.* 1995, Shattil 1995, Ruoslahti and Engvall 1997, Slepian *et al.* 1998, Stouffer *et al.* 1998).

4.Atherosclerosis

4.1 Definition of atherosclerotic lesions

The original definition of macroscopic atherosclerotic lesions of arteries has most often been based on the protocols of two international studies, International Atherosclerosis Project (Guzman *et al.* 1968) and World Health Organisation Study Group (Uemura *et al.* 1964):

Any flat or slightly elevated intimal lesion stained distinctly by Sudan IV and not showing any other types of changes underlying it is classified as a fatty streak. A raised lesion that does not exhibit ulceration, hemorrhage, necrosis or thrombosis is regarded as fibrous plaque. The area with one or several of the aforementioned is regarded as a complicated lesion. The X-ray positive area of the artery wall is regarded as the area of calcification regardless of the other changes. Correspondence of this classification to the recently adapted Stary classification is presented in Table 2.

TABLE 2. Comparison of the Stary classification (Stary et al. 1994, 1995) with the classifications used in the present study series.

Stary classification	Guzman *et al. (1968)*, Uemura *et al. (1964),* Current study
Early lesions	
Type I	Not macroscopically analysable
Type II	Fatty streak, fatty area, area of fat change
Intermediate lesions	
Type III	Fatty plaque, fatty lesion, essentially the same as type II lesion
Advanced lesion	
Type IV	Fibrous lesion/plaque, raised/elevated lesion/plaque
Type V	Fibrous lesion/plaque, raised/elevated lesion/plaque
Type VI	Complicated lesion, plaque rupture/erosion, thrombosis, hematoma

5. Epidemiology of prothrombotic gene polymorphisms in myocardial infarction

Studies on the genetic predisposers to acute coronary events have thus far been performed on case series of event survivors and in most studies the genotyping has been done in a retrospective manner even years after the event. Thus possible genetic differences in survival are very likely to confound the analyses if the studied polymorphism increases the risk for MI and its complications, such as SCD. The role of genetics of *non-lipid* prothrombotic factors in the development of acute coronary events and in cases of fatal MI/SCD has been studied in only a limited amount of studies. Genotype frequencies of all the polymorphisms (in the Finnish population for those reportedly studied among Finns) are presented in Table 3.

5.1 Platelet glycoprotein polymorphisms

The HPA-1/Pl$^{A1/A2}$ polymorphism of platelet glycoprotein GPIIIa. GPIIb/IIIa is the fibrinogen receptor protein in platelets responsible for platelet aggregation, and GPIIIa is also expressed in the endothelium as part of vitronectin rececptors responsible for intimal hyperplasia. Approximate frequencies of genotypes in the Finnish population are 73.5% for A1/A1, 25.5% for A2/A1 and 1.0% for A2/A2 (Kekomaki *et al.* 1995). Platelets from individuals possessing the A2 allele have been shown to bind more fibrinogen and be more aggregable (Lasne *et al.* 1997, Zotz *et al.* 1997, Feng *et al.* 1999, Goodall *et al.* 1999, Roos *et al.* 1999) compared to A1 homozygotes, even though these associations have been questioned (Meiklejohn *et al.* 1999). The A2 allele was first reported to be associated with MI in men under 60 (Weiss *et al.* 1996) with Q-wave MI (Goldschmidt and Bray 1996). Subsequent studies have found the A2 allele to be associated with MI (especially Q-wave) in early middle-age (Carter *et al.* 1996b, 1997, Zotz *et al.* 1998, Araujo *et al.* 1999, Ardissino *et al.* 1999, Tereshchenko *et al.* 1999) and especially among smokers (Zotz *et al.* 1998, Ardissino *et al.* 1999). Zotz *et al.* (1998) also found the A2 allele to be overrepresented among MI patients when evaluated in the acute phase, but this association levelled off when those who had survived for one year after the MI were evaluated. This suggests that the A2 allele may affect survival after MI and possibly explains the lack of an association in several studies that have used MI survivors with sample collection months to years after the culprit event, as their case patients (Herrmann *et al.* 1997, Durante-Mangoni *et al.* 1998, Gardemann *et al.* 1998, Joven *et al.* 1998, Kekomaki *et al.* 1999, Bottiger *et al.* 2000). Anderson *et al.* (1999b) found a modest role for the A2 allele in increasing the risk of MI as they included both recent MIs and survivors to their case group.

The lack of results in the report of the Pl^A polymorphism in the large prospective Physicians' Health Study (PHS) (Ridker *et al.* 1997c) has been previously critisized thoroughly (Bray 1999) and will be returned to in Discussion. In the most recent study, Aleksic *et al.* (2000) failed to find an association between the Pl^{A2} allele and incident CAD in a prospective nested case-control study. Sufficient stratification of cases according to the coronary event/MI phenotype was not achieved in the study, as 15% of individuals in the subgroup of acute events in their study were individuals with fatal CAD without AMI/thrombosis (Folsom *et al.* 1997). In addition, individuals who had suffered their first CAD event at a young age were excluded from the initial study cohort. The study did, however, provide firm evidence that the Pl^{A2} allele may not be considered as a general risk factor of all incident manifestations of CAD.

Burke *et al.* (1999) have also reported preliminary results on the association of the A2 allele with SCD. They found that the A2 allele was especially frequent in victims of SCD above 45 years of age and especially in those with plaque erosions as the cause of SCD.

Several studies on the association of the Pl^A polymorphism with CAD have failed to show positive results (Batalla *et al.* 1998, Durante-Mangoni *et al.* 1998, Garc *et al.* 1998, Mamotte *et al.* 1998, Sperr *et al.* 1998, Anderson *et al.* 1999b, Wu and Aleksic 1999, Bottiger *et al.* 2000, Aleksic *et al.* 2000). Garcia-Ribes *et al.* (1998) found that individuals who were subjected to catheter interventions because of vessel occlusions were more often carriers of the A2 allele. Gardemann *et al.* (1998) found carriers of the A2 allele to have higher CAD scores in a restricted low-risk subgroup, and Carter *et al.* (1997) found that, when compared to controls, men with multiple-vessel stenosis, but not those with one or two diseased vessels, were slightly more often carriers of the A2 allele.

Two studies on the association of the Pl^A polymorphism in patients with restenosis after angioplasty reported conflicting results (Abbate *et al.* 1998, Mamotte *et al.* 1998). Studies in patients with stent restenosis have shown the A2 allele to increase the risk for stent thrombosis (Walter *et al.* 1997, Kastrati *et al.* 1999, Mehilli *et al.* 1999, Kiss *et al.* 2000). One study failed to confirm this, even though the odds ratio (OR) for A2 allele to be associated with stent thrombosis was similar to that of the other studies, but only the study size kept the confidence interval wide and the OR from reaching statistical significance (Laule *et al.* 1999). Walter *et al.* (1999a and 1999b) have recently shown that the increased risk of stent thrombosis among men with the A2 allele can be attenuated with the use of vehement antithrombotic therapy combined with statin therapy.

Increased risk of stent thrombosis could also be attenuated with strong antithrombotic regime in the most recent study on stent thrombosis and the Pl^A polymorphism (Kastrati *et al.* 2000).
This regime included aspirin, ticlopidine, heparin during the procedure and in some patients GPIIb-IIIa inhibitors during and after the procedure. Recently, it was also found that after coronary bypass surgery using venous grafts, men with the A2 allele are at an increased risk of complications (bypass occlusion, myocardial infarction and death) compared to A1 homozygotes, even though all men received aspirin (Zotz *et al.* 2000). All studies on the Pl^A polymorphism are summarised in Table 4.

The HPA-2 (Thr145Met) polymorphism of platelet glycoprotein GPIbα. GPIbα-V-IX complex is responsible for platelet adhesion after fissures or disruption of coronary plaques. Approximate genotype frequencies in the Finnish population are 76-83% for AA (ThrThr), 16-22% for AB (ThrMet) and 1-2% for BB (MetMet) (Kekomaki *et al.* 1995, Kaski *et al.* 1996). The polymorphism is located in the vicinity of the thrombin binding site (Murata *et al.* 1997, Gonzalez-Conejero *et al.* 1998) and the Met allele carriers have been found to possess more active platelets under high-shear conditions (Douglas et al. 2000), even though no genotypic differences in binding to von Willebrand factor have been found (Li *et al.* 2000). The AB genotype was first reported to be associated with increased risk for premature CAD in Japanese (Murata *et al.* 1997). This association could not be confirmed in Caucasians (Sperr *et al.* 1998) and in another study on the Japanese (Ito *et al.* 1999), although the latter study did not address subjects with premature CAD. More recently the B allele was suggested to be associated with an increased risk of MI/UAP (Gonzalez-Conejero *et al.* 1998), although another recent study of young patients with Q-wave MI (Ardissino *et al.* 1999) could not find an association. This could reflect the possible role of GPIbα-V-IX complex in the formation of platelet-rich mural thrombi.

The C807T polymorphism of platelet glycoprotein GPIa. GPIa/IIa receptors mediate platelet adhesion to collagen. Approximate genotype frequencies in the Finnish population are 40% for CC, 53% for CT and 7% for TT (Mikkelsson *et al.*, unpublished data) corresponding roughly to those in other Caucasian populations, 34-39%, 52-54% and 6-13%, respectively (Moshfegh *et al.* 1998, Santoso *et al.*1999). There is a great variability in the platelet surface expression of GPIa (Kunicki *et al.* 1993, Corral *et al.* 1999), of which a major portion is explained by the C807T polymorphism with the T allele associated with the highest receptor levels (Kritzik *et al.* 1998). However, Corral *et al.* (1999) suggested that this difference has no functional consequencies. The TT genotype was first suggested to increase the risk of MI (Moshfegh *et al.* 1998), which was later confirmed by a very large study (Santoso *et al.* 1999). They found the risk of MI associated with the T allele to be especially strong in individuals under 50, but no association with CAD was found. These two studies included MI survivors, so a slight possibility of selection bias exists. More recent studies on the C807T polymorphism have failed to confirm these earlier results (Croft *et al.* 1999b, Corral *et al.* 1999) and even showed a non-significant association to the contradictory direction. However, major differences exist in allele frequencies among controls between the studies. Another possible confounder is the linkage between the C807T polymorphism and the HPA-5 polymorphism of GPIa and the association with increased risk of MI may be due to a certain haplotype (Kroll *et al.* 2000).

5.2 Polymorphisms of coagulation cascade and fibrinolytic system

Factor V Leiden GA polymorphism. The point mutation causing the Leiden phenotype results in defective lysis of factor V by activated protein C (Bertina *et al.* 1994, Dalhback 1997). Approximate frequencies of genotypes in the Finnish population are 96.5-97% for GG, 3.0-3.5% for GA and possibly about 0.1% for AA (Hakala *et al.* 1995, Kontula *et al.* 1995). The increased risk of the GA genotype for venous thromboembolism seems established (Hakala *et al.* 1995, Dahlback 1997, Margaglione *et al.* 1999, Ridker *et al.* 1999). The possible role of the GA in MI patients has been studied extensively and several studies have shown that the GA genotype is not associated with increased risk for MI (Emmerich *et al.* 1995, Kontula *et al.* 1995, Dacosta *et al.* 1998, Doggen *et al.* 1998a, Junker *et al.* 1998, Araujo *et al.* 1999, Ardissino *et al.* 1999, Feng *et al.* 1999, Gardemann *et al.* 1999a, Mangoni *et al.* 1999, Redondo *et al.* 1999, Ridker *et al.* 1999), although it has been suggested to increase the risk of MI in women under 40 with additional risk factors, such as smoking or obesity (Siscovik *et al.* 1997). Due to very low incidence of MI in this group and to the low prevalence of the A allele, it does not seem to be an important risk factor for MI on population-basis. The possibility that the very rare AA genotype could be associated with the risk of MI has not been studied due to its very low frequency in the general population.

The G20210A polymorphism of Prothrombin (Factor II). Prothrombin is the inactive form of thrombin, which when formed is a powerful mediator of thrombotic events. Approximate genotype frequencies in Finns are 99% for GG, 1% for GA and for the AA possibly under 0.1% (Hakala *et al.* 1999). The A allele has been found to be associated with elevated plasma levels of prothrombin and the GA variant has been found to be associated with increased risk of venous thromboembolism (Poort *et al.* 1996, Hakala *et al.* 1999, Margaglione *et al.* 1999, Ridker *et al.* 1999,). However, most studies have failed to find an association of the GA with MI (Eikelboom *et al.* 1998, Araujo *et al.* 1999, Ardissino *et al.* 1999, Croft *et al.* 1999a, Feng *et al.* 1999, Gardemann *et al.* 1999a, Redondo *et al.* 1999, Ridker *et al.* 1999), in these studies the frequency of the GA genotype of controls has been between 3 and 4%, whereas in studies suggesting the GA genotype might increase the risk for MI (Doggen *et al.* 1998a, Franco *et al.* 1999), the GA frequency of controls has been only 1% and the risk for MI has not been statistically significant. The A allele has been suggested to increase the risk of MI in women under 40, who are smokers or obese (Rosendaal *et al.* 1997). As in the case of Factor V Leiden, this increase in risk is not highly relevant on population-basis. It has been impossible to study the importance of the AA genotype as a risk factor for MI due to its rarity.

Plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism. PAI-1 has an important role in inhibiting the activation of plasminogen to plasmin, which is a powerful fibrinolytic protein. Approximate genotype frequencies in the Finnish population are 27-30% for 5G/5G, 50-53% for 5G/4G and 20% for 4G/4G (Pastinen *et al.* 1998). The 4G allele has been suggested to be more common in the eastern part of Finland where CAD incidence is higher compared to the rest of the country (Jousilahti *et al.* 1998, Wartiovaara *et al.* 1999). The 4G allele has been found to be associated with higher plasma levels of PAI-1 (Eriksson *et al.* 1995, Ye *et al.* 1995, Ossei-Gerning *et al.* 1997, Margaglione *et al.* 1998). The PAI-1 levels are also affected by the ACE ID polymorphism (Kim *et al.* 1997, Margaglione *et al.* 1998). High levels of PAI-1 increase the risk of CAD (Scarabin *et al.* 1998). The 4G allele was first suggested to increase the risk of MI (Eriksson *et al.* 1995). Numerous subsequent studies on MI survivors were summarized into a meta-analysis (Iacoviello *et al.* 1998a). A slight increase in the risk of MI was found in the carriers of the 4G allele and this risk seemed to be more pronounced in the presence of other conventional risk factors. The same conclusion was reached by two large subsequent studies (Anderson *et al.* 1999a, Gardemann *et al.* 1999b). The 4G allele has also been found to increase the risk for MI in the Finnish population (Pastinen *et al.* 1998, Mikkelsson *et al.* 2000) and to be associated with increased cardiovascular mortality (Heijmans *et al.* 1999).

R353Q and HVR4 polymorphisms of Factor VII. Factor VII in its active form is a part of the first step of the activation of the extrinsic coagulation cascade. Approximate genotype frequencies for R353Q are 62-69% for RR, 28-34% for RQ and 2.5-4.5% for QQ (Iacoviello *et al.* 1998b, Ardissino *et al.* 1999). Those for HVR4 are 14% for H7H7, 43% for H6H7, 42% for H6H6, 1-1.5% for H5 carriers and 0.5% for H8 carriers (de Maat *et al.* 1997, Iacoviello *et al.* 1998b). The QQ genotype of the R353Q polymorphism and the H7H7 genotype of the HVR4 polymorphism have been reported to be associated with the lowest plasma levels of factor VII (Green *et al.* 1991, Lane *et al.* 1996, de Maat *et al.* 1997, Wang *et al.* 1997, Iacoviello *et al.* 1998b, Feng *et al.* 2000). The plasma levels of factor VII have been found to correlate with the risk for MI (Salomaa *et al.* 1994, Junker *et al.* 1997, Redondo *et al.* 1999). Some groups have found the Q allele and the H7H7 genotype to be associated with decreased risk of MI (Iacoviello *et al.* 1998b, Feng *et al.* 1999, Iacoviello *et al.* 1999, Di Castelnuovo *et al.* 2000, Feng *et al.* 2000, Girelli *et al.* 2000), whereas several others could not confirm the association of the QQ genotype with MI (Lane *et al.* 1996, Grant 1997, Doggen *et al.* 1998b, Ardissino *et al.* 1999, Sanmartin *et al.* 2000). A possible confounding factor may have been differences in patient selection, as high levels of factor VII may predispose to fatal MI and influence survival (Heinrich *et al.* 1994, Ruddock and Meade 1994, Holm *et al.* 1998).

Factor XIII Val34Leu polymorphism. Factor XIII is an important factor in stabilizing fibrin in the forme thrombus. Genotype frequencies in the Finnish population are approximately 57% for ValVal, 37% for ValLeu and 6% for LeuLeu (Wartiovaara *et al.* 1999). The polymorphism has been found to somehow interact with plasma PAI-1 levels. (Kohler and Grant 1998a, Wartiovaara *et al.* 1999). The Leu allele was suggested to decrease the risk for MI (Kohler *et al.* 1998b) and this association was confirmed in subsequent studies, also in the Finnish population (Kohler *et al.* 1999, Wartiovaara *et al.* 1999, Canavy *et al.* 2000, Franco *et al.* 2000), except for one study (Corral *et al.* 2000). The frequency of the protective Leu allele was found to be lower in the eastern part of Finland where the incidence of CAD is the highest (Jousilahti *et al.* 1998, McCormack *et al.* 1998, Wartiovaara *et al.* 1999).

Alu-repeat I/D polymorphism of tissue plasminogen activator (T-PA). T-PA is vital for the activation of the fibrinolyte plasmin. Approximate genotype frequencies are 21% for DD, 50% for ID and 29% for II (Ridker *et al.* 1997b). Plasma levels of T-PA have been found to increase the risk of MI (Ridker *et al.* 1993). Basal endothelial T-PA levels have been found to be unaffected by this polymorphism (Van den Eijnden-Schrauwen *et al.* 1995), but vascular release of T-PA is highest in men with the II genotype (Ladenvall *et al.* 2000). However, the II genotype was reported to be associated with MI (Van der Bom *et al.* 1995), but this association could not be confirmed in other studies (Iacoviello *et al.* 1996, Steeds *et al.* 1998), although a trend was found in smokers under the age of 60 (Ridker *et al.*1997b).

A common Ala455Val polymorphism in the thrombomodulin gene has been studied in two reports. Thrombomodulin modulates the effects of thrombin on thrombus formation. Approximate genotype frequencies are 56 to 65% for AlaAla, 32 to 36% for AlaVal and 3 to 8% for ValVal (Ireland *et al.* 1997, Norlund *et al.* 1997). Thrombomodulin activates protein C as a co-factor to thrombin (Sadler 1997). Thrombomodulin plasma levels are inversely associated with MI (Salomaa 1999). The Ala allele was suggested to increase the risk of MI (Norlund *et al.* 1997) but this could not be confirmed in subsequent studies (Ireland *et al.* 1997, Park *et al.* 2000). Other rare (prevalence under 1%) variants of thrombomodulin have been studied in MI patients (Ireland *et al.* 1997, Doggen *et al.* 1998c, Le Flem *et al.* 1999). Even though these variants might sligthly elevate the risk of MI, their importance in the population level is likely to be small.

Numerous different fibrinogen polymorphisms have been studied, the most relevant being BclI and HaeIII. High levels of fibrinogen are associated with an increased risk of CAD and future coronary events (Kannel *et al.* 1987b, Scarabin *et al.* 1998, Van der Bom *et al.* 1998). Frequencies of *Bcl* I genotypes 77% for B1B1 and 22% for B2B1 and 1% for B2B2 in Finns (Vaisanen *et al.* 1997). The –455G/A (*Hae* III) polymorphism has genotype frequencies of 57-64% for GG, 30-40% for GA and 4-7% for AA (Green *et al.* 1993, Scarabin *et al.* 1993, Behague *et al.* 1996, Gardemann *et al.* 1997, Tybjaerg-Hansen *et al.* 1997, Wang *et al.* 1997, de Maat *et al.* 1998, van't Hooft *et al.* 1999).
The A allele has been consistently associated with elevated fibrinogen levels (Green *et al.* 1993, Scarabin *et al.* 1993, Thomas *et al.* 1996, Gardemann *et al.* 1997, Tybjaerg-Hansen *et al.* 1997, de Maat *et al.* 1998, van Der Bom *et al.* 1998, van't Hooft *et al.*1999), increased severity of CAD and its progression (Behague *et al.* 1996, de Maat *et al.* 1998) and CAD incidence in diabetic patients (Carter *et al.* 1996a, Lam *et al.* 1999), but not with the risk of incident CAD (Gardemann *et al.* 1997, Tybjaerg-Hansen *et al.* 1997, Wang *et al.* 1997, Lee *et al.* 1999) or MI in the general population (Green *et al.* 1993, Scarabin *et al.* 1993, Behague *et al.* 1996, Gardemann *et al.* 1997, van Der Bom *et al.* 1999). This polymorphism could thus be considered to be a marker of clinically silent CAD progression. The *Bcl* I polymorphism has been found to associate with plasma levels of fibrinogen (Humphries *et al.* 1987, Heinrich *et al.* 1995, Zito *et al.* 1999), although Vaisanen *et al.* couldn't confirm this in healthy Finnish men (1997). B2 allele of the *Bcl* I polymorphism has been associated with increased severity of CAD (Behague *et al.* 1996) and with AMI (Zito *et al.* 1997, 1999).

5.3 Other possibly prothrombotic polymorphisms

The C677T polymorphism of methylenetetrahydrofolate reductase (MTHFR). MTHFR is a B2-vitamine-dependent enzyme in the biosynthesis of homocysteine (Nygård *et al.* 1999). Approximate genotype frequencies in the Finnish population are 54% for CC, 38% for CT and 8% for TT (Pastinen *et al.* 1998). This variant explains 10 to 15% of the variance in the plasma levels of homocysteine (Ma *et al.* 1996, Dunn *et al.* 1998, Gudnason *et al.* 1998), which is a potent predictor of the risk of MI (Christensen *et al.* 1999, Nygård *et al.* 1999). Most of the studies on the association of the C677T polymorphism with CAD (Wilcken *et al.* 1996, Anderson *et al.* 1997, Brugada *et al.* 1997, van Bockxmeer *et al.* 1997, Dunn *et al.* 1998, Nygård *et al.* 1999) and MI (Adams *et al.* 1996, Ma *et al.* 1996, Anderson *et al.* 1997, Brugada *et al.* 1997, Pastinen *et al.* 1998, Araujo *et al.* 1999, Ardissino *et al.* 1999, Fernandez-Arcas *et al.* 1999, Nygård *et al.* 1999) have failed to find an association. One study has suggested the TT genotype to be associated with MI in very young age (Inbal *et al.* 1999) and another one that the TT genotype is associated with more extensive CAD in high-risk individuals (Gardemann *et al.* 1999c). It has recently been suggested that TT homozygosity might be a risk factor for premature (<45 years) CAD and that this effect would be especially strong in individuals with low folate levels and/or no classic risk factors (Gallagher *et al.* 1996, Kluitmans *et al.* 1996, Mager *et al.* 1999, Tokgozoglu *et al.* 1999).

Stromelysin-1 promoter 5A/6A polymorphism. Stromelysin-1, also known as matrix metalloproteinase-3, is a powerful proteolytic enzyme and contributes to the weakening of the fibrous caps of atheroma plaques, making them prone to rupture (Terashima *et al.* 1999). Approximate genotype frequencies in Finns are 12% for 5A5A, 56% for 5A6A and 32% for 6A6A (Humphries *et al.* 1998). The 6A allele has been found to be associated with decreased expression of the gene (Ye *et al.* 1996). The 5A5A genotype has been found to be associated with slower progression of CAD (Ye *et al.* 1996, Humphries *et al.* 1998) and with fewer clinical events (de Maat *et al.* 1999) compared to 5A6A genotype and especially 6A homozygotes. Confusingly, a recent study on Japanese AMI patients found the 5A allele to be an important risk factor for AMI (Terashima *et al.* 1999).

The angiotensin converting enzyme (ACE) I/D polymorphism. ACE is responsible for the conversion of angiotensin, an important regulator of blood pressure, to its active form. Approximate frequencies of the respective genotypes in the Finnish population are 20% for DD, 45 for ID and 35% for II (Pastinen *et al.* 1998). The DD genotype has been found to be associated with the highest plasma ACE levels followed by ID and then II (Rigat *et al.* 1990, Tiret *et al.* 1992). The DD genotype was first reported to be strongly associated with increased risk for MI (Cambien *et al.* 1992). Subsequently, the DD genotype was suggested to be associated with premature CAD (Miettinen *et al.* 1994) and CAD incidence among diabetics (Huang *et al.* 1998) in the Finnish population. On the contrary, a study on Finnish MI patients could not replicate the association of the DD genotype with MI (Perola *et al.* 1995). Inconsistent results were also obtained in many of the studies on MI patients, and as a summary a meta-analysis (Samani *et al.* 1996) found the DD genotype to increase the risk of MI only slightly (OR 1.26). Recent studies on the ACE I/D polymorphism in larger patient materials (Agerholm-Larsen *et al.* 1997, Pastinen *et al.* 1998, Heijmans *et al.* 1999, Pfohl *et al.* 1999) have failed to find an association between the ACE polymorphism and CAD or MI. The most recent meta-analyses summed up the results so far and concluded that the DD genotype is not useful as a clinical risk marker for MI except possibly in certain high-risk groups such as diabetic patients (O'Malley *et al.* 1999, Agerholm-Larsen *et al.* 2000, Keavney *et al.* 2000). However, these conclusions may be slightly confounded by the fact that they are based on studies of MI survivors, as the DD genotype has been found to be a possible predictor of fatal MI (Evans *et al.* 1994, Biggart *et al.* 1998).

Several studies have found the DD genotype to be associated with increased risk of essential hypertension (Zee *et al.* 1992, Morris *et al.* 1994, Schunkert *et al.* 1996, Fornage *et al.* 1998, O'Donnell *et al.* 1998, Turner *et al.* 1999), but many studies have also failed to confirm this association (Kreutz *et al.* 1995, Johnson *et al.* 1996, Perola 1999, Sagnella *et al.* 1999). Recently, it was suggested that only males might be affected (Fornage *et al.* 1998, O'Donnell *et al.* 1998, Taitonen *et al.* 1999, Turner *et al.* 1999, Higaki *et al.* 2000). The studies on ACE genotype and LVH have failed to show a consistent association (Kupari *et al.* 1994, Prasad *et al.* 1994, Schunkert *et al.* 1994, Gharavi *et al.* 1996, Kiema *et al.* 1996, Lindpaintner *et al.* 1996, Pontremoli *et al.* 1996, Clarkson *et al.* 1997, Hamon *et al.* 1997, Mayet *et al.* 1997, Perticone *et al.* 1997, Celentano *et al.* 1999, Dellgren *et al.* 1999, Estacio *et al.* 1999, Gomez-Angelats *et al.* 2000, Jeng *et al.* 2000, Pontremoli *et al.*2000).

Careful phenotype dissection in studies of hypertension and LVH has been suggested to be very important in exploring the discrepancies between study results (Perola 1999). The ACE polymorphism did not associate with baroreflex sensitivity (BRS) in the Finnish population (Ylitalo *et al.* 2000) nor was it associated with decreased HRV (Busjahn *et al.* 1998).

Angiotensin II type 1 receptor A1166C polymorphism. This is the main receptor of active angiotensin II in regulating the arterial tone. Approximate frequencies of the genotypes in the Finnish population are 62-63% for AA, 32-33% for AC and 5% for CC (Pastinen *et al.* 1998). There is no biologic evidence of the functionality of this polymorphism. The CC genotype was first reported to increase the risk of MI in men with the DD genotype of the ACE I/D polymorphism (Tiret *et al.* 1994). The C allele as well as the whole angiotensin II type 1 receptor gene locus have been reported to be associated with increased susceptibility to hypertension (Bonnardeaux *et al.* 1994, Perola 1999). Subsequent studies found the C allele to be associated with increased arterial stiffness (Benetos *et al.* 1995, 1996) and coronary stenosis (Nakauchi *et al.* 1996). Thus far the association of the CC genotype with MI has been confirmed by a few small studies (Berge *et al.* 1997, Fernandez-Arcas *et al.* 1999, Canavy *et al.* 2000) but no association was found in a study performed in the Finnish population (Pastinen *et al.* 1998) and in a very large study on British men (Keavney *et al.* 2000). The CC genotype in men with the ACE DD genotype has been found to be associated with increased coronary artery stenosis (Rice *et al.* 1999) and an increased risk of malignant arrhythmias (Anvari *et al.* 1999), but the association with MI (Tiret *et al.* 1994) could not be confirmed in a very large recent study (Keavney *et al.* 2000). The question about the possible association of the A1166C polymorphism with LVH remains open (Hamon *et al.* 1997, Osterop *et al.* 1998).

Angiotensinogen M235T polymorphism. Angiotensinogen is the unactivated form of angiotensin. Approximate frequencies of the genotypes in the Finnish population are 35% for MM, 42% for MT and 23% for TT (Pastinen *et al.* 1998). The T allele has been found to be associated with the highest plasma levels of angiotensin (Staessen *et al.* 1999, Winkelmann *et al.* 1999). The T allele was first suggested to be associated with increased risk of CAD (Katsuya *et al.* 1995). Subsequently the T allele was found to be associated with the extent of coronary lesions and higher CAD scores and the TT genotype with CAD (Jeunemaitre *et al.* 1997, Gardemann *et al.* 1999c, Watzinger *et al.* 1999, Winkelmann *et al.* 1999, Fatini *et al.* 2000), with one exception (Reinhardt *et al.* 2000). The T allele has also been suggested to increase the risk of hypertension (Jeunemaitre *et al.* 1992, Tiret *et al.* 1995, Kunz *et al.* 1997, Tiret *et al.* 1998, Staessen *et al.* 1999) although this association could not be confirmed in some studies (Fernandez-Llama *et al.* 1998, Taitonen *et al.* 1999, Zhang *et al.* 2000).

The TT genotype has also been suggested to be associated with a modest increase in the risk of MI (Winkelmann *et al.* 1999) but this could be confirmed neither in the Finnish (Pastinen *et al.* 1998) nor in the Spanish population (Fernandez-Arcas *et al.* 1999). The role of the M235T polymorphism in LVH is still controversial (Fernandez-Llama *et al.* 1998, Karjalainen *et al.* 1999, Kim *et al.* 2000, Pontremoli *et al.* 2000). No role for this polymorphism could be found in regulating BRS (Ylitalo *et al.* 2000).

The T344C polymorphism of the CYP11B2 aldosterone synthase. Aldosterone synthase is responsible for conversion of aldosterone in the liver. Approximate frequencies of genotypes in the Finnish population are 29% for TT, 49% for CT and 22% for CC (Hautanen *et al.* 1999). This enzyme is essential for the production of aldosterone. Studies on the effect of the T344C polymorphism on serum and urine aldosterone levels have been controversial (Schunkert *et al.* 1999). The C allele has been previously associated with the size and mass of the left ventricle (Kupari *et al.* 1998), although this association was not confirmed by larger studies (Schunkert *et al.* 1999, Hengstenberg *et al.* 2000). The C allele has also been found to be associated with decreased BRS (Ylitalo *et al.* 2000). Most recently it has been suggested to increase the risk of MI in dyslipidemic smokers (Hautanen *et al.* 1999), although also this association has been questioned (Hengstenberg *et al.* 2000, Patel *et al.* 2000).

TABLE 3. Percentual frequencies (%) of different genotypes of the reviewed polymorphisms (* not studied in the Finnish population).

HPA-1	HPA-2	C807T	ACE	ATII1	ATG	ALDOST	FV	PT	BclI
73.5 A1A1	80.0 AA	40.0 CC	35.0 II	62.5 AA	35.0 MM	29.0 TT	97.0 GG	97.0 GG	77.0 B1B1
25.5 A2A1	19.0 AB	53.0 CT	45.0 ID	32.5 AC	42.0 MT	49.0 CT	3.0 GA	3.0 GA	22.0 B1B2
1.0 A2A2	1.0 AA	7.0 TT	20.0 DD	5.0 CC	23.0 TT	22.0 CC	0.5 AA	0.1 AA	1.0 B2B2

PAI-1	R353Q *	HVR4 *	FXIII	T-PA *	THROMB *	MTHFR	STROM	Hae III *
30.0 5G5G	65.0 RR	42.0 H6H6	57.0 ValVal	21.0 DD	64.0 AlaAla	54.0 CC	12.0 5A5A	60.0 GG
50.0 4G5G	31.0 RQ	43.0 H6H7	37.0 ValLeu	50.0 ID	33.0 AlaVal	38.0 CT	56.0 5A6A	35.0 GA
20.0 4G4G	4.0 QQ	14.0 H7H7	6.0 LeuLeu	29.0 II	3.0 ValVal	8.0 TT	32.0 6A6A	5.0 AA
		1.5 H5+/H8+						

HPA-1: GPIIIa Pl^A polymorphism, HPA-2: GPIb Thr145Met polymorphism, C807T: GPIa C807T polymorphism, ACE: ACE I/D polymorphism, ATII1: angiotensin II type1 receptor A1166C polymorphism, ATG: angiotensinogen M235T polymorphism, ALDOST: CYP11B2 aldosterone synthase T344C polymorphism, FV: factor V Leiden polymorphism, PT: prothrombin G20210A polymorphism, BclI: beta-fibrinogen BclI polymorphism, PAI-1: PAI-1 4G/5G polymorphism, R353Q: factor VII R353Q polymorphism, HVR4: factor VII VNTR polymorphism, FXIII: factor XIII Val/Leu polymorphism, T-PA: T-PA Alu-repeat polymorphism, THROMB: thrombomodulin Ala455Val polymorphism, MTHFR: MTHFR C677T polymorphism, STROM: stromelysin 5A6A polymorphism, HaeIII: beta-fibrinogen HaeIII/455GA polymorphism

TABLE 4. The studies on the Pl^A polymorphism and acute coronary events and complications of therapeutic coronary inventions

Author	Design	Patient phenotype	Association
Weiss et al. 1996	case-control	MI and UAP surv. , DNA collected acutely	yes, especially <60 yrs.
Ridker et al. 1997	prosp. nested case-control	MI survivors (85%) and fatal MI	no
Carter et al. 1996,1997	case-control	MI survivors	yes, especially <50 yrs.
Herrmann et al. 1997	case-control	of angiographic patients, those with prev. MI	no
Samani et al. 1997	case-control	MI survivors, incorrect statistical analysis	yes, after corrections
Scaglione et al. 1998	case-control	MI survivors, DNA collected acutely	no
Pastinen et al. 1998	case-control	MI survivors, DNA collected in the acute phase	yes, espec. <60 yrs.
Zotz et al. 1998	case-control	MI survivors, DNA collection in acute phase	yes, especially young
Zotz et al. 1998	event-no event	MI survivors follow-up by Pl^A genotypes	A2 more events
Gardemann et al. 1998	case-control	of angiographic patients, those with prev. MI	no
Durante-Mangoni 1998	case-control	of angiographic patients, those with prev. MI	no
Joven et al. 1998	case-control	MI survivors	no
Anderson et al. 1999	case-control	of angiographic patients, those with MI, also acute	yes
Ardissino et al. 1999	case-control	survivors of Q-wave MI, all under 45 yrs.	yes
Tereschenko et al. 1999	case-control	MI survivors	yes, espec. <60 yrs.
Araujo et al. 1999	case-control	MI survivors, DNA collected in the acute phase	yes, espec. <60 yrs.
Kekomaki et al. 1999	case-control	MI survivors	no
Aleksic et al. 2000	prosp. nested case-control	incident CAD, all different manifestations	no
Brscic et al. 2000	event-no event	follow-up after AMI by Pl^A genotypes	A2 more events
Burke et al. 1999	autopsy case-control	autopsied SCD victims	SCD due to plaque erosion
Mamotte et al. 1998	follow-up after angioplasty, restenosis		no
Abbate et al. 1998	follow-up after angioplasty, restenosis		A2 more often restenosis
Walter et al. 1997	follow-up after coronary stenting, thrombosis		A2 with stent thrombosis
Kastrati et al. 1999	follow-up after coronary stenting, thrombosis		A2 with stent thrombosis
Mehilli et al. 1999	follow-up after coronary stenting, thrombosis		A2 with stent thrombosis
Laule et al. 1999	follow-up after coronary stenting, thrombosis		no, see text page 25
Kiss et al. 2000	follow-up after coronary stenting, thrombosis		A2 with stent thrombosis
Kastrati et al. 2000	follow-up after coronary stenting, thrombosis		no, see text page 26
Zotz et al. 2000	follow-up after coronary by-pass surgery		A2 with MI and death

AIMS OF THE STUDY

Platelets have been found to have a key role in the development of MI, acute coronary syndromes and SCD. Genetic variation in platelet glycoprotein receptors responsible for thrombus formation has been suggested to be associated with the risk of MI in clinical patient series. However, autopsy studies on the association of such variance with atherosclerosis and SCD do not exist. The aims of the studies included in this thesis were:

1. To study the association of the GPIIIa Pl^A polymorphism with coronary thrombosis, fatal MI and sudden cardiac death

2. To assess the association of the GPIIIa Pl^A polymorphism with aortic and coronary atherosclerosis.

3. To try to achieve an insight into the pathogenetic role behind the association of the Pl^A polymorphism with complicated coronary lesions and coronary thrombosis

MATERIALS AND METHODS

1. Autopsy series of middle-aged men and ethics

Helsinki Sudden Death Study (HSDS) was designed to study the risk factors of sudden out-of-hospital cardiac death and can be conceived as a complementary study to the national WHO MONICA Project. The HSDS study comprised two consecutive series of altogether 700 Caucasian Finnish men aged between 33 and 70, who were subjected to a medicolegal autopsy at the Department of Forensic Medicine, University of Helsinki in 1981 to 1982, and ten years later, in 1991 to 1992. The mean age of both series was 53 years. The reason for the medicolegal autopsy was an unexpected sudden death occurring outside hospital, often unwitnessed. In Finland, all cases of sudden out-of-hospital cardiac death in the studied agegroup are subjected to medicolegal autopsy unless they have previously had a clinically diagnosed condition with a high probability of causing an untimely and sudden demise, such as severe chronic heart failure. Thus nearly all the men aged 33 to 70 who suffered sudden cardiac death outside hospital during the study years are included in this study with over 40% of total deaths in the agegroup during the studied period. Causes of deaths were: cardiac causes in 41.1% (n=288), of which 79.9% (n=230) due to coronary heart disease without critical valvular disease, significant non-ischemic cardiomyopathy or other cardiac diseases, other diseases in 20.0% (n=140) and suicides or accidents in 38.9% (n=272). The study was approved by the Ethics Committee of The Department of Forensic Medicine, University of Helsinki.

2. Clinical characteristics and risk factor data collection

A spouse, a relative or a close friend of the deceased could be interviewed in 71.4% (n=500) of cases. We used a formatted questionnaire with questions delineating past and recent smoking and drinking habits as well as previous illnesses. On the basis of the interviews in men with all data available (n=441), men were classified as smokers and non-smokers. Ex-smokers were included to the class of smokers for statistical analysis. The average daily alcohol consumption of the deceased was calculated from information given by the interviewed persons. One bottle of beer, a glass of wine and a shot of spirits were each considered to contain 12 grams of pure alcohol and to equal one drink. Based on the questions on previous illnesses, 107 men had suffered from hypertension and 113 men from diabetes. Body mass index (BMI) and age were verified as part of the routine autopsy protocol.

3. Measuring the percentage of stenosis in silicone rubber casts of the coronary arteries

At autopsy, coronary angiography was performed using vulcanizing liquid silicone rubber mixed with lead oxide as the contrast medium. The proximal, middle and distal stenosis of the main trunks of the three main epicardial coronary arteries, left anterior descending (LAD), left circumflex (Lcx), and right (RCA) coronary artery were measured from the rubber cast model. The percentage of the stenosis was obtained by dividing the diameter (millimeters) of the greatest stenosis with the diameter of the nearest proximal undamaged part of the cast model of the artery, resulting in 9 measurements of the degree of stenosis for each individual. The highest of these measurements was chosen to represent the degree of coronary stenosis in each individual. These measurements were available in altogether 670 men.

4. Measuring the area of atherosclerosis by morphometry of coronary arteries and the aorta

The aorta and the coronary arteries were fixed in 10% buffered formalin and stained for fat by the Sudan IV staining method. The following atherosclerotic changes were evaluated for all arteries according to standard protocols (Uemura *et al.* 1964, Guzman *et al.* 1968): fatty streaks (1), fibrous plaques (2), calcification (3) and complicated lesions (4). (1) Any flat or slightly elevated intimal lesion that was stained distinctly by Sudan IV and did not show any other types of change underlying it was classified as a fatty streak. (2) A raised lesion that did not exhibit ulceration, hemorrhage, necrosis or thrombosis was regarded as fibrous plaque. (3) The X-ray positive areas in the radiologic examination of the vessels were regargded as areas of calcification. (4) If there was an area with one or several of the aforementioned changes, ulceration, hemorrhage, necrosis or thrombosis, it was regarded as a complicated lesion. The areas of atherosclerotic lesions and the total areas of aortic and coronary segments were assessed using a standard planimetric technique. The proportional areas of these various atheromatous changes were calculated based on the total surface area of the arteries. The data on the atherosclerotic changes of coronary arteries was available in 512 men from both series and that of the aorta in 287 men from the latter series.

5. Characteristics and phenotypes of myocardial infarction

The presence of MI in the series was confirmed by a macroscopic and histologic examination of the myocardium. The presence/absence of neutrophil granulocytes was considered diagnostic of an acute MI and the presence/absence of fibrous scar tissue diagnostic of an old MI. Based on the autopsy findings and nitro blue tetrazolium (NBT) staining (Vargas *et al.* 1999) the MI was classified as either transmural or non-transmural (Table 1). Only NBT staining was not considered diagnostic of MI even though it supported a diagnosis of sudden coronary death. The presence of recent or organizing macroscopic coronary thrombosis was recorded while opening the coronary arteries.

In the entire series of 700 men, 184 were found to have MI and 85 had died of AMI with or without an old MI. Of the AMI cases 39 were associated with coronary thrombosis, of which 24 were acute. An old non-fatal MI scar without AMI was found in additional 99 cases, of which a macroscopic organizing thrombus was observed in 14 cases and an acute thrombus without AMI in 5 cases and additional 10 men had suffered an acute, fatal, occluding coronary thrombosis without histologic features of MI, due to their short survival time. These 10 were included to MI cases. Of those altogether 194 men with MI, 68 (35.1%) were associated with coronary thrombosis, whereas MI in the remaining 126 (64.9%) was due to severe coronary stenosis without thrombosis and an acute thrombus was found in 39 cases. Men with thrombosis and MI were on average younger (mean 56.6 years) compared to men with MI in the absence of thrombosis (mean 59.2 years). An acute myocardial infarction was more often and an old infarct scar less often found in men with thrombosis compared to men with MI without thrombosis (Data not shown).

6. DNA extraction and $PI^{A1/A2}$ genotyping

In the 1981-82 series DNA was extracted from paraffin-embedded samples of cardiac muscle using a method described by Isola *et al.* (1994). In the 1991-92 series DNA isolation was performed from frozen (-70°C) cardiac muscle samples by the standard phenol-chloroform method. The polymorphism of cytosine/thymidine in exon II of the glycoprotein IIIa gene was detected by PCR and restriction digestion. 10-30 ηg of genomic DNA extracted from frozen cardiac muscle samples taken at autopsy was used in each amplification. DNA was amplified with a PTC 100 (Perkin-Elmer, Foster City, California) for 37 cycles of denaturation at 94°C for 45s, annealing at 53°C for 45s, and extension at 72°C for 60s. The final extension step was at 72°C for 4 minutes. The 266 bp-product was then incubated at 37°C for one hour with 10 units of *Msp*I. The resulting fragments were then separated by size in a 2% agarose gel and visualized by ethidium bromide staining. Ladder as well as A2 homozygous control sample were included in the gels. Genotyping was successful in altogether 666 cases. In the 1991-92 series 99.7% of the samples were successfully genotyped, whereas 91.8% of the samples from the 1981-82 series could be genotyped.

7. Statistical analysis

Characteristic differences between causes of deaths were bivariately analysed with Student t-tests. Analyses of the effect of genotype on myocardial infarction with/without thrombosis and comparisons between acute thrombosis cases and other SCD victims were based on logistic regression, where the confounding effects of age, BMI, smoking, alcohol consumption (in grams), hypertension and diabetes were taken into account by including them into the model as covariates. Alcohol consumption was not used as a covariate in study I as the data was not completely analysable at the moment of analyses. We also analysed the trend for the prevalence of genotypes in different age-groups and in groups of causes of deaths using chi-square tests and logistic regression. The statistical analysis for the association of areas of atherosclerotic changes and the percentage of stenosis (with logarithmic transformation of data of stenosis due to skewness of distribution) with the PI^{A} genotype was based on the analysis of covariance where the confounding effects of age, BMI, smoking, alcohol consumption, diabetes and hypertension were taken into account by including them into the model as covariates. Alcohol was not used as a covariate in studies I and II as the alcohol data was not completely analysable at the moment of analyses For the analysis of the presence/absence of individual atherosclerotic changes we used logistic regression analysis and accounted for the confounding effects of age, BMI, smoking, diabetes and hypertension.

All the data analyses were performed in all men and also separately in men with and without the interview data. The computation was carried out with STATISTICA/WIN (Version 5.0, Statsoft Inc., Tulsa, Oklahoma, USA) and BMDP Statistical Software (Version 1993, SPSS Science, Chicago, Illinois, USA) on a SUN/UNIX mainframe.

RESULTS

1. Prevalence of $Pl^{A1/A2}$ Alleles (Studies I-IV)

In the population of the 1991-92 study series of 272 men, the frequency of Pl^{A1} was 87% and that of Pl^{A2} 13%. The respective frequencies for genotypes were 75.0% for $Pl^{A1/A1}$, 22.4% for $Pl^{A1/A2}$, and 2.6% for $Pl^{A2/A2}$. The frequencies of Pl^{A1} and Pl^{A2} were identical (87% vs. 13%) in the subpopulation of 131 men with smoking data. The genotypes for the 272 men were in the Hardy-Weinberg equilibrium. The frequencies of alleles in this series were similar to the allele frequencies reported on population-basis in Finland (A2 14%, A1 86%) (Kekomäki *et al.* 1995). No significant differences existed in these parameters between the two populations or between genotypes.
The frequencies of Pl^{A1} and Pl^{A2} in the genotyped population of both series of altogether 666 men were 85% and 15%, respectively. The allele frequencies were almost identical in both autopsy series. The genotype frequencies were 73.1% for $Pl^{A1/A1}$, 24.2% for $Pl^{A1/A2}$, and 2.7% for $Pl^{A2/A2}$. The frequencies of Pl^{A1} and Pl^{A2} were identical (85% vs. 15%) in the subpopulation with interview data.

2. Association of $Pl^{A1/A2}$ genotypes with the causes of the sudden death (Study III)

In both study series combined, the frequency of A2 allele was similar among cases of SCD, violent deaths and deaths due to other diseases ($p>0.1$). However, the frequency of the A2 allele decreased with age in the series ($p<0.05$). Frequency of the A2 allele in men dying suddenly under the age of 50 (n=252) was 31.3% and it decreased to 20.0% in men over 60 (n=181). This decrease was observed only among cases of SCD, in whom the A2 allele was found in 39.7% of the 68 men under 50, in 26.2% of the 107 men between 50 and 60 and in 21.7% of the 106 men over 60 ($p<0.05$). In cases of violent deaths and deaths due to other diseases, the frequency of men with A2 allele did not change significantly with age ($p>0.1$). When we compared the groups with different causes of death in men under 50, the A2 allele was associated with an increased risk of SCD compared to death due to violent causes or other diseases (OR 2.5, 95%CI 1.2 to 5.3; $p=0.01$).

3. Coronary thrombosis, myocardial infarction and $Pl^{A1/A2}$ polymorphism (Studies I, III)

In the 1991-92 series, we could find no direct association between MI and the Pl^{A} polymorphism before (p=0.9) or after (p=0.6) adjusting for smoking. However, the prevalence of the men possessing the Pl^{A2} allele was significantly higher (p<0.001) in men with MI caused by coronary thrombosis than in men with MI without thrombosis. Of the 22 men with MI and coronary thrombosis 11 had the A2-allele, whereas in the 47 men with MI without thrombosis it was present in only 6 (OR 6.6; 95% CI 2.1 to 22.8). When interview data was included in the analysis (data available for 40 of the cases with MI, 15 with thrombosis and 25 without it), the association of the Pl^{A2} allele still showed a significant association (p<0.001) with MI and thrombosis. The association was significant also in the group of men with no interview data.

When both series were combined, of cases of fatal acute thrombosis (n=39), 19 (48.7%) were carriers of A2 allele compared to 59 (24.4%) of the 242 men with SCD without acute thrombosis (OR 3.4, 95%CI 1.5 to 6.3; p<0.01). In men under 60, 17 (60.7%) of the 28 men with acute fatal thrombosis had the A2 allele and it was found in 38 (25.9%) of the 147 men with SCD without acute thrombosis (OR 4.6, 95%CI 2.0 to 11.2; p<0.0005). 30 (44.8%) of the 67 men with MI and acute or old coronary thrombosis carried the A2 allele, whereas it was found in 25 (20.3%) of the 123 men with MI in the absence of thrombosis (OR 3.6, 95%CI 1.4 to 9.2; p=0.005). In men under 60, 23 (60.5%) of the 38 men with MI and coronary thrombosis possessed the A2 allele compared to 11 (17.5%) of the 63 men with MI in the absence of thrombosis (OR 8.0, 95% CI 2.3 to 28.2; p=0.001). The associations of the A2 allele with thrombosis weakened in men over 60 (p=0.1). (Table 5) The above associations of the A2 allele with thrombosis were similar both in men with interview data on smoking, alcohol consumption, diabetes and hypertension and in the excluded men without interview data (Data not shown).

4. Atherosclerotic changes and $Pl^{A1/A2}$ genotypes (Studies II, IV)

Fatty streaks, fibrous lesions and complicated lesions were found in the coronary arteries of 499 (97.5%), 428 (83.6%) and 238 (46.5%) individuals, respectively, out of a total of 512 men. In these men, the average atherosclerotic ratios (in percent) were: 9.9% (standard deviation, SD 8.5) for fatty streaks, 8.3% (SD 7.0) for fibrous lesions and 6.8% (SD 8.4) for complicated lesions. Coronary arteries showed variable degrees of stenosis in 611 (91.2%) of the 670 men. The mean coronary stenosis of the most affected artery in the study population was 46.0% (SD 29.0). The mean percentage areas of fat ($p=0.6$), raised fibrous lesions ($p=0.2$), and complicated lesions ($p=0.2$) showed no association with Pl^A polymorphism in the 1991-92 series. However, when the results were adjusted for smoking in the subgroup of 131 men, men possessing the Pl^{A2} allele had significantly ($p<0.05$) larger areas of complicated lesions in their coronaries compared to the Pl^{A1} homozygotes. In both study series combined, fibrous lesions were also more often found in A1 homozygotes ($p<0.05$; OR 1.6, 95%CI 1.0 to 2.8) compared to men with the A2 allele, although after the adjustment for interview data the association slightly weakened ($p=0.07$; OR 1.5). On the contrary, the percentage area of complicated lesions was greater in men with the A2 allele ($p=0.2$ and $p=0.01$ before and after adjustments).

In men (n=125) with data on all risk factors and with no complicated lesions in their coronary arteries, fibrous lesions were more often found in the coronary arteries of A1 homozygotes (OR 2.9 95% CI 1.2 to 6.3; $p<0.01$) and the average area of these fibrous lesions was greater ($p=0.06$) compared to men with the A2 allele. A1 homozygotes also had more stenotic coronary arteries ($p<0.05$) compared to men with the A2 allele.

Fatty streaks, fibrous lesions and complicated lesions were found in the aorta in 287 (100%), 261 (90.9%) and 194 (67.6%) individuals, respectively, out of a total of 287 men with data available in the 1991-92 series. In these men, the average atherosclerotic area (in percent) was: 13.6% (SD 10.7) for fatty streaks, 5.9% (SD 5.3) for fibrous lesions and 5.2% (SD 9.2) for complicated lesions. The A1 homozygous genotype was significantly more frequently ($p=0.05$) found in men with fibrous lesions compared to those without fibrous lesions in the aorta. No association was found between the polymorphism and the presence/absence of other atherosclerotic variables. The areas of the respective atherosclerotic changes were not associated with the Pl^A polymorphism, although there was a trend towards a larger area of complicated lesions in men with the A2 allele ($p=0.09$). When analyzed by ageclasses, this effect was highly significant in men over the age of 60 ($p=0.002$ for agegroup-genotype interaction).

5. Coronary narrowings and the $Pl^{A1/A2}$ polymorphism (Studies I, IV)

For multivariate analysis, we chose the highest percentage of stenosis, measured from silicone casts, to represent the severity of coronary stenosis. The possession of the Pl^{A2} allele was significantly ($p=0.01$) associated with less severe coronary stenosis in the 1991-92 series. This association remained significant ($p<0.01$) when smoking habits were brought into the model and the association was significant also in the group of men with no data on smoking habits. No further association was found for the Pl^{A} polymorphism in comparison of one-vessel disease to multiple-vessel stenosis. In order to discover the effect of the Pl^{A} genotype on subclinical stenosis, we divided the men into three groups based on the measurements of their coronary silicone rubber casts: men with smooth healthy coronary arteries or narrowings below 25%, men with moderate coronary narrowings between 25-50%, and men with severe stenosis of over 50% in any of the main coronary artery trunks.

There was a significant gradual decrease in the Pl^{A2}-positive genotype (Table 6), across the range from the first group of men with stenosis under 25% to the third group with over 50% stenosis (OR 0.45, 95% CI 0.22 to 0.98), and also when comparing the second group with stenosis between 25% and 50% to the third group (OR 0.65, 95% CI 0.36 to 1.3). This association remained significant and similarly gradual after we adjusted the interview data and also in men without the interview data. The A1 homozygotes tended to have worse coronary narrowings compared to men with the A2 allele ($p=0.06$ and $p=0.1$ before and after adjusting for interview data) in both series combined.

Table 5. Distribution of $PlA^{1/A2}$ genotypes in men with sudden cardiac death (SCD) and acute fatal thrombosis, without acute thrombosis and without acute thrombosis and myocardial infarction (MI).

	Under 60 yrs.		Over 60 yrs.	
	A1/A1	A2+	A1/A1	A2+
SCD, ACUTE CORONARY LESION	11	17 (**60.7%**)	9	2 (18.2%)
SCD, OLD OR RECENT MI, NO ACUTE CORON. LESION	56	17 (23.3%)	59	19 (24.4%)
SCD, NO MI, NO ACUTE CORONARY LESION	53	21 (28.4%)	15	2 (11.8%)

Table 6. Distribution of $PlA^{1/A2}$ genotypes among men in Study I with different degrees of stenosis in the most affected coronary artery.

	STENOSIS <25%	**STENOSIS 25-50%**	**STENOSIS >50%**
A1/A1	**57**	**80**	**67**
A2/A1 + A2/A2	**28 (32.9%)**	**25 (23.8%)**	**15 (18.3%)**

P<0.01 FOR TREND IN MANOVA.

DISCUSSION

1. Evaluation of the study population, materials and methods

Our approach to analyse the risk of coronary thrombosis in SCD is based on association analysis with one candidate gene polymorphism, the Pl^A polymorphism of GPIIIa, platelet fibrinogen receptor. This approach is used because numerous studies have previously used the same methodology in context with this polymorphism. Our approach is also supported by the fact that genotypic differences in the receptor protein function have been reported to exist between the Pl^A genotypes in numerous studies. Due to the abundant availability of human tissue for studies and the lack of suitable animal models, very few if any studies on this polymorphism have used animal models. We used RFLP-PCR to genotype individuals and to prevent misgenotyping a ladder as well as control samples in the genotype analyses.

Our use of certain subgroup analyses, mostly different agegroups, is largely due to the fact that previous studies have suggested this polymorphism to be important in early middle age. Another factor is the small amount of men under 50 with SCD, which is why we have used both 50 and 60 years as cut-off points for agegrouping.

The strengths of the present study compared to clinical MI patient series are that the measurements of atherosclerotic variables and the percentage of coronary stenosis as well as the presence of AMI and old MI scars were measured directly from the arteries and the myocardium. Also the presence of acute thrombosis could be confirmed. It is possible that few developing AMI cases could not be diagnosed in cases with acute thrombus without AMI due to short survival time (10 cases in the entire series), but an acute occluding thrombus even without the histologic diagnosis is a pathognomic feature of a developing AMI. We thus achieved very good phenotyping of the MI cases (transmural vs. non-transmural MI, Table 1). This is not often achieved in prospective study series. Also an important strength is that the cases are fatal AMI cases as opposed to survivors in clinical series, thus circumventing the survival bias in clinical studies.

We were also able to define the phenotype of CAD better than clinical angiography series, as we could differentiate lesions with swift thrombus-dependent growth from stable lesions with possibly slower development. In addition, the presence of CAD/MI in controls could be excluded by the detailed autopsy, which is not often achieved in clinical series and may be a major confounder in many study populations. These three issues, namely, survival bias, heterogeneity of CAD pathology and suitable control population, are often the most important issues in explaining inconsistencies between association studies on CAD.

Limitations of the present study include the fact that the complete risk factor data was not available from all individuals. Relatives and friends of many of the deceased could not be reached or relatives/friends did not exist. However, almost all of the results of studies included in this thesis remained significant when analyses were performed separately in men with the risk factor data and those without it. In addition, cholesterol levels of the deceased were not available as antemortem measurements had only been performed in few individual cases. Carter *et al.* (1996b) suggested an interaction between the Pl^{A2} allele and cholesterol on MI. Several succeeding studies, including a larger study by the same study group, found no association between the Pl^{A} genotype and total cholesterol, HDL cholesterol or triglycerides (Carter *et al.* 1997, Samani and Lodwick 1997, Kekomaki *et al.* 1999, Aleksic *et al.* 2000). A difference in LDL cholesterol between the Pl^{A} genotypes was suggested to exist in CAD patients, but not in controls (Batalla *et al.* 1998). However, in several large studies included in this thesis, multivariate analysis including cholesterol levels did not alter the association of the Pl^{A} genotype with coronary events. Finally, we cannot exclude the possibility that the association of the Pl^{A2} allele with coronary lesions, thrombosis and SCD may be due to a linkage disequilibrium with another gene locus.

2. The association of the A2 allele with coronary thrombosis and myocardial infarction

In this series of studies, we have described an association between the A2 allele of the Pl^{A} polymorphism of the platelet fibrinogen receptor GPIIIa and SCD due to coronary thrombosis in early middle age. Because our study population consisted entirely of men, the results may not be directly extrapolated to women. We were also unable, due to the small number of such individuals, to reliably analyse the association of the A2 homozygous genotype with coronary thrombosis, even though 4.5% of men under 60 with thrombosis were A2 homozygotes compared to 0.8% among control men.

Senti *et al.* (1998), Zotz *et al.* (1998), Ardissino *et al.* (1999) and Melus *et al.* (1999) found that the A2 allele interacted significantly with cigarette smoking. This may contribute to the effect of the A2 allele on SCD risk in the current series, as the majority of SCD victims (approx. 80%) were smokers. Weiss *et al.* (1996), Zotz *et al.* (1998), Ardissino *et al.* (1999) found that the increased risk of MI in carriers of the A2 allele was especially strong in individuals under the age of 60 and Goldschmidt and Bray (1996), Ardissino *et al.* (1999) that this was especially pronounced in men with Q-wave MI. Interestingly Goldschmidt-Clermont *et al.* (1999a) also found that the A2 allele was highly prevalent in siblings of young Caucasian CAD patients.

Burke *et al.* (1999) in their preliminary results found the A2 allele to increase the risk of SCD in early middle age and that this risk was pronounced in those who had coronary thrombosis due to plaque erosion. Plaque erosion has been found not to be associated with the traditional risk factors of MI, with the exception of cigarette smoking being the only identified risk factor (Burke *et al.* 1997, Arbustini *et al.* 1999b, Virmani *et al.* 1999, Taylor *et al.* 2000). Thus, the fact that the A2 allele and cigarette smoking seem to be predictors of thrombosis due to plaque erosion may, in part, offer the pathogenetic background for the reported interactive association of the A2 allele and smoking on the risk of MI.

Two studies consisting of Finnish men have previously found conflicting results on the association of the Pl^A polymorphism with MI. Pastinen *et al.* (1998) found the A2 allele to increase the risk of MI, whereas Kekomaki *et al.* (1999) failed to confirm this. DNA in the latter patient series was collected retrospectively even years after the primary event and the results are likely to be confounded by the suggested survival bias related to the A2 allele (Zotz *et al.* 1998, Brscic *et al.* 2000).

Zotz *et al.* (1998) also found the A2 allele to be associated with decreased survival when patients were re-evaluated one year after MI, which may explain differences between studies that have evaluated survivors even years after the initial event and those studies that have evaluated their patients in the acute phase of MI. In addition, a very recent study showed that men with the A2 allele were clearly overrepresented (37% of individuals) in the group of young men with adverse coronary events after their first AMI as compared to those with event-free survival (21%) (Brscic *et al.* 2000) despite the fact that a large proprotion of the individuals were likely to receive at least aspirin (medication not mentioned in the article).

3. Confounding factors in previous studies

Three studies do not support the theory that the A2 allele is highly prevalent in young men (especially smokers) who suffer Q-wave MI. The first one is the large PHS study. The entire study population consisted of American physicians. There are numerous points of criticism for the lack of results in the PHS study: (1) Cardiovascular mortality rate in the study was 15% of that of the general population because of low-risk status in terms of traditional risk factors. (2) Also 85% of individuals who had a non-fatal MI in the study used aspirin (Steering commitee of the PHS study group 1989). This is a major confounding factor because aspirin has been found to inhibit the ligand-binding of A2-positive platelets ten times more effectively compared to A1 homozygous platelets (Cooke *et al.* 1998). This finding has been confirmed in subsequent studies (Michelson *et al.* 1998, 2000). It has even been suggested that the efficacy of aspirin in the secondary prevention of coronary events may be dependent on the Pl^A genotype (Goldschmidt-Clermont *et al.* 1999b). The PHS study population was also genetically mixed (Ridker *et al.* 1997a) and (3) no ethnic subgroup analyses were performed, which is an important confounding factor in genetic association studies (Lander 1994). (4) In addition, no separate analyses were performed for Q-wave MI vs. non-Q-wave MI.

The second study which failed to confirm the association of the A2 allele with MI was performed by Samani and Lodwick (1997) in individuals with MI in the acute phase. However, (1) the frequency of A2 allele in their controls differed significantly from that reported on population-basis (the authors themselves suggest otherwise but it becomes evident from the article that they have used allele frequency and compared it with genotype frequency on population-basis) and when their cases were compared to population-based controls, A2 allele was significantly more frequent in MI cases. Yet again, (2) no subgroup analyses were performed for Q-wave vs. non-Q-wave infarctions.

The third study not compatible with the above presented theory was performed by Scaglione *et al.* (1998). This study included MI patients who were analysed in the acute phase. One-third of the patients had suffered a non-Q-wave infarction, but no subgroup analyses were performed for Q-wave vs. non-Q-wave infarctions. The lack of results in this study could partly be due to mixed types of MI, although this remains entirely speculative.

There may also be differences in the emphasis of risk factors in the different MI subgroups as men with non-Q-wave MI are older, have more hypertension and diabetes, whereas men with Q-wave MI are more often smokers, have high cholesterol and/or low HDL levels and familial predisposition to MI. It may be reasonable to study both MI groups together and also separately when studying prothrombotic risk factors of MI. In studies including patients with UAP, the classification of these individuals according to the Braunwald classification might provide useful information on the likelihood of thrombotic involvement. Angiography is useful in identifying occlusive thrombi and nearly half of the non-occlusive ones, but the definitive diagnosis of the presence of a thrombus can only be achieved with either angioscopy or by strict postmortem examination. Also the nature of the lesion, whether thrombus-dependent in its recent progression or a stable lesion with slow progression, is not often conclusively achieved with angiography, even though certain key features of lesions, such as eccentricy and steepness of the lesion as well as filling defect of the contrast media associated with the culprit lesion have been used in several studies (Ambrose *et al.* 1988, Mizuno *et al.* 1992, Wilensky *et al.* 1993, Hussain *et al.* 1995, Nesto *et al.* 1998, Abela *et al.* 1999, Arbustini *et al.* 1999a).

4. Pathogenetic mechanisms behind the association of the $Pl^{A1/A2}$ polymorphism with coronary thrombosis

In the present studies we have also found the A2 allele to be associated with less extensive and stenotic fibrous lesions both in the aorta and the coronary arteries. We have also found that men with the A2 allele have more extensive complicated lesions both in the aorta and the coronary arteries. These results suggest that the association of the A2 allele with the risk of coronary thrombosis and SCD may, at least in part, result from the association of the A2 allele with vulnerable coronary plaques with thinner fibrous caps compared to A1 homozygotes. This is also in line with the studies that have found that the Pl^{A} polymorphism is not associated with clinically signficant coronary stenosis. While A1 homozygotes possibly have more subclinical coronary stenosis, this difference may be levelled off by the increased incidence of thrombosis in men with the A2 allele, resulting in similar incidence of clinically significant coronary disease when individuals are evaluated by angiography. This is another possible example of the effect of CAD heterogeneity on the results of association studies.

The above genotypic differences in fibrous lesion characteristics may, instead of platelet fibrinogen receptors, also be due to the action of endothelial vitronectin receptors which are dimers with GPIIIa as a major component. These receptors mediate VSMC proliferation and fibrous tissue generation after endothelial injuries (Brown *et al.* 1994, Hoshiga *et al.* 1995, Shattil 1995, Ruoslahti and Engvall 1997, Slepian *et al.* 1998, Stouffer *et al.* 1998). Another explanation for the association between A2 allele and thrombosis is that this polymorphism affects platelet fibrinogen binding. Increased fibrinogen binding in men with the A2 allele has been shown in numerous *in vitro* studies (Lasne *et al.* 1997, Zotz *et al.* 1997, Feng *et al.* 1999, Goodall *et al.* 1999, Roos *et al.* 1999, Michelson *et al.* 2000, Vijayan *et al.* 2000), of which Vijayan *et al.* have even shown that the thrombus formation in men with the A2 allele leads to more efficient rearrangement of the actin cytoskeleton of platelets and to clot retraction which makes the thrombus more resistant to thrombolysis (Byzova and Plow 2000). *In vitro* studies with different agonists have failed to show consistent genotypic differences in platelet adhesion and aggregation. These studies were recently summarized in the most recent study on genotypic differences in platelet activity (Andrioli *et al.* 2000). However, a recent study on bleeding time among healthy individuals found that bleeding time in shortened among carriers of the A2 allele compared to A1 homozygotes (Szczeklik *et al.* 2000), which is in accordance with the increased fibrinogen binding found in previous studies. Thus, the discrepancies between studies in response to agonists may be due to differences in outside-in signalling and/or changes in agonist effects after fibrinogen binding. It is very likely that the increased risk of thrombosis/MI associated with the A2 allele may result from alteration of the function of both platelet and endothelial/VSMC GPIIIa.

5. Possible therapeutic implications of the findings of the present study series

As long as specific gene therapy is unavailable, genetic risk markers represent uncontrolled risk factors, but since the effect of most of the genetic variants associated with the risk of SCD is likely to be mediated through the known pathogenesis of CAD and MI, interventions on conventional risk factors through lipid and weight lowering, smoking cessation and aspirin administration will considerably decrease the overall risk of SCD in individuals with elevated genetic risk of SCD (Kaprio 2000).

Since aspirin is the recommended primary prevention method for men with uncontrolled risk factors for CAD and aspirin has been suggested to be especially effective in preventing the increased platelet aggregability of men with the A2 allele in *in vitro* studies (Cooke *et al.* 1998, Michelson *et al.* 2000) and these individuals have been found to have an increased risk of MI/SCD in early middle age, a tempting idea would be to administer aspirin as a means of primary prevention to men with the A2 allele (especially smokers) in early middle age. Studies in clinical patients have, however, shown that the A2 allele may in fact be associated with inferior effect of aspirin in preventing platelet aggregability (Undas *et al.* 1999, Kapoor *et al.* 2000, Kiss *et al.* 2000, Szczeklik *et al.* 2000). In support of this, aspirin in combination with ticlopidine in large doses is needed to attenuate the increased risk of stent thrombosis found among the A2 allele carriers, while aspirin alone is not sufficient in decreasing the risk of stent thrombosis and complications after by-pass surgery in men with the A2 allele (Goldschmidt-Clermont *et al.* 2000, Kastrati *et al.* 2000, Kiss *et al.* 2000, Zotz *et al.* 2000). This finding also raises the question, whether A1 homozygotes could be adequately medicated with a single antithrombotic as opposed to men with the A2 allele. Prospective studies on the usefulness of aspirin and/or e.g. clopidrogel in the primary prevention of coronary events and sudden cardiac death in men with inherited predisposition to coronary thrombosis, such as the A2 allele, are at present still lacking.

SUMMARY AND CONCLUSIONS

In this thesis of studies on the association of the glycoprotein IIIa Pl^A polymorphism with aortic and coronary atherosclerosis, coronary thrombosis and MI in autopsied victims of SCD, we have found that men carrying the A2 variant of this polymorphism:

1. Are at an increased risk of dying suddenly from CAD at early middle age compared to men homozygous for the A1 allele. More often show coronary thrombosis, both acute and old, as the cause behind the SCD compared to severe CAD/old MI in A1 homozygotes

2. Less frequently possess fibrous lesions both in the aorta and the coronaries compared to A1 homozygotes. This is also found already in the uncomplicated stage of atherosclerosis when no plaque ruptures or thrombosis are found

3. Have less stenotic coronary arteries, already in the uncomplicated stage of the disease, when no disruptions, fissures or thrombosis can be found in the coronary plaques. In the complicated stage of the disease, show larger areas of complicated lesions both in the aorta and in the coronaries

From these results we have summarized that the A2 allele of the Pl^A polymorphism is an important risk factor of SCD due to coronary thrombosis in early middle age and it may elicit its effect through alterations in endothelial, VSMC and platelet GPIIIa. The endothelial effect of the A2 allele of the Pl^A polymorphism may explain why coronary plaques of men with this variant are more vulnerable and prone to rupture, whereas the effect on platelet fibrinogen receptors may explain the increased risk of thrombus formation after abrupt changes in plaque geometry.

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Jussi Mikkelsson

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