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Review Article

Inherited and Acquired Thrombophilic Factors in Young Patients with Acute Coronary Syndrome or Ischemic Stroke

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Abstract

Cardiovascular disease is indisputably one of the most important health problems in the world. Cardiovascular disease is the number-one cause of disability and death in the United States. Despite important progress in diagnosis and prevention, cardiovascular diseases such as acute coronary syndrome, stroke, and peripheral vascular disease are responsible for disability and death at a stupefying rate. By 2030, researchers indicate that non-communicable diseases will account for more than three-quarters of deaths worldwide, and cardiovascular disease will be responsible for more deaths than infectious diseases, maternal and perinatal conditions, and nutritional disorders in low income countries. In order to reduce the morbidity and mortality related to cardiovascular disease, population-based strategies may be useful in patients with well established diseases but also for healthy subjects at high risk to developing cardiovascular disease. It has been recently hypothesized that individual polymorphisms may have less or no independent effect on venous or arterial thrombosis, but may act in synergy with other genetic or established factors predisposing to cardiovascular disease especially in young patients. The combination of inherited or acquired thrombophilic risk factors with the classical cardiovascular risk factors seems to increase significantly the risk to develop acute coronary syndrome or ischemic stroke in young patients. Therefore, a correct lifestyle decreasing the effect of classical cardiovascular risk factors could play a key role in reducing the incidence of cardiovascular disease and lowering the cost to cure million of patients every year in the world. In particular, a correct lifestyle is strongly recommended in young healthy subjects with inherited or acquired thrombophilic risk factors.

Keywords: Inherited thrombophilic factors; Acquired thrombophilic factors; Cardiovascular disease; Acute coronary syndrome; Ischemic stroke; Young patients; and Antiphospolipid antibodies

Abbreviations

ACS: Acute Coronary Syndrome; APA: Antiphospholipid Antibodies; ATF: Acquired Thrombophilic Factors; CRF: Cardiovascular Risk Factors; CVD: Cardiovascular Disease; ITF: Inherited Thrombophilic Factors; WHO: World Health Organization

Introduction

To date Cardiovascular Disease (CVD) is the most important single contributor to global mortality in the world and prospectively, it will continue to dominate mortality trends. By 2005, the total number of CVD deaths (acute coronary syndrome, stroke and rheumatic heart disease) showed an increment globally to 17.5 million from 14.4 million in 1990. Of these, 7.6 million were attributed to coronary heart disease and 5.7 million to stroke. More than 80 percent of the deaths occurred in low and middle income countries [1].

By 2030, prospective data indicate that non-communicable diseases will account for more than three-quarters of deaths worldwide and in particular CVD alone will be responsible for more deaths in low income countries than infectious diseases, maternal and perinatal conditions, and nutritional disorders combined [2,3].

Therefore, CVD may be considered the most important single contributor to mortality worldwide and it will remain still in dominance position in the future.

In order to reduce the morbidity and mortality related to cardiovascular disease, population-based strategies and cost-effective interventions accessible and affordable may be useful in patients with well established disease but also for healthy subjects at high risk to developing CVD.

A correct identification of Inherited Thrombophilic Factors (ITF) or Acquired Thrombophilic Factors (ATF) as risk factors for the developing of CVD especially in young patients, could allow to design effective strategies able to reduce significantly the cost to cure million of patients every year in the world.

Thrombophilia can be defined as an increased tendency towards thrombosis through enhanced coagulation and/or platelet aggregability. It comprises several rare inherited abnormalities, associated with thrombosis at a young age. Acute Coronary

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Syndromes (ACS) have intravascular thrombogenesis as their main pathogenetic mechanism, the latter being influenced by a complex interplay involving multiple genetic and environment factors related to atherosclerosis, thrombosis and their interaction [4]. The classical Cardiovascular Risk Factors (CRF) such as diabetes, hypercholesterolemia, hypertension, obesity, family history and smoking have been well characterized [5,6], while the role of thrombophilic conditions has been less well characterized [7].

It has been recently hypothesized that individual polymorphisms may have less or no independent effect on venous or arterial thrombosis, but they may act in synergy with other genetic or established factors predisposing to cardiovascular disease [8,9]. However, the synergistic effect of prothrombotic polymorphisms and traditional Cardiovascular Risk factors on the risk of CVD in young patients has so far been only partially investigated

Many studies provide conflicting data concerning the clinical importance of gene polymorphisms in the pathogenesis of arterial disease and myocardial infarction [10,11,12].

Inherited Thrombophilic Factors and Cardiovascular Disease

Among the single point genetic mutations evaluated, the main clinical manifestation of the *F*5 R506Q is deep venous thrombosis [13], while its role in arterial thrombosis has been only partially investigated. A study of 560 men under 70 years of age (mean age 56.2 years) with myocardial infarction, born in the Netherlands and living in the Leiden region, revealed a small increase in risk in carriers of *F*5 R506Q and *F*2 G20210A [10].

A single nucleotide change of glutamine to arginine was identified at position 20210 by Poort et al. in 1996 [14]. The presence of the abnormal gene is associated with increased circulating prothrombin levels. A preliminary study performed in 79 young women (18–44 years old) with myocardial infarction and 381 controls found an increased risk of myocardial infarction with this polymorphism (OR = 4.0; 95% CI = 1.1-15.1), especially in combination with other risk factors such as smoking [12].

More recent meta-analyses have confirmed a significant role of this prothrombin variant for coronary artery disease, particularly for ACS before 55 years of age with limited extent of coronary atherosclerosis at angiography [15]. Frost et al., in 1995, found a common C677T variant of the methylenetetrahydrofolate reductase (*MTHFR*) gene [16]. Increased levels of homocysteine have been linked with the TT homozygous genotype but have only been demonstrated when plasma folate values are low [17]. Some studies investigating a link between the *MTHFR* polymorphism and arterial thrombosis, in particular myocardial infarction, have shown an association [18,19] but other studies did not show a correlation [20,21]. Similarly, ischemic stroke did not seem to be linked with the *MTHFR* polymorphism, despite an association between the *MTHFR* variant and homocysteine levels [22,23].

The complex pathogenesis of thrombosis means that a single gene defect probably determines only a small effect; moreover, the impact of a given polymorphism will depend on gene–environment interactions that may be specific for a given cohort of patients.

Table 1: Results of stepwise logistic regression analysis of inherited thrombophilic and acquired cardiovascular risk factors for acute coronary syndrome.

Factor	Odds Ratio	SE*	95% CI†
F5 R506Q	6.84	5.6	1.37-34.02
Homocysteine	4.37	2.33	1.54-12.45
Hypertension	3.66	1.92	1.31-10.25
Hypercholesterolemia	6.31	3.29	2.27-17.55
Diabètes mellitus	10.04	8.91	1.76-57.17
Smoking habit	11	5.79	3.92-30.86

***SE:** Standard Error

A recent case-control study [24] was designed to evaluate the role of the most common ITF and ATF factors in the pathogenesis of ACS in young patients, and to evaluate whether the association with traditional cardiovascular risk factors could have an increased impact on the development of the disease. In this study the multivariate analysis confirmed a significant role of classical cardiovascular risk factors, such as smoking habit, hypertension, hypercholesterolemia and diabetes mellitus in the pathogenesis of ACS (Table 1). Moreover, pathological levels of homocysteine were a significant predictor of ACS in this group of young patients.

Additionally, this study that evaluated young patients residing in Italy, demonstrated an association between the presence of *F*5 R506Q and the risk to develop ACS. The difference prevalence of *F*5 R506Q reported in many studies could be due to the different distribution of this mutation in the world population. In fact, the *F*5 R506Q was not found in any of 1600 chromosomes of indigenous populations from Africa, Southeast Asia, Australasia and America, while a high prevalence was found among Europeans [25]. This study is in agreement with a previous study that evaluated young women (mean age 39.6 years) residing in contiguous counties of western Washington state, in which a significant risk of *F*5 R506Q for acute myocardial infarction has been reported [9]. Inherited prothrombotic factors could have a higher effect in young compared to older patients because atherosclerosis has had less time to progress [15,26]. In young patients with acute myocardial infarction, atherosclerosis is not always evident at angiography and classical cardiovascular risk factors are less frequent respect to older patients. Recently, *F*5 R506Q was associated with an increased risk of myocardial infarction in a large cohort of 1880 young Italian patients [27].

Role of the Association Between ITF or ATF and Traditional Cardiovascular Risk Factors

It has been recently hypothesized that individual polymorphisms may have less or no independent effect on venous or arterial thrombosis, but they may act in synergy with other genetic or established factors predisposing to cardiovascular disease [8,9]. However, the synergistic effect of prothrombotic polymorphisms and traditional cardiovascular risk factors on the risk of ACS in young patients has so far been only partially investigated.

The interaction of prothrombotic polymorphisms with the traditional CRF, in particular smoking habit, was associated to a significant rise in the risk of arterial thrombosis [28]. Moreover, the evaluation of three prothrombotic polymorphisms indicated only a mildly increased risk of acute myocardial infarction, but when the presence of one or more of the prothrombotic polymorphisms was

Table 2: Results of stepwise logistic regression analysis of cardiovascular risk factors and risk of ACS with and without the simultaneous presence of the evaluated prothrombotic polymorphisms.

Cardiovascular risk factors (CRF)	Inherited risk factors (IRF)	Patients	Controls	OR*	95	%	CI
No	No	4	42	1			
No	Yes	1	13	0.81	0.08	-	7.88
Yes	No	30	34	9.26	2.97	-	28.88
Yes	Yes	23	11	21.95	6.28	-	76.8

*All odds ratios are relative to the reference group, i.e. the group of patients who had neither CRF nor IRF. Age and sex-adjusted logistic regression led to similar results (for both ORs and 95% CIs). CRF = Cardiovascular Risk Factors, IRF: Inherited Thrombophilic Factors

evaluated in combination with the classical CRF, the estimated risk increased nine fold with hypertension, hypercholesterolemia, or diabetes and almost 18-fold with current smoking [8]. These results are in agreement with the study of Roosendaal et al in which the effect of a similar association was found in a group of young women with myocardial infarction [9].

In a more recent study, Dragoni et al [24] found an additional effect of the combination between ITF and CRF supporting a role of specific gene-environment interactions on the risk of developing ACS (Table 2). These data indicated that the association between ITF and traditional CRF seems to increase further the risk to develop ACS in young patients.

As to the role of acquired thrombophilic risk factors, the lupus anticoagulant has been indicated as a major risk factor for arterial thrombotic events (myocardial infarction and ischemic stroke) in young women and the association of lupus anticoagulant with the traditional CRF was associated with a higher risk to develop CVD [29].

It is interesting to note that in very young patients less than 40 years old with a mean age of 26.6 years without cardiac pathologies, multivariate analysis selected the presence of Antiphospholipid Antibodies (APA) as significant factor associated with an increased risk to develop acute ischemic stroke [30]. Moreover, in this group of young patients classical CRF, evaluated singularly, had not effect in the developing of acute ischemic stroke while combining them with the APA has increased the risk significantly (Table 3). It is interesting to note that APA can be found also in healthy subjects with a prevalence ranging from 1 to 5% and this prevalence seems to be higher with ageing [31]. Therefore, an association between APA and classical CRF could be frequent also in normal healthy subjects.

These data reinforce the hypothesis that CVD is a multi factorial disease and that the association between ITF or ATF with classical CRF seems to increase significantly the risk to develop these pathologies. Therefore, in young patients with acute coronary syndrome or ischemic stroke could be useful to perform a thrombophilic screening in order to point out the presence of inherited or acquired thrombophilic factors. The identification of single point genetic mutation predisposing to thrombosis in affected subjects would permit also to carry out a family study in order to identify the same mutation in the relatives, and consequently to select normal subjects, still in good health, with an increased risk to develop CVD.

It is interesting to note that, while the presence of ITF is a congenital condition, the effect of CRF such as overweight, hypertension, hypercholesterolemia, diabetes and smoking habit

Table 3: Combined effects on ischemic stroke of the association between Antiphospolipid Antibodies (APA) and cardiovascular risk factors.

Factors	*OR*	95 % C.I.
		Lower-Upper
Association of APA and cardiovascular risk factors	29.31	3.28-261.69
Sex	1.91	0.82-4.43
Age	1	0.94-1.06

could be significantly modified by a specific therapy and by a correct lifestyle. Therefore, in young subjects with no prior history of coronary heart disease or acute ischemic stroke who have inherited or acquired thrombophilic factors, a correct lifestyle avoiding the additional effect of one or more traditional CRF could really reduce the risk of developing CVD.

A sedentary lifestyle characterized by an insufficient physical activity is one of the 10 leading risk factors for global mortality. People who are sedentary have a 20% to 30% increased risk of all-cause mortality compared to subjects who practice moderate physical activity for at least 150 minutes per week as recommended by the World Health Organization (WHO) [32]. The practice of moderate-intensive aerobic physical activity for a total of 150 minutes each week is estimated to reduce the risk of ischemic heart disease by approximately 30%, the risk of diabetes by 27%, and the risk of breast and colon cancer by 21–25%. Additionally, it lowers the risk of stroke, hypertension, and depression. Globally in 2010, 23% of adults aged 18+ years were insufficiently active (men 20% and women 27%).

As a consequence of reduced physical activity, the worldwide prevalence of obesity in infants and children increased between 1980 and 2008.

According to country estimates for 2008, over 50% of both men and women in the WHO European Region were overweight, and about 20% of them were obese [33].

It is important to outline that childhood obesity is a severe risk factors for cardiovascular disease, type 2 diabetes, orthopedic problems and mental disorders.

WHO recommendations for preventing and managing obesity [33] outline the need for coordinated projects to indicate a correct lifestyle, adequate diet and to increase the everyday levels of physical activity in order to prevent the occurrence of classical cardiovascular risk factors.

The primary prevention of acute coronary syndrome and acute ischemic stroke is essential because, even if antithrombotic treatment is effective in these patients, the recurrence of these diseases is

common after a first event and it is associated with increased morbidity and mortality [34]. The combination of inherited or acquired thrombophilic risk factors with the classical cardiovascular risk factors seems to increase significantly the risk to develop acute coronary syndrome or ischemic stroke in young patients. A correct lifestyle is essential to reduce the incidence of CVD and to decrease the cost to cure million of patients every year in the world. Moreover, a correct lifestyle is strongly recommended in healthy subjects with inherited or acquired thrombophilic risk factors.

Conclusion

Some individual polymorphisms may have less or no independent effect on venous or arterial thrombosis, but they may act in synergy with other genetic or established factors predisposing to cardiovascular disease especially in young patients. Classical cardiovascular risk factors such as diabetes, hypercholesterolemia, hypertension, obesity, family history and smoking have been well characterized, and they seem to play a key role also in young patients with CVD.

Moreover, the combination of inherited or acquired thrombophilic risk factors with the classical cardiovascular risk factors seems to increase significantly the risk to develop acute coronary syndrome or ischemic stroke in young patients. As a consequence, a correct lifestyle decreasing the effect of classical cardiovascular risk factors could play a key role in reducing the incidence of cardiovascular disease and in decreasing the cost to treat million of patients every year in the world. In particular, since the young healthy subjects with inherited or acquired thrombophilic risk factors seem to have a higher risk to develop CVD, a correct lifestyle is strongly recommended in these subjects. Therefore, there must be an educational and training course for young people and the government, the family and the school are in the forefront in order to obtain these objectives.

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