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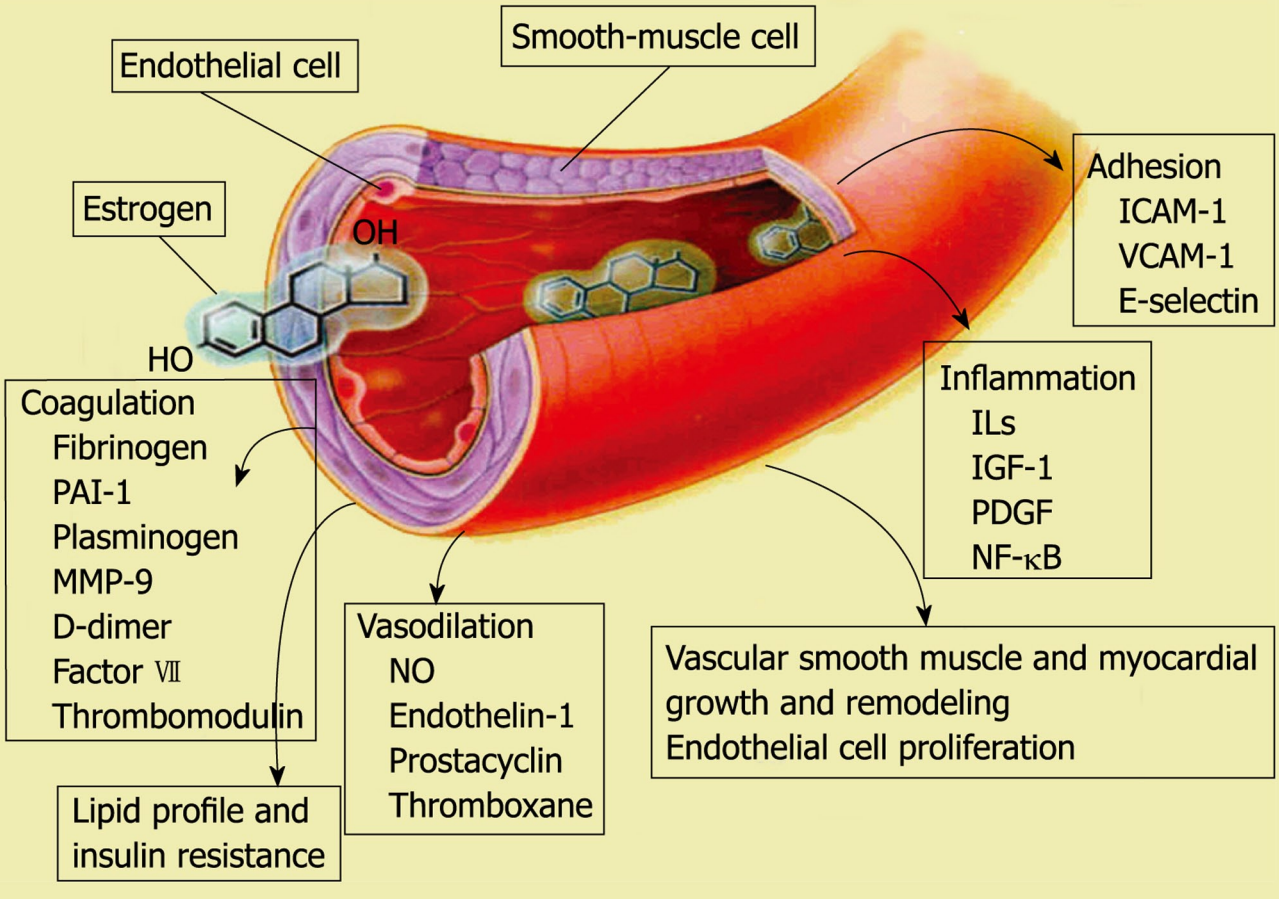

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Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
Editorial Board of *World Journal of Cardiology*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-5908-0036
Fax: 0086-10-8538-1893
E-mail: wjc@wjgnet.com
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Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
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SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1892
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EDITORIAL OFFICE
Li Ma, Director
World Journal of Cardiology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-5908-0036
Fax: 0086-10-8538-1893
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EDITORIAL

What is the purpose of launching *World Journal of Cardiology*?

Lian-Sheng Ma

Lian-Sheng Ma, Beijing Baishideng BioMed Scientific Co., Ltd., Room 903, Building D, Ocean International Center, No.62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Author contributions: Ma LS solely contributed to this paper.
Correspondence to: Lian-Sheng Ma, Professor, President and Editor-in-Chief, Beijing Baishideng BioMed Scientific Co., Ltd., Room 903, Building D, Ocean International Center, No.62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China. l.s.ma@wjgnet.com
Telephone: +86-10-59080036 Fax: +86-10-85381893
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Abstract

The first issue of *World Journal of Cardiology* (*WJC*), whose preparatory work was initiated on December 13, 2009, will be published on December 31, 2009. The *WJC* Editorial Board has now been established and consists of 313 distinguished experts from 40 countries. Our purpose of launching *WJC* is to publish peer-reviewed, high-quality articles *via* an open-access online publishing model, thereby acting as a platform for communication between peers and the wider public, and maximizing the benefits to editorial board members, authors and readers.

Key words: Maximization of personal benefits; Editorial board members; Authors; Readers; Employees; *World Journal of Cardiology*

Peer reviewer: Alberto Cuocolo, MD, Professor, Department of Biomorphological and Functional Sciences, University Federico II, Via Pansini 5, 80131 Napoli, Italy

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INTRODUCTION

I am very pleased to announce that the first issue of *World Journal of Cardiology* (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330), whose preparatory work was initiated on August 13, 2009, will be published on December 31, 2009. The *WJC* Editorial Board has now been established and consists of 313 distinguished experts from 40 countries. What is the purpose of launching *WJC*? And what is the scope and how are the columns designed?

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. To realize these desired attributes of a journal and create a well-recognized journal, the following four types of personal benefits should be maximized.

MAXIMIZATION OF PERSONAL BENEFITS

The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others.

Maximization of the benefits of editorial board members

The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution.

Maximization of the benefits of authors

Since *WJC* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJC* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading.

Maximization of the benefits of readers

Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion[1].

Maximization of the benefits of employees

It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal[2,3]. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJC* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

SCOPE

The major task of *WJC* is to rapidly report the most recent developments in the research by the cardiologists. *WJC* accepts papers on the following aspects related to cardiology: arrhythmias, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, paediatrics, nursing, and health promotion. We also encourage papers that cover all other areas of cardiology as well as basic research.

COLUMNS

The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (8) Original Articles: To originally report the innovative and valuable findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce Consensuses and Guidelines reached by international and national academic authorities worldwide on the research in cardiology.

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wjc@wjgnet.com
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EDITORIAL

Cardiovascular disease: A global problem extending into the developing world

Temilolu Olayinka Aje, Michael Miller

Temilolu Olayinka Aje, Michael Miller, Division of Cardiology, Department of Medicine, University of Maryland School of Medicine, Rm S3B06, 22 South Greene St., Baltimore, MD 21201, United States
Author contributions: Aje TO wrote the manuscript; Miller M edited and revised the manuscript.
Correspondence to: Michael Miller, MD, Division of Cardiology, Department of Medicine, University of Maryland School of Medicine, Rm S3B06, 22 South Greene St., Baltimore, MD 21201, United States. mmiller@medicine.umaryland.edu
Telephone: +1-410-3286299 Fax: +1-410-3284382
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Abstract

This article reviews the current status of cardiovascular disease (CVD) on the international scale. Presently viewed as an epidemic that has migrated from westernized societies to developing countries, several important issues are elaborated upon. They include the basis for the increasing prevalence of CVD and the associated societal implications. The challenges related to lack of resources and infrastructure support may also impede successful implementation of proven strategies to reduce CVD. In addition to traditional risk factors such as cigarette smoking, hypertension, obesity, hyperlipidemia, diabetes mellitus and insulin resistance, many developing countries must also contend with other risk biomarkers. Included in this grouping are human immunodeficiency virus/acquired immunodeficiency syndrome and other infectious/inflammatory processes as well as nutritional and vitamin deficiencies that make preventive measures more difficult to prioritize. Taken together, greater partnering between local governments, affiliated hospitals and international societies is needed to enhance and facilitate efforts aimed at optimizing standard of care measures in developing countries in order to reduce cardiovascular risk.

Key words: Heart disease; Developing world; Epidemic; Risk factors; Urbanization; Prevention

Peer reviewers: Serafino Fazio, Associate Professor of Internal Medicine, Department of Internal Medicine, Cardiovascular and Immunologic Sciences, University Federico II, Via S. Pansini 5, 80131 Naples, Italy; Jun R Chiong, MD, MPH, FACC, FCCP, Associate Professor of Medicine, Director, Advanced Heart Failure Program, Loma Linda University, 11234 Anderson Street, Suite 4404, Loma Linda, CA 92354, United States

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CARDIOVASCULAR DISEASE - A GLOBAL PROBLEM

Cardiovascular disease (CVD) has typically been viewed as an affliction of wealthy, industrialized societies. In fact, during the past century minimal if any effort aimed at cardiovascular (CV) prevention has been allocated to developing countries. This in part reflected the higher prevalence of infectious diseases that provided the rationale for not investing time and resources toward chronic diseases. However there is an emerging body of data suggesting that this policy may not only be erroneous but also dangerous. Based upon statistics by the World Health Organization, approximately 80% of the 17 million CV deaths worldwide in 2003, occurred in developing countries[1].

As shown in Figure 1, CVD represents the number one cause of death in all regions except for sub-Saharan Africa; however when the analysis extends beyond adults aged 30 years and older, CVD is number one cause of death in all regions[2].

These findings in Figure 2 raise a number of questions: (1) Why is CVD so prevalent in developing countries? (2) What are the implications of this prevalence? (3) Why has there not been as strong a focus on controlling this epidemic? and (4) What can be done to control this continuing epidemic?

EPIDEMIOLOGICAL AND NUTRITION TRANSITION

It is widely believed that there are 4 stages of epidemiological transition, ranging from famine and pestilence (stage 1) to degenerative diseases (stage 4). In terms of overall health, each country falls somewhere along this spectrum. Sub-Saharan Africa is the main region that falls under the first stage, while stage 4 regions are the more industrialized nations. Emerging outcomes data now suggest a trend towards stage 4 even for less industrialized countries. While communicable diseases such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), tuberculosis, and malaria continue to be associated with high mortality rates, especially in developing countries, considerable progress has been made during the past decades to reduce the burden of disease resulting from these conditions. Consequently, a more favorable prognosis has been achieved in affected infants who are now more likely to survive into adulthood. The ensuing survival rates in turn increase the exposure to risk factors such as cigarette smoking that alters the shift toward enhanced CV risk. Another factor to be considered is the "early malnutrition wars" and their casualties. For example, Amuna *et al*[4] have hypothesized that exposure of fetuses to early malnutrition led to adaptation to a "thrifty phenotype". However, when exposed to a more affluent environment and greater caloric means, these "super efficient" specimens are less able to metabolize the nutrients (i.e. fats) that they are exposed to. With increased energy intake at the expense of expenditure, increased fat storage in adipose tissue, skeletal muscle, heart and liver may lead to metabolic dysregulation resulting in inflammation, insulin resistance (IR), metabolic syndrome and increased risk of CVD. An alternative explanation is that there has been a significant increase in the rate of urbanization in most developing countries (Figure 3 below). The result of urbanization is a more frequent exposure to CV related risk factors.

Once in these urban areas, diet and lifestyle changes adopted include high caloric food intake combined with a sedentary lifestyle. With this combination, there has been an appreciable jump in the prevalence of CV disease risk factors. Some of the forces that drive people towards high caloric foods include time constraints (forced to eat on the go), strong advertising and availability[6]. Similar forces come into play when considering the adoption of sedentary lifestyles.

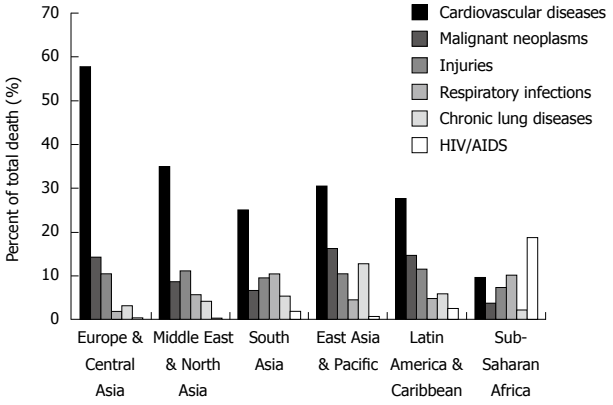

Figure 1 Cause of death by percentage in each region[2].

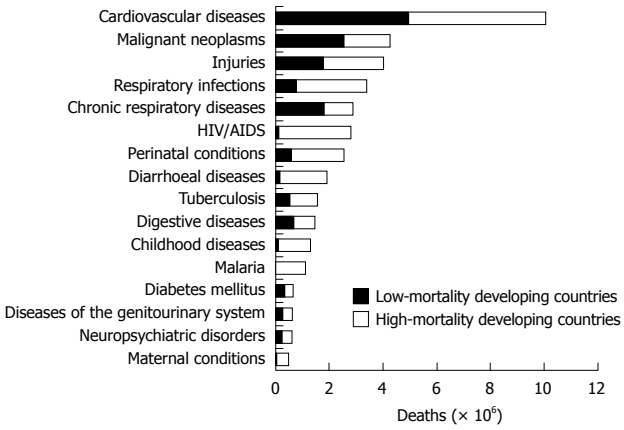

Figure 2 Deaths attributable to 16 leading causes in developing countries, 2001[3].

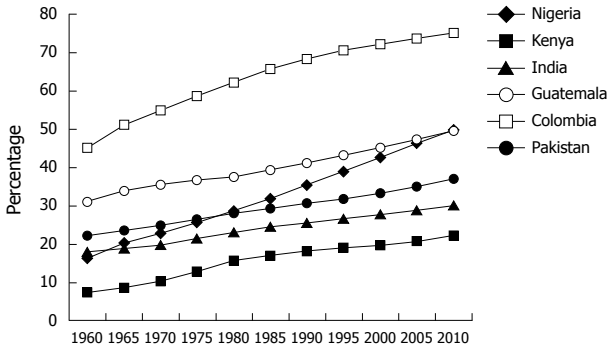

Figure 3 Trends of urban populations in developing countries[5].

RISK FACTORS

A decades worth of studies have identified risk factors for CVD, the more prevalent ones being hypertension, smoking, obesity (due to poor diet and/or lack of physical activity), hyperlipidemia and genetic predisposition. If there is truly an increase in the prevalence of CVD, one should naturally expect that there has been an increase in one or more of these risk factors. The data supporting this will be explored further.

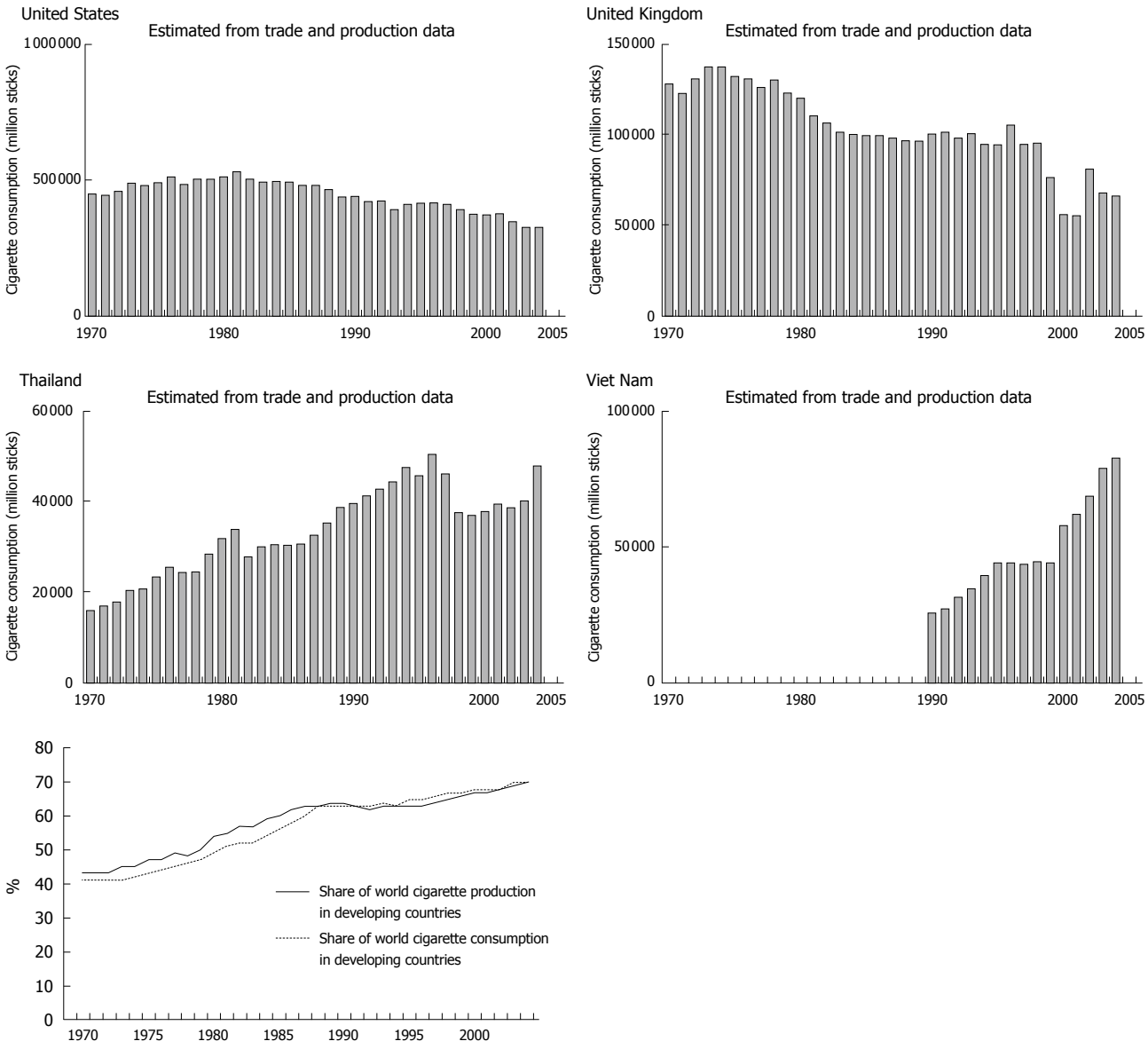

Figure 4 Cigarette consumption in select countries-comparing industrialized to non-industrialized countries[8,9].

Smoking

Tobacco use has been established as a risk factor for CVD since the 1940s. This includes both active and passive use[7]. Due to aggressive anti-smoking campaigns, tobacco use has declined significantly in the United States over the past 40 years[8]. Unfortunately, the trend has been the reverse in developing countries (Figure 4).

The reasons for this increase in tobacco use include but are not limited to, urbanization and aggressive marketing by tobacco companies, especially in light of strict regulations in developed countries forcing these companies to shift their business practices elsewhere. Of particular concern is the fact that young women who are typically less likely to smoke are viewed as an untapped market and are heavily targeted[10].

Hypertension

It is difficult to assess the degree to which there has been an increase in the prevalence of hypertension in most developing countries because there are few studies. However there are studies demonstrating the high levels of prevalence today. To support the argument that it is associated with urbanization, numerous studies have demonstrated the difference in prevalence between urban and rural areas. For instance, in Mozambique, the prevalence of hypertension amongst adults is about 33%, while the odds ratio (OR) of hypertension being more frequent in urban areas compared to rural was 2 [95% confidence intervals (CI): 1.2-3][11]. Fezeu *et al*[12] identified an increase in the blood pressure of adults in Cameroon over a 10-year period (Table 1).

Hypertension is also highly prevalent in Latin America-prevalence rates ranging from 8.6% to as high as 29% of the adult population based on the city[13]. Pre-hypertension has also been assessed in a number of studies, with prevalence rates ranging from 30% in Jamaican adults[14] to as high as 34% in Taiwanese adults[15].

Table 1 Difference in systolic blood pressure (SBP) over 10-year period in Cameroon

Increase in SBP	Women	Men	*P*
Rural setting (mmHg)	18.2	18.8	< 0.001
Urban setting (mmHg)	8.2	6.5	< 0.001

Table 2 Change in obesity prevalence over a 10-year period in Asian countries[17] (%)

Country	1996	2006
Bangladesh	2.7	8.9
Nepal	1.6	10.1
India	10.6	14.8

Obesity

Obesity is an intriguing and paradoxical CV risk biomarker in developing countries. This is because in developing countries such as Sub-Saharan Africa, epidemics of famine that culminate in malnutrition are believed to predominate. However, urbanization of some regions has in fact induced higher obesity rates. Amongst Cameroonian adults (older than 15), 21.6% of men are overweight. The number is higher amongst women at 28.6%. The prevalence of obesity is high as well - 6.5% in men, 19.5% in women[16]. Abubakari *et al*[17] found an approximate 10% rate of obesity in West Africa. Furthermore, in Cameroon, women were more likely to be obese (OR: 3.16, 95% CI: 2.51-3.98). To further support the theory that urbanization plays a significant role in West Africa, prevalence rates of obesity were compared in urban and rural settings. Not surprisingly, urban residents were 2.7 fold more likely to be overweight[18]. Although, it may be difficult in some developing countries to establish changes in the prevalence of obesity due to a lack of baseline comparison data, some studies have been able to demonstrate such increases. For example, in South Asian women, significant increases in obesity rates were identified between 1996 and 2006, as described in Table 2.

Lipids

Hyperlipidemia has long been associated with the development of CVD in industrialized nations[19]. There has been an increase in the prevalence of hyperlipidemia in developing countries that can partly be attributed to urbanization - some reports have demonstrated a higher prevalence in urban *vs* rural areas[20]. In rural China, greater than 30% of adults older than 35 years of age have total cholesterol levels greater than 200 mg/dL. Elevated LDL (greater than 130 mg/dL) ranged from 13.8% of adult males to 17.2% of adult females[21]. Amongst Latin American populations, the prevalence of hypercholesterolemia varied from 6%-20% depending on the city[13]. For comparison, the prevalence of elevated total cholesterol (> 240 mg/dL) in US adults from 2003-2006 was 16.3%[22].

Diabetes

This is another CV risk factor that has become more prevalent in developing countries in recent years. A 2008 review found an increase in the prevalence of diabetes in Nigeria and Ghana. From 1963 to 1998, the prevalence rose from 0.2% to 6.3% of the adult Ghanaian population while amongst Nigerians, the prevalence rose from 1.65% to 6.8% from 1985 to 2000[23]. Not only has there been a rise in the prevalence of diabetes in developing countries, but further increases have been projected in selected regions (i.e. Latin America)[24]. A number of studies have also described a significant prevalence in parts of Asia as well[25,26].

IR

Current data indicate a worldwide surge in the prevalence of diabetes, with particularly worrisome rates in the developing world. As concerning as these new data are, even more concerning is the prevalence of IR, particular among young people. IR is another risk factor that is linked to the progression of CVD, both as an independent risk factor[27] as well as through its association with other risk factors such as obesity and hypertension. The link between IR and CVD is thought to occur through two processes known to be associated with CVD, namely hyperuricemia[28] and inflammation[29]. With this said, is IR a problem in developing countries? Amongst Bolivian children, the prevalence of IR was 39.4%[30]. In another study of obese Chinese children, 77% of the study participants were insulin resistant[31]. The fact that levels this high are being seen in children is more concerning when one considers that these numbers, without early intervention, are only going to rise as they grow into adulthood.

NON-TRADITIONAL RISK FACTORS

Management of CVD in developing countries presents a unique challenge. Because the majority of the limited available resources are devoted to communicable diseases, convincing evidence would need to be provided to justify resource diversion for CV prevention. Among the considerations would be whether the top causes of mortality within developing countries, including respiratory infections, HIV/AIDS, malnutrition and emotional stress, feature prominently in CV risk assessment.

HIV/AIDS

There are an estimated 33 million people living with HIV worldwide and 67% of affected subjects reside in Sub-Saharan Africa[32]. Observational data have linked HIV to coronary artery disease (CAD) (Figure 5).

Endothelial dysfunction is a critical early stage in the development of atherosclerosis. In addition to traditional CV risk factors[34], there is also evidence to implicate HIV in promoting endothelial cell dysfunction. This may occur through several postulated mechanisms. They include the HIV directly activating pro-inflammatory cytokines and

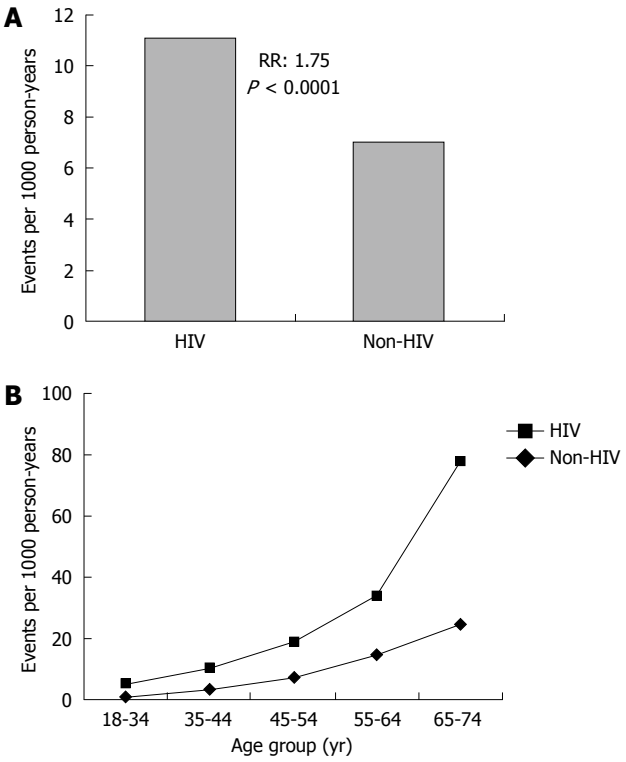

Figure 5 Association between coronary events and human immunodeficiency virus (HIV)[33]. A: Myocardial events amongst patients grouped by HIV-infection status; B: Myocardial events grouped by age. Light line represents HIV positive patients, dark line represents patients without HIV.

procoagulant proteins as well as increasing endothelial cell adhesiveness and apoptosis resulting in endothelial cell damage[35]. Another mechanism may be through the use of highly active antiretroviral therapy. For example, abacavir and didanosine have been associated with increased risk of myocardial infarction (MI) (OR: 1.89, 95% CI: 1.47-2.45 and OR: 1.49, 95% CI: 1.14-1.95) within 6 mo of use[36].

Other infections as risk factors

Due to poor sanitation, close living quarters and low socio-economic status, there remains a high prevalence of infectious pathogens and in part explains the higher prevalence of mortality due to respiratory infections in developing countries. Might any of these pathogens also be linked to elevated CV risk? The influenza virus is a common pathogen worldwide and has been shown to be prevalent amongst children in developing countries[37,38]. This becomes significant when one considers that a history of being infected with influenza A or B (determined by the presence of IgG antibodies) is associated with an increased risk of myocardial infection[39]. Another pathogen that has been associated with the development of CV disease is *Chlamydia pneumonia*[40]. Other pathogens that have been linked to CAD include *Mycoplasma pneumonia* and *Helicobacter pylori*. Nevertheless, more research into the direct causality link between pathogens and development of CVD is warranted.

Vitamin D, B12 and folate

Vitamin D deficiency has been observed in limited studies in populations of people in developing countries[41-43]. Yet despite the fact that some developing countries are in tropical regions (with a lot of sun exposure), a high prevalence of Vitamin D deficiency exists; low vitamin D levels have been associated with increased coronary calcification[44]. Hyperhomocysteinemia and vitamin B12 deficiency have also been linked to development of CVD[45]. B12 is usually obtained from meat products, which in most developing countries may be relatively sparse. Folate is a co-factor in the homocysteine metabolism pathway and it has been proposed that its deficiency can also result in disease in a manner analogous to B12 deficiency. As adequate folic acid levels may be difficult to attain, most developed countries have policies in place that mandate fortification of certain foods with folate. Unfortunately, these policies are absent in developing countries, resulting in high prevalence of folate deficiency.

Psychosocial factors

Amongst Congolese children, greater than 50% meet the symptom criteria for Post Traumatic Stress Disorder (PTSD)[46], while in responders of an Afghanistan survey greater than 20% met criteria for PTSD[47]. Depression has been observed in about a quarter of Brazilian women infected with the HIV[48]. These examples demonstrate the prevalence of psychosocial stressors within the developing world and become more problematic when one considers the association between psychosocial disease and CVD. Specifically, the INTERHEART study[49] examined the association between "stress factors" (stress at work and at home, financial situation and major life events) and acute MI. The OR between cases (people with MI) and controls, depending on the stressor, ranged from 1.38 to 2.17. In addition, depression has been described as a risk factor for CAD[50] and while confounders such as smoking may promote this process, there are direct pathophysiological considerations such as platelet dysfunction and systemic inflammation that may accentuate CV risk.

IMPLICATIONS OF INCREASED PREVALENCE OF CVD RISK FACTORS/ CVD

Although data support increased CV risk in developing countries, what are the potential strategies and implications that should be focused upon? Unfortunately, few developing countries are sufficiently equipped to handle medical emergencies such as acute MI and stroke due to lack of resources and trained personnel. Another effect of a CV epidemic is loss of manpower due to earlier onset of disease (by an average of 10 years). In fact, in developing countries (i.e. India) more than 50% of CV deaths occurred before 70 years of age as compared to less than 25% of CV deaths in developed countries[51].

There are a variety of reasons why healthcare policies are geared towards infectious diseases. First, the pediatric population is at high risk and is accompanied by a strong visceral response to treat urgently. In contrast, CV disease is viewed as a chronic process that can be controlled at a personal level.

CONTROLLING CV DISEASE IN DEVELOPING COUNTRIES

Despite the increased prevalence of CV risk factors in developed countries, the first half of this decade saw a peak and decline in CV related mortality[52], related in part to risk factor modification. Nonetheless, developing countries present an uncommon scenario as policies that have worked in developed countries may not be applicable. Thus, the ideal approach may be a dual one - identifying proven strategies in developed countries and then modifying them as necessary for the individual country being targeted.

Prevention at the population level

The most obvious risk factor that should be targeted at this level is smoking. One approach might be to increase taxation of tobacco products and use the extra revenue gained to fund such programs. Another population based prevention strategy is developing national food guidelines/recommendations. Most countries have distinctive cuisines and developing guidelines that incorporate locally grown and healthy products are more likely to be accepted by the general populace. This is of particular importance considering the globalization of Western world fast food chains. The higher prevalence of CV risk factors in urban *vs* rural areas should be considered when it comes to implementing national health guidelines because it presents an opportunity to implement change before risk factors become more prevalent in rural areas. For example, should fortification (as done in Westernized regions) with folate be incorporated into food products?

Primary prevention

Screening people who may be at high risk for CV disease may forestall the progression to advanced disease. In developing countries where the prevalence of psychosocial stressors is high, routine screening for PTSD and depression ought to be considered. In some countries, there is a shortage of physicians in general (including specialists), hence the primary care approach could be modified for use by non-physicians as primary care providers. Bischoff *et al*[53] has suggested that nurse based care would be an appropriate approach in Cameroon - this could be extended to other parts of Sub-Saharan Africa as well. Upon identifying those at risk, the next issue becomes how to manage them. How do we deliver cost effective therapies to those in need? Standardized recommendations need to be developed for each country. For instance, should we recommend a standard 3-mo trial of diet and exercise after identifying risk factors in a patient, and due to the cost of medications, should primary care providers be more aggressive with this approach if necessary?

Secondary prevention

Post MI and post stroke care should be placed on standard of care regimens based upon clinical outcome data when feasible. However, due to the high cost of medications, unique combinations of appropriate medicines that balance cost and quality adjusted life years need to be developed for each region. For instance giving just aspirin and β-blocker while sub-standard may be more cost effective than aspirin, β-blocker, angiotensin converting enzyme-inhibitor and statin (standard post MI regimen)[2]. Another factor that needs to be addressed when it comes to secondary prevention is the availability of emergency care resources. A model that could be implemented is a partnership between local hospitals and hospitals in developed countries, whereby physicians from developed countries travel to developing countries to teach local personnel how to use donated equipment.

Overall, there is clearly a need for more research in the field of CV disease in developing countries. The data regarding traditional and, to a lesser degree, non-traditional risk factors however is limited. Research should be geared towards identifying the unique factors that are at play in the developing world. This is especially important because most developing countries are still reeling from communicable disease epidemics and would only be further crippled by a CV epidemic.

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EDITORIAL

Present concepts in management of atrial fibrillation: From drug therapy to ablation

Giovanni B Forleo, Luca Santini, Francesco Romeo

Giovanni B Forleo, Luca Santini, Francesco Romeo, Division of Cardiology, Department of Internal Medicine, University of Rome "Tor Vergata", Viale Oxford, 81, 00133 Rome, Italy
Author contributions: Forleo GB and Santini L wrote the paper; Romeo F revised the paper critically for important intellectual contents.
Correspondence to: Francesco Romeo, Professor, MD, Director, Division of Cardiology, Department of Internal Medicine, University of Rome "Tor Vergata", Viale Oxford, 81, 00133 Rome, Italy. romeocerabino@tin.it
Telephone: +39-6-20904009 Fax: +39-6-20904043
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Abstract

Atrial fibrillation (AF) management requires knowledge of its pattern of presentation, underlying conditions, and decisions about restoration and maintenance of sinus rhythm, control of the ventricular rate, and anti-thrombotic therapy. Maintenance of sinus rhythm is a desirable goal in AF patients because the prevention of recurrence may improve cardiac function, relieve symptoms and reduce the likelihood of adverse events. Anti-arrhythmic drug therapy is the first-line treatment for patients with paroxysmal and persistent AF based on current guidelines. However, currently used drugs have limited efficacy and cause cardiac and extracardiac toxicity. Thus, there is a continued need to develop new drugs, device and ablative approaches to rhythm management. Additionally, simpler and safer stroke prevention regimens are needed for AF patients on life-long anticoagulation, including occlusion of the left atrial appendage. The results of the Randomized Evaluation of Long-Term Anticoagulant Therapy study are encouraging in these settings. Knowledge on the pathophysiology of AF is rapidly expanding and identification of focally localized triggers has led to the development of new treatment options for this arrhythmia. Conversely, the clinical decision whether to restore and maintain sinus rhythm or simply control the ventricular rate has remained a matter of intense debate. In the minority of patients in whom AF cannot be adequately managed by pharmacological therapy, the most appropriate type of non-pharmacological therapy must be selected on an individualized basis. Curative treatment of AF with catheter ablation is now a legitimate option for a large number of patients. The evolution of hybrid therapy, in which two or more different strategies are employed in the same patient, may be an effective approach to management of AF. In any case, planning a treatment regimen for AF should include evaluation of the risks inherent in the use of various drugs as well as more invasive strategies.

Key words: Antiarrhythmic medications; Atrial fibrillation; Catheter ablation

Peer reviewers: Jonathan S Steinberg, MD, Chief, Division of Cardiology, Al-Sabah Endowed Director, Arrhythmia Institute, St. Luke's and Roosevelt Hospitals, Professor of Medicine, Columbia University College of Physicians & Surgeons, 1111 Amsterdam Ave, New York, NY 10025, United States; Mehmet Ozaydin, Associate Professor, Sevket Demirel Kalp Merkezi, 32100, Isparta, Turkey; Klaus Kettering, MD, Department of Cardiology, University of Mainz, Langenbeckstrasse 1, D-55131 Mainz, Germany

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance seen in clinical practice[1], accounting

for approximately one-third of hospitalizations for this condition. AF may occur in isolation or in association with structural heart disease, contributing substantially to cardiac morbidity and mortality. The estimated prevalence of AF is 0.4%-1% in the general population, increasing with age[2,3], and it is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality, especially in women[4,5]. Although there are clear guidelines for the acute management of symptomatic AF[6,7], the best long-term approach for patients with a first or recurrent AF is still debated with regard to quality of life, risk of re-hospitalizations, and possible disabling complications, such as thromboembolic stroke, major bleeding, and death. Management of patients with AF requires knowledge of its pattern of presentation (paroxysmal, persistent, or permanent), underlying conditions, and decisions about restoration and maintenance of sinus rhythm, control of the ventricular rate, and anti-thrombotic therapy. The goal of treatment is to reduce symptoms and risk of thromboembolic events and to avoid tachycardia-induced unfavorable myocardial remodeling. As epidemiological studies shed light on the importance of AF, treatment progressed from the occasional use of cardiac glycosides, such as digoxin to control ventricular rate, to the use of powerful anti-arrhythmic drugs which has been the mainstay of AF treatment for decades. Regardless of the strategy initially chosen, attention must also be directed to anti-thrombotic therapy for prevention of thromboembolism.

ANTI-THROMBOTIC STRATEGIES FOR PREVENTION OF ISCHEMIC STROKE AND SYSTEMIC EMBOLISM

Pharmacologic agents

AF is associated with substantial morbidity and mortality, mostly due to the consequences of thromboembolism. Currently, acetylsalicylic acid (a platelet inhibitor) and vitamin K antagonists, including Warfarin, are the only approved anti-thrombotic agents for stroke prevention in patients with AF. Although there is modest benefit from anti-platelets agents, randomized trials have shown that it is consistently and substantially less effective than vitamin K antagonists[8]. Patients with AF who are at low risk for stroke or who have contraindications to Warfarin should take aspirin 81 to 325 mg daily[6]. In high-risk patients with non-valvular AF, anticoagulation with Warfarin is recommended to reduce the risk of stroke and thromboembolic events[9].

It is crucial to estimate the risk of stroke before deciding the anticoagulation therapy for individual AF patient. The threshold risk that warrants anticoagulation is still controversial. To stratify the risk of ischemic stroke in AF patients and to identify patients who benefit most and least from anticoagulation, several clinical schemes have been proposed[10]. An easy score to estimate the risk of stroke in such patients is the CHADS2 risk score. It is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age over 75 years, a history of hypertension, diabetes, or recent heart failure. According to guidelines[6], aspirin is recommended in low-risk patients with a CHADS2 score of 0. In high-risk patients with a CHADS2 score $\geqslant$ 2, only oral anticoagulant therapy is recommended. In intermediate risk patients with a CHADS2 score of 1, physicians can choose between aspirin and warfarin depending on the individual patient.

For primary and secondary prevention in most AF patients under age of 75 years, an INR of 2.5 (target range, 2.0-3.0) is recommended. A target INR of 2.0 (target range, 1.6-2.5) seems reasonable for primary prevention in patients older than 75 years who are considered at high risk of bleeding.

While the available vitamin K antagonists are highly effective for the prevention and/or treatment of most thrombotic diseases, the significant inter- and intra-patient variability in dose-response, the narrow therapeutic index, and the numerous drug and dietary interactions associated with these agents have led clinicians, and investigators to search for alternative agents.

Three new orally administered anticoagulants (apixaban, dabigatran and rivaroxaban) are in the late phase of development and several others are still in the (or moving through) early phase of investigation. Direct thrombin inhibitors are new oral agents with predictable efficacy, rapid onset of action and no need of laboratory monitoring. According to the results of the Randomized Evaluation of Long-Term Anticoagulant Therapy trial[11], Dabigatran etexilate, an oral thrombin inhibitor, showed similar efficacy to Warfarin in reducing stroke and embolism (primary outcome) at the dose of 110 mg, but lowered the rate of major hemorrhage by 20%. In contrast, higher doses (150 mg) of Dabigratan were more effective than Warfarin in reducing the primary outcomes, but had similar rates of major hemorrhage. Therefore, the two effective doses, with different benefit risk profiles, make it possible to tailor the therapy to individual patient.

Although the only adverse effect of Dabigratan was dyspepsia, many aspects of the therapy are still controversial. First, while the Dabigratan doses were blinded, patients with at least one risk factor for stroke received Warfarin (open-label). Compared with Warfarin (0.53% per year), the rate of myocardial infarction was higher in - Dabigratan-treated group (0.72% per year at dose of 110 mg and 0.74% at 150 mg). Finally, the price of Dabigratan is 10 times higher than the Warfarin.

Also questionable is the the addition of clopidogrel to aspirin in patients considered unsuitable for warfarin therapy. The results of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events[12], which is the largest trial ever performed in patients with AF who cannot take warfarin, have clearly shown that the combination of clopidogrel (75 mg/d) and aspirin (75-100 mg/d) reduced major vascular events, particularly stroke, compared with placebo, al-

though at the expense of an increase in major bleeding. Whereas no conclusive data are available at present, this combination-treatment alternative is not recommended yet in guidelines.

Non-pharmacological approaches to prevent thromboembolism

It has been documented that the left atrial appendage (LAA) is the main source of left atrial thrombus, especially in non-rheumatic AF. Several surgical and percutaneous endovascular techniques have been explored to occlude the LAA. As an alternative of the surgical closure, percutaneous exclusion of the LAA is a new approach used to prevent strokes in high-risk patients with AF and contraindication to long-term oral anticoagulant therapy[13]. Devices have recently been developed that will exclude the LAA from the circulation and potentially replace the standard Warfarin therapy for patients with AF. Two percutaneous approaches to LAA obliteration have been studied to date. The PLAATO device has been tested in patients with a contraindication to anticoagulant and at least one additional risk factor for stroke[14]. This device is no longer being evaluated or supported in the United States. The Watchman device has been recently investigated in the Embolic Protection in Patients with Atrial Fibrillation trial[15]. The study enrolled 707 patients randomly assigned in a 2:1 ratio to percutaneous closure of the LAA using the Watchman device plus short-term Warfarin or to conventional Warfarin therapy. After 1065 patient/year of follow-up, the rate of the primary composite end point (stroke, cardiovascular death and systemic embolism) was 32% lower in the Watchman group than in the conventional therapy group, a result that met the prespecified criterion for non-inferiority. However, 12.3% of patients had serious procedural complications, including pericardial effusion, acute ischemic stroke, device embolization and post-implantation sepsis.

In conclusion, although clinical application of these devices could provide a new therapeutic option, the concerns about procedural safety and the need for long-term follow-up should be addressed before this potentially important technology is put into a wide use.

LONG-TERM MANAGEMENT OF AF

The long-term management of this arrhythmia includes two generally acceptable strategies: (1) one strategy attempts restoration and/or maintenance of sinus rhythm with pharmacological and non-pharmacological anti-arrhythmic approaches; (2) in the second approach, the ventricular rate is controlled with no commitment to restore or maintain sinus rhythm. Regardless of whether the rate- or rhythm-control strategy is pursued, attention must also be paid to the anti-thrombotic therapy for prevention of thromboembolism.

Newly discovered AF

An attempt to restore sinus rhythm is a reasonable approach to a first episode of AF. After this episode, the arrhythmia-free period is unpredictable, and it may not be necessary to prescribe either long-term anti-arrhythmic or anti-coagulant drugs for all patients after the first episode. Intravenous administration of anti-arrhythmic drugs (AADs) class I c or Ⅲ represents the first choice to obtain cardioversion of a new onset AF and they are widely used particularly for the emergency cases. Cardioversion might even be performed initially without the use of antiarrhythmic drugs. This approach may result in the maintenance of sinus rhythm for a year or more in about 25% patients. If arrhythmia recurs and if symptoms persist despite AAD, repeated cardioversion with the addition of anti-arrhythmic drugs should be considered.

Recurrent AF treatment: lessons from multi-center trials in rate vs rhythm control

A few randomized trials comparing outcomes of rhythm-*vs* rate-control strategies have been published. In particular, the AF Follow-up Investigation of Rhythm Management (AFFIRM), Rate Control versus Electrical Cardioversion for AF (RACE), and Strategies for Treatment of AF (STAF) trials compared a strategy of rate control and a rhythm control approach using AADs[16-18]. In addition, the Atrial Fibrillation and Congestive Heart Failure trial[19] compared these strategies in patients with congestive HF. The analysis of these trials demonstrated no difference in mortality or stroke rate between patients assigned to one strategy or the other. These results are generally interpreted as that either rate control or rhythm control is a suitable strategy in AF patients.

However, it would be incorrect to extrapolate that it is not worthwhile to restore sinus rhythm for a multitude of reasons. First, these trials did not compare the sinus rhythm and AF. Indeed, in one study (RACE), only 39% of patients in the rhythm-control group had sinus rhythm at the end of follow-up. Consequently, a significant limitation of these studies is the non-efficacy of rhythm-control strategy with AAD. Many patients in the rate control arm were spontaneously in sinus rhythm by the end of the study period from 10% in STAF and RACE to 35% in AFFIRM. Therefore, the results of these studies may reflect the ineffectiveness of the rhythm control methods used. When the data from these trials are analyzed according to the patient's actual rhythm, the benefit of sinus rhythm over AF becomes apparent[20]. This benefit might have been reduced by AAD, which increased the risk of death. The reduced mortality with sinus rhythm has also been demonstrated in virtually every study that has monitored this end point.

Another methodological concern is that in the rhythm control group, continuous anticoagulation was encouraged but could be stopped at the physician's discretion whereas in the rate-control group, continuous anticoagulation was mandated by the protocol. Importantly, most strokes were diagnosed after discontinuation of anticoagulation or at sub-therapeutic intensity (International Normalized

Ratio below 2.0). In addition, while recurrent AF was detected in only one-third of those in the rhythm-control groups who developed stroke, and at the time of ischemic stroke, patients in the rate-control groups typically had AF. We strongly believe that adequate anticoagulation with Warfarin would have substantially lowered in the rhythm-control groups.

Finally, it is also important to acknowledge that the patients enrolled in these trials do not represent the full spectrum of AF patients. In particular, the patients with severe symptoms of AF who would benefit most from sinus rhythm were largely excluded from the AFFIRM trial. Clearly, in such patients the goal is still to maintain the sinus rhythm, for which, search for better drugs and techniques should continue.

RATE CONTROL DURING AF

A more cost-effective approach is to control the ventricular rate without attaining the sinus rhythm. Drugs that prolong the AV node refractory period are generally effective for rate control. The efficacy of pharmacological interventions designed to achieve rate control in AF patients is about 80% in clinical trials[21]. However, the adverse effects of the drugs such as bradycardia and heart block may occur, especially in the elderly. Radiofrequency ablation of the atrioventricular junction with pacemaker implantation (the "ablate and pace" strategy) can improve symptoms and LV function in some patients, but the growing concern about the negative effects of long-term right ventricular pacing makes this a drawback rather than a primary treatment strategy.

Randomized studies suggest combining β-blockers or calcium channel blockers with digoxin to achieve a better rate control at rest and during exercise[22,23]. The oldest drug, digoxin, still is used frequently. The advantage of digoxin is that it has positive inotropic effects, making it highly suitable for patients with left ventricular dysfunction. The disadvantage is that it acts by increasing vagotonus and thus has limited or virtually no rate-controlling properties during exercise. Digoxin, used intravenously or orally, should be reserved only for heart failure patients. β-blocking agents may be the drugs of choice in patients with systolic dysfunction and/or coronary artery disease. Importantly, the negative inotropic action of β-blockers can cause deterioration in patients with (decompensated) systolic heart failure. However, if carefully titrated, β-blockers may even improve left ventricular function and survival in patients with poor left ventricular function. Intravenous β-blockers, verapamil, or diltiazem may be used to immediately slow a fast ventricular rate associated with AF. Non-pharmacological therapies should be administered to patients with symptomatic AF in whom a rapid ventricular rate cannot be slowed by drug therapy.

The aims to control the heart rate in AF patients treated with drugs are to minimize symptoms and prevent excessive tachycardia. However, the optimal level of heart rate for AF patients remains unclear. Rate control in RACE and AFFIRM trial defined a resting heart rate < 80 or < 100 beats/min, respectively. However, a sub-study of the AFFIRM[24] showed that the rate-control approach was successfully achieved in two-thirds of the patients. Additionally, to obtain adequate rate control, atrioventricular node ablation and pacemaker implantation was performed in 5.3% patients, and 17.3% patients had a pacemaker implanted for symptomatic bradycardia.

Unfortunately, these studies give no data on the influence of the level of rate control on mortality and morbidity. It is essential to achieve good rate control to minimize symptoms and the risk of tachycardia-mediated cardiomyopathy, and a 24-h heart rate that mimics normal sinus rhythm is a reasonable end point. As it still remains unknown whether strict rate control is associated with an improved prognosis, a long-term prospective, randomized trial would be useful.

RESTORATION AND MAINTENANCE OF SINUS RHYTHM

Direct-current cardioversion of AF

Management of AF includes treatment of underlying causes and precipitating factors. Immediate cardioversion should be performed in patients with AF and acute myocardial infarction, chest pain, hypotension, severe heart failure, or syncope. Elective direct-current cardioversion has a higher success rate and a lower incidence of cardiac adverse effects than medical cardioversion in converting AF to sinus rhythm. Unless transesophageal echocardiography shows no thrombus in the LAA before cardioversion, oral Warfarin should be given for 3 wk before elective cardioversion, and continue for at least 4 wk after maintenance of sinus rhythm. Direct-current cardioversion involves delivery of an electrical shock synchronized with the intrinsic activity of the heart by sensing the R wave of the ECG to ensure that electrical stimulation does not occur during the vulnerable phase of the cardiac cycle.

Different techniques are used to perform an electrical cardioversion, each with specific indications, advantages and limitations[25] (Table 1). The method most frequently used to restore sinus rhythm is external direct current cardioversion, which was found to be a safe and effective technique, since biphasic waveform defibrillators are widely available[26,27]. However, this technique requires high energies and needs general anaesthesia or deep sedation. An alternative method to obtain restoration of sinus rhythm is esophageal cardioversion that could obviate these limitations of the external one, which uses lower energy and avoids general anaesthesia and is extremely well tolerated by patients and can be easily performed in an outpatient setting[28,29]. Recently the two techniques have been compared[30] and the results showed that AF might be cardioverted safely and effectively by either a transthoracic or a transesophageal

Table 1 Different electrical cardioversion techniques: advantages, disadvantages and efficacy

	Advantages	Disadvantages	Efficacy (%)
External cardioversion	Safety Effectiveness Feasibility Outpatient regimen (not in all the centers)	General anaesthesia (physical presence of anaesthesiologist) Need of high energies	94
Oesophageal cardioversion	Efficacy with lower energies Outpatient regimen No general anesthesia First choice in obese and COPD patients Safety in patients with pacemaker or ICD Atrial pacing back up	High cost of the catheter Contraindicated in patients with oesophageal diseases	95
Internal cardioversion	Very high effectiveness Use of very low energy No general anaesthesia	Need of an electrophysiology laboratory Invasive approach Pain perception	93

approach. The sedation of moderate depth using midazolam renders cardioversion by either approach acceptable. As transesophageal cardioversion shows no clear advantage, transthoracic cardioversion using a conscious sedation by midazolam should remain the approach of first choice.

Another technique performed during the last two decades is the internal cardioversion[31], but its advantage is limited to a small percentage of unsuccessful external cardioversions or in those patients who are more difficult to defibrillate such as overweight or obese patients, patients with chronic obstructive pulmonary disease or those with implanted devices which may be injured by high energy shocks.

Treating AF with medical therapy

Anti-arrhythmic drug therapy is the first line of treatment for patients with paroxysmal and persistent AF based on current guidelines. However, the currently available anti-arrhythmic agents have poor efficacy and are associated with significant side effects, both cardiac and non-cardiac. Consequently,the limited efficacy and proarrhythmic risks of AAD for AF have led to the development of nonpharmacologic therapeutic approaches.

Patients who do not receive AAD have a 1-year AF recurrence rate of about 75%. With anti-arrhythmic drugs, sinus rhythm may be maintained in 50%-65% of cases. The choice of anti-arrhythmic agents should be guided by the presence or absence of structural heart disease, tolerability, ease of administration and side effect profile. The optimal pharmacological means to restore and maintain sinus rhythm in AF patients remains controversial.

Several drugs including amiodarone, propafenone, flecainide, and sotalol have been shown to be effective in the prevention of AF recurrences. These agents often do not totally abolish the arrhythmia, but increase the length of the arrhythmia-free interval. The best available agent for rhythm control is amiodarone[32,33]. In the Canadian Trial of Atrial Fibrillation, amiodarone was compared with propafenone and sotalol for suppression of AF. Amiodarone was associated with a 35% rate of AF recurrence at 16 mo compared with a 63% rate of recurrence in the other drugs. Amiodarone has been approved by the Food and Drug Administration for the treatment of ventricular arrhythmias but not for the AF management. Even so, it is widely prescribed and it is an excellent choice for patients with structural heart disease or congestive heart failure as most other anti-arrhythmic medications are contraindicated in heart failure patients. Amiodarone is less proarrhythmic than other agents but can adversely affect lungs, thyroid, and other organs[34]. After 5 years, 30% of patients on amiodarone are expected to discontinue the therapy because of side effects[35]. Dronedarone, a new derivative of amiodarone, lacks the iodine component that is largely responsible for the multiple organ toxicities. Recent randomized trials[36,37] showed that dronedarone was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia. In the ATHENA trial which randomized 4628 moderate- to high-risk AF patients, dronedarone resulted in a significant reduction (hazard ratio 0.76) in the primary endpoint of cardiovascular hospitalizations or death. However, the efficacy of dronedarone to suppress AF seems not as strong as that of amiodarone. Moreover, the potential adverse effects of dronedarone in patients with symptomatic heart failure and severe left ventricular systolic dysfunction remains an unresolved concern[38].

Discontinuation rates for AAD are consistently high in most trials. The careful use of these medications as demonstrated in AFFIRM can minimize this risk but can not eliminate it entirely[39]. A careful history taking and physical examination are mandatory in order to evaluate any potentially negative effect that the therapy for the arrhythmia may have on the underlying heart disease. However, in some patients the efficacy is lower than desired, and the prediction of anti-arrhythmic *vs* arrhythmogenic effects of AAD in a particular case is nearly impossible.

Rapidly developing experimental work has provided new insights into AF pathophysiology that will lead to new mechanism-based therapies. Oxidative stress and

inflammation may be involved in the genesis of AF. Agents that modulate non-ionic current targets (termed 'upstream' therapies) targeting inflammation, oxidative injury, atrial myocyte metabolism, extracellular matrix remodeling, and fibrosis, may help modify the substrate for AF maintenance and have theoretical advantages as novel therapeutic strategies[40]. Angiotensin Ⅱ type 1 receptor antagonists, immunosuppressive agents, statins and omega-3 polyunsaturated fatty acids have shown potential anti-arrhythmic effects related to the treatment of underlying heart disease in some but not in all studies[41-43]. These agents could be explored to prevent or delay atrial remodeling in AF patients, even in the absence of routine indications for such therapy, but the potential value of these novel therapeutic options is still under active investigations.

Non-pharmacological treatment for AF

For many years, a pharmacological approach was the only therapeutic modality available for managing AF. Because anti-arrhythmic therapy has several limitations, including unacceptable rates of AF recurrence and other proarrhythmic sequelae, non-pharmacological approaches have become increasingly important therapeutic alternatives. Recent observations on the mechanisms of AF have resulted in the development of different non-pharmacological treatment to eliminate the triggers and to modify the electrophysiological substrate for the prevention and treatment of the disorder.

Role of cardiac rhythm management devices in AF patients: Pacemakers play an important role in the non-pharmacological management of AF. Atrial or dual-chamber pacing has been proven to prevent or delay the progression to permanent AF in patients with sinus node dysfunction as compared with ventricular pacing[44,45]. However, its utility as a treatment for paroxysmal AF in patients without conventional indications for pacing has not been proved.

There may be additional benefits associated with the use of particular sites of pacing, specific pacing algorithms designed to target potential triggers of AF, and pace-termination of atrial tachycardia. Anti-tachycardia pacing algorithms incorporated in implantable cardioverter-defibrillators and pacemakers are currently under investigation and may offer a valuable alternative to anti-arrhythmic drug therapy in elderly patients with left ventricular dysfunction at high risk of proarrhythmia or worsening heart failure.

Low energy internal defibrillation which was assumed to be safe, has prompted the development of implantable devices for terminating AF. These devices can be patient-activated or programmed to deliver automatically therapies include pacing and/or shocks, once atrial tachyarrhythmias are detected. Studies have shown that despite shock discomfort, quality of life was improved in patients with atrial defibrillators and the need for repeated hospitalizations was reduced. But due to the bad feedback from physicians regarding the shock discomfort, industry did not further develop such systems. Moreover, the cost of these devices remains a concern for the treatment of a non-lethal arrhythmia.

Advantages and limitations of atrial defibrillators and approaches to reduce shock related discomfort may be an important concern in some patients and would need further reviews.

Newer implantable pacemakers not only play a role in the management of AF for the available algorithms and therapies, but also offer an important diagnostic tool. The data storage capabilities permit detection of multiple episodes ofAF, including asymptomatic ones. The evaluation of the AF Burden may be useful to assess the thromboembolic risk profile of the patients and to optimize the antiarrhythmic drug therapy.

Surgical approach: With the surgical technique introduced by Cox and colleagues[46] to create conduction barriers at the critical area in order to reduce the critical mass within both atria, the possibility of a surgical cure of AF was raised. There are different surgical ablative techniques that can effectively modify the atrial substrate[47-49]; by making a series of atrial incisions and cryolesions, this procedure results in the interruption of the multiple reentry circuits necessary for the propagation of AF (Figure 1D).

These procedures require thoracotomy and cardiopulmonary bypass, however, and they are associated with morbidity as well as the risk of serious complications. Most surgical procedures are performed in conjunction with other cardiac operations (concomitant MAZE) particularly mitral-valve surgery. A success rate of around 95% over 15 years of follow-up was reported in patients undergoing mitral valve surgery[50,51]. Other studies gave a success rate of around 70%. The surgical procedures using alternate energy sources, thoracoscopic and catheter-based epicardial techniques may become more acceptable alternatives for a wider population of AF patients.

Catheter ablation: Over the past decade, catheter-based AF ablation (CA) has been proposed as a definitive cure in a broad spectrum of patients, from patients with paroxysmal AF to those with long-lasting persistent AF. With continuing advances in this field, more patients will be offered this treatment option. A number of different ablation strategies have been used, including pulmonary vein isolation, targeting of fractionated electrograms, autonomic ganglionated plexi ablation, compartmentalizing the atria with linear lesions and various combinations and modifications of these lesion sets (Figure 1A-C). The optimal ablation strategy for both paroxysmal and long-lasting persistent AF is unknown.

Randomized, controlled trials (Table 2) comparing radiofrequency energy (RF) ablation with anti-arrhythmic medications in the treatment of AF have been published[52-57]. Most studies included patients with paroxysmal or persistent AF who had failed at

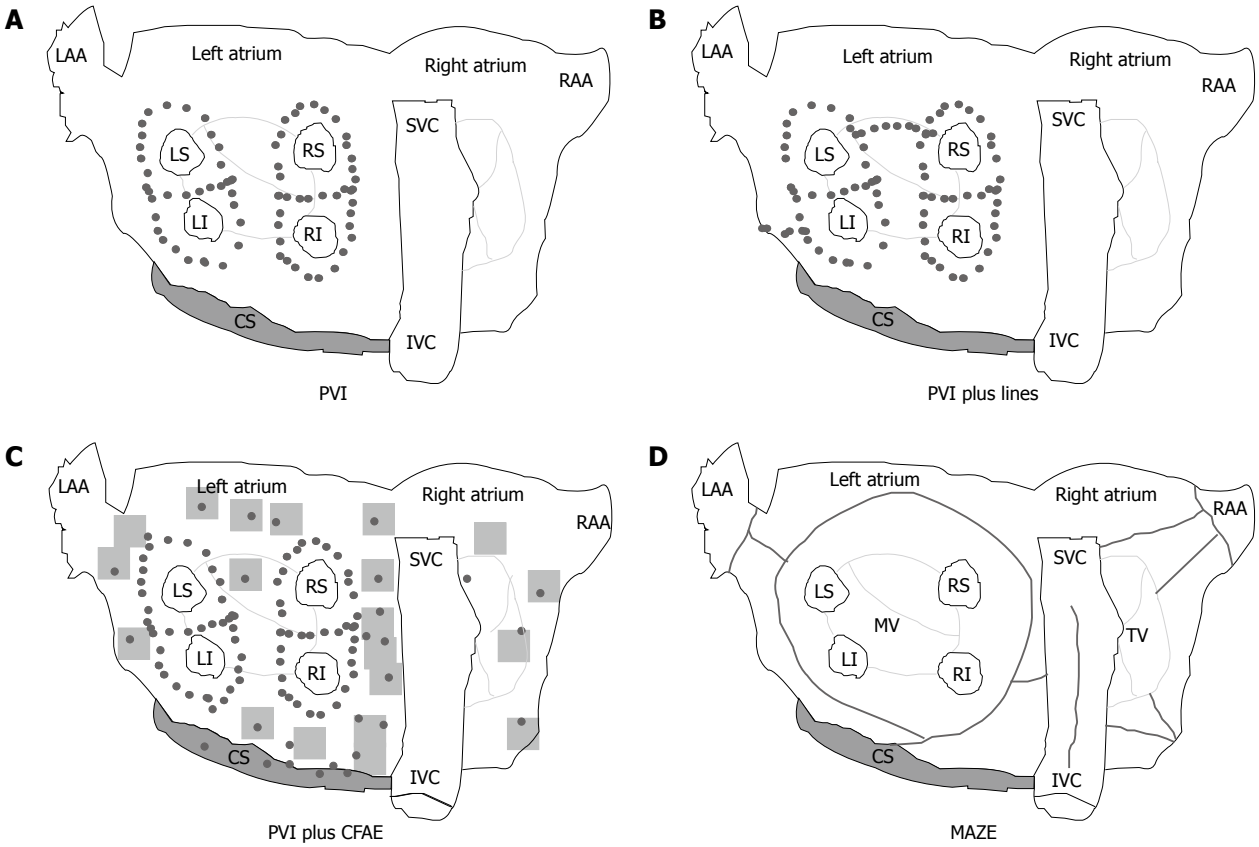

Figure 1 Various approaches to cure atrial fibrillation. A-C: most procedures used for ablation of atrial fibrillation (AF) include one or a combination of the techniques. A: Isolation of the pulmonary veins (PVs) with or without demonstration of PV-left atrial conduction block; B: PVI with additional left atrial linear ablations (mitral isthmus and roof); C: Ablation of the complex fractionated atrial electrograms (CFAE). The shaded areas indicate CFAE. D: Illustration of atrial lesions in the modified Cox/MAZE Ⅲ procedure. Violet tags indicate the anatomic location of the lesions. IVC: Inferior vena cava; LAA: Left atrial appendage; LI: Left inferior pulmonary vein; LS: Left superior pulmonary vein; PVI: Pulmonary vein isolation; RI: Right inferior pulmonary vein; RS: Right superior pulmonary vein; SVC: Superior vena cava; RAA: Right atrial appendage.

Table 2 Randomized trials comparing radiofrequency ablation with antiarrhythmic medications

Study	*n*	Follow-up (mo)	Patients free of AF			No. of ablation procedures	Major complications (ablation arm) (%)	Type of AF
			Ablation strategy (%)	AAD strategy (%)	*P*			
Wazni *et al*[48] (2005)	70	12	88	37	< 0.001	1	6.3	Paroxysmal persistent
Oral *et al*[50] (2006)	146	12	74	58	0.05	1.4	0	Permanent
Stabile *et al*[49] (2006)	137	12	56	9	< 0.001	1	4.4	Paroxysmal persistent
Pappone *et al*[51] (2006)	198	12	86	22	< 0.001	1	2.0	Paroxysmal
Jaïs *et al*[52] (2008)	112	12	88	24	< 0.001	1.8	1.9	Paroxysmal
Forleo *et al*[53] (2009)	70	12	80	57	0.001	1	2.9	Paroxysmal persistent

All studies demonstrated the superiority of catheter ablation over anti-arrhythmic drugs in AF patients with regard to maintenance of sinus rhythm. AF: Atrial fibrillation; AAD: Anti-arrhythmic drug.

least one or two anti-arrhythmic medications or who were intolerant of anti-arrhythmic medications. These studies demonstrated the superiority of catheter ablation over anti-arrhythmic drugs in AF patients with regard to maintenance of sinus rhythm and improvement of symptoms, exercise capacity, and quality of life. Thus, the primary selection criterion for catheter ablation should be the presence of symptomatic AF refractory or intolerant to at least one class 1 or 3 antiarrhythmic medication. The current guidelines recommend catheter ablation in this setting. However, one trial assessed the efficacy of ablation in patients with permanent AF[58], whereas another study randomized patients as first-line therapy[52] suggesting that catheter ablation can be considered early in the management of the patients. A recent systematic review showed that in patients with paroxysmal and persistent AF and structurally normal hearts, ablation therapy results in a 65% reduction in the RR of AF recurrence compared with standard antiarrhythmic therapy[59].

Of note, a recent study that compared the cost of ablation as first-line treatment of symptomatic AF *vs*

anti-arrhythmic drug therapy, demonstrated that CA was cost neutral 2 years after the initial procedure. Accumulating evidences from clinical studies have documented long-term improvement in quality of life, functional capacity, and left ventricular function in patients with impaired systolic function who undergo CA for AF[60-63]. A major advantage of CA is that patients with low ejection fraction are at an increased risk of AAD adverse effects,while its disadvantages include a higher procedural risk in these patients. Nevertheless, many aspects of the therapy are still controversial, from ablation techniques to procedural endpoints, patient management, definition of success and long-term results. The definition of a successful intervention for the management of AF remains a challenge. It is uncertain whether elimination of AF or transformation into an asymptomatic form of AF unrecognized by the patient or the physician represents the cure of the disease. The distinction has great significance from the point of view of preventing thromboembolic episodes in patients with risk factors for stroke associated with AF.

Controversies exist with regard to the procedural safety of AF ablation. Reports from highly sophisticated centers claim very low complication rates. However, recent surveys showed that this procedure is associated with approximately 5% rate of major complications[64,65]. Pulmonary vein stenosis, pericardial effusion, embolic cerebral and peripheral vascular complications constitute the most frequent complications. Continuing advances in this field might reduce the rate of major complications, and the increasing number of pulmonary veins (PV) ablation procedures has allowed electrophysiologists to become aware of the peculiarities and potential dangers of these procedures. Useful tools are required in order to develop the ablation strategy and to avoid more complex procedures with longer durations and higher periprocedural risks. Phased-array intracardiac echocardiography has been shown to be helpful in minimizing complications associated with ablation procedures, allowing real-time monitoring of both PV ostium and RF delivery[66].

Techniques and endpoints for AF ablation: It is likely that in humans AF is caused by different mechanisms. Recent observations have focused attention on the PV as a source of ectopic activity determining AF[67]. However, a predisposing atrial substrate of sufficient mass capable of maintaining re-entrant circuits is necessary and other anatomical structures are critical in this regard.

Since its original description in 1998, the technique of CA of AF has undergone several modifications[68]. Isolating or encircling all accessible PV is identified as the cornerstone of any ablation approach, and most of the trials did use PV isolation as an endpoint for radiofrequency ablation. This approach, called "empirical PV isolation", targets all of the PVs without regard to the initiation of ectopic beats (Figure 1A). However, PVI as a stand-alone strategy is insufficient to eliminate recurrent AF in most patients with persistent/permanent AF. In these patients, there is considerable evidence that ablation of residual triggers or drivers of AF outside the PV is required[69].

Various adjunctive atrial modifications such as wider ablation around the veins, linear lines, or ablation of complex fractionated atrial electrograms (CFAE) have been proposed. Substrate modification can be achieved by additional linear lesions (Figure 1B) in the LA, but the optimal lesion set to be deployed has yet to be elucidated. The most common sites of linear lesions are the LA roof between the superior aspects of the left and right upper PV isolation lesions, and the mitral isthmus between the mitral valve and the left inferior PV.

Elimination of CFAE is another possible approach (Figure 1C)[70]. However, in a large proportion of patients, Oral *et al*[71] showed that ablation of CFAE is not sufficient to eliminate the driving mechanisms of AF, suggesting the routine isolation of all PVs.

It is uncertain whether all patients need further substrate modifications for AF treatment. Studies have shown that the combined approach of PVI and CFAE ablation in persistent/permanent AF yielded mixed results[69,72]. Therefore, the role of this strategy should be proven in larger series. Tools allowing the differentiation between active and passive CFAE sites are crucial for the understanding and treatment of persistent AF.

The ablation procedure is often guided by 3D electroanatomical mapping systems. Currently, the Ensite NavX (St Jude Medical, Minnetonka, MN, USA) and Carto (Biosense Webster Inc, Diamond Bar, CA, USA) systems are increasingly used during CA of AF because they facilitate the difficult interventional ablation procedure while providing accurate visualization of the atrial anatomy and provide a guide for atrial substate modifications. The 3-dimensional mapping systems also shorten the fluoroscopic time and assist in identifying the critical substrate during the ablation, preventing gap formation and guiding post-ablation atrial tachycardia or flutter ablation. Additionally, image integration improves the safety and long-term success rate.

Most ablation procedures are being performed with close- or open-irrigation RF catheters[73], which are capable only for focal ablations. Achieving PVI with this technique,however, remains lengthy, technically challenging and requires a high degree of skill. Balloon and coil platforms, using different energy sources, are being tested as potential alternatives for focal RF catheters, with the hope of providing a safer, faster and more effective technology[74-76]. Cryo-balloon has emerged as a promising tool allowing PV isolation in a safe and effective manner. Results from early pre-clinical and clinical studies showed that the use of cryoablation is associated with a very low rate of complications including thrombogenicity, PV stenosis and esophageal injury[77]. It has been suggested that cryothermal balloon ablation for paroxysmal AF results in a clinical success

rate comparable to studies using radiofrequency ablation. However, the clinical success of cryoballoon PVI in paroxysmal AF has not been achieved in patients with persistent AF[78], likely because of the need for additional atrial substrate modification in this subgroup. Extensive substrate modifications using focal cryoablation catheters is technically feasible but plagued with the need for prolonged application time and the inability to create "dragging" ablation lesions due to cryocatheter adherence to tissues, significantly limited their use.

Despite these differences in technique, there remain remarkable consistencies in the AF outcome data between centers, with overall single-procedure efficacy of > 70% in achieving long-term arrhythmia control for patients with paroxysmal AF but significantly lower success rates in achieving a similar outcome for patients with persistent or permanent AF.

Assessment of "successful" rhythm control

Recent clinical trials that compared strategies of rhythm control with rate control in patients with AF lacked information about the best appropriate endpoints for determining "successful" rate or rhythm control in individual patients. Various endpoints have been used for judging the success of rhythm control strategies, including time to first recurrence of AF, any AF recurrence, AF burden, and a reduction in symptoms.

Time to first recurrence of AF has been frequently utilized, however, it has a poor value in the clinical care of patients. Of note, suppression of AF in a patient at high risk of stroke does not obviate the need for concomitant Warfarin treatment. A reasonable endpoint for rhythm control is a marked reduction in the frequency and duration of symptomatic AF episodes. For this reason we strongly believe that asymptomatic patients should not be treated with a rhythm control strategy. In addition, it is not essential to eliminate all episodes of AF when evaluating the success of the therapy, most patients can live comfortably with occasional episodes of AF, which is an entirely acceptable endpoint. Unfortunately, a few patients are bothered by even infrequent brief AF episodes. For such patients, it is a difficult task to find a strategy that eliminates nearly all AF recurrences.

Continuous monitoring of patients is another approach that can be used to measure the success of antiarrhythmic therapy. Although continuous loop recording with regular transtelephonic data transmission throughout a uniform period of follow-up would be the "gold standard" for assessment of cardiac rhythm, it is impractical, inconvenient, and expensive.

CONCLUSION

AF remains the most common and most challenging arrhythmia. Current treatment guidelines state that rhythm and rate control strategies should consider equivalent therapeutic approaches, but recognize that no "one size fits all". Physicians have to determine strategies most appropriate for particular clinical conditions. More attention should be paid to the severity of symptoms (symptomatic burden) but less to the frequency and duration of AF, and treatment should be delivered accordingly. Currently, the limited efficacy and proarrhythmic risks of anti-arrhythmic drugs highlights the importance for safer and more effective treatment options for AF. Several new nonpharmacologic treatment modalities have been developed; however, they are not applicable to all patients with AF; therefore, drug therapy will remain an important option.

In the minority of patients in whom AF cannot be adequately managed by pharmacological therapy, the most appropriate type of nonpharmacological therapy must be selected on an individualized basis.

Ablative techniques that offer the potential of a complete cure from AF are gaining popularity in the treatment of highly symptomatic patients with AF who are refractory to drug therapy. Nevertheless, many aspects of the therapy are still controversial. Even though the results of published studies favor ablation therapy, large, well-designed, multi-center clinical trials are needed to confirm the efficacy and safety of this approach.

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OBSERVATION

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Prostate-specific antigen kallikrein and the heart

Salvatore Patanè

Salvatore Patanè, Cardiology Unit, New Cutroni Zodda Hospital, Barcellona P.d.G(Me), Provincial Health Authority of Messina, 98051 Barcellona Pozzo di Gotto(Me), Italy
Author contributions: Patanè S contributed to this work and wrote this work.
Correspondence to: Salvatore Patanè, MD, Cardiology Unit, New Cutroni Zodda Hospital, Barcellona P.d.G(Me), Provincial Health Authority of Messina, 98051 Barcellona Pozzo di Gotto(Me), Italy. patane-@libero.it
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Abstract

Currently, there is growing interest regarding prostate-specific antigen (PSA) and the cardiovascular system. Increased PSA serum levels have been reported after prolonged cardiopulmonary resuscitation, cardiac surgery, extracorporeal cardiopulmonary bypass, acute myocardial infarction (AMI) and coronary artery stenting. The possible role of PSA in cardiac events has been questioned due to the finding of PSA decrease during AMI and by the correlation of variation in PSA levels with coronary lesions and occurrence of major adverse cardiac events. Complexed PSA forms and uncomplexed PSA forms are observed in the bloodstream but the increasing formation of irreversible bound PSA seems to be a crucial finding during AMI. Large studies need to be carried out to confirm these preliminary results and to *elucidate unclear* aspects. These findings present many potential directions for future research including the role of uncomplexed forms of PSA, the possible distribution of PSA in the heart, the relative expression levels in heart disease states, the mode of expression regulation and other potential specific substrates. The journey of PSA investigation could be longer than initially expected.

Currently, a growing interest has been directed towards prostate-specific antigen kallikrein (PSA) and the cardiovascular system[1]. Increased PSA serum levels have been demonstrated after prolonged cardiopulmonary resuscitation[2,3], cardiac surgery[4], extracorporeal cardiopulmonary bypass[5-8], acute myocardial infarction (AMI)[9-15] and coronary artery stenting[16]. However, the possible role of PSA in cardiac events has been questioned due to the finding of PSA decrease during AMI and by the correlation of variation in PSA levels with coronary lesions and occurrence of major adverse cardiac events[17,18]. Recently, a decrease in PSA was also reported in a patient with coronary spasm and without significant coronary stenoses[19]. PSA is a 33 kDa single chain glycoprotein that was first identified in seminal plasma[20] and was subsequently isolated from prostate tissue[21,22]. It has been identified as a member of the human kallikrein family (hK3) of serine proteases[1,23-26] and was initially considered only as a marker for the detection of prostate cancer[27]. Other malignant and non-malignant, non-prostatic and non-cardiovascular diseases[27-32] are also associated with increased PSA serum levels and the PSA unspecificity to prostate, semen, and gender has been demonstrated[1,33-35]. Recently, attention

has been focused on PSA as a ubiquitous protein by the finding of PSA in neuronal cells[35].

The inactive precursor form of PSA, proPSA, is converted rapidly to active PSA by hK2 and other proteases also seem to have a role in the formation of active PSA[1,36]. PSA expression has been shown to be primarily regulated by steroid hormones through androgen receptor-mediated transcription[27,35,37-42]. Two forms of PSA are observed in the bloodstream: complexed PSA forms and uncomplexed (free) PSA forms. Irreversible PSA complexes are formed with serum protease inhibitors and other acute-phase proteins[43-48]. Measurements of PSA levels are more reliable if interpreted in combination with information about C-reactive protein (CRP)[4]. The levels of increased bound PSA seem to have a significant correlation with high-sensitivity CRP and to a 14-d follow-up, with the occurrence of heart failure[48].

A higher occurrence of major adverse cardiac events after AMI and the finding of more frequent and more severe coronary lesions have been reported with elevation of PSA during AMI[1,15,17,48]. PSA in serum has been considered to be a biologically active factor[1,49], but the increasing formation of irreversible bound PSA seems to be a crucial finding during AMI[48]. Large studies need to be carried out to confirm these preliminary results and to elucidate unclear aspects. These findings present many potential directions for future research including the role of uncomplexed forms of PSA, the possible distribution of PSA in the heart, the relative expression levels in heart disease states, the mode of expression regulation and other potential specific substrates. The journey of PSA investigation could be longer than expected[1].

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Oxidative status and cardiovascular risk in women: Keeping pink at heart

Cristina Vassalle, Antonella Mercuri, Silvia Maffei

Cristina Vassalle, Antonella Mercuri, Silvia Maffei, G. Monasterio Foundation & Institute of Clinical Physiology-CNR, I-56124, Pisa, Italy

Author contributions: Vassalle C has conceived and written the manuscript, including acquisition and analysis and interpretation of data available in literature; Mercuri A and Maffei S have critically revised the manuscript for important intellectual content.

Correspondence to: Dr. Cristina Vassalle, PhD, G. Monasterio Foundation & Institute of Clinical Physiology-CNR, Via Moruzzi 1, I-56124, Pisa, Italy. cristina.vassalle@ifc.cnr.it

Telephone: +39-50-3152199 Fax: +39-50-3152166

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Abstract

Although cardiovascular disease (CVD) has always been perceived as a pathology regarding essentially males, incidence and death from cardiovascular events dramatically increase after menopause in women. Obviously, while many aspects of CVD are similar in both sexes, it is now clear that there are significant differences as well. Exploration of these gender-related differences in CVD might provide a basis for the development of new strategies in the management of patients with CVD from a gender point of view. In particular, a growing amount of data suggested the possible major role of oxidative stress in female patients and the possibility to integrate this new biomarker in future study evaluating CVD risk in women.

Key words: Cardiovascular; Risk factors; Menopause; Gender; Women; Oxidative stress

Peer reviewers: Antigone Lazou, Professor of Physiology, Lab of Animal Physiology, Sch of Biology, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece; Veselin Mitrovic, MD, Professor, Department of Cardiology, Kerckhoff-Klinik GmbH, Benekestrasse 2-8, 61231 Bad Nauheim, Germany

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INTRODUCTION

It is well known that coronary heart disease (CHD) represents the main cause of mortality and morbidity for men but also for women over age 50 years[1]. However, it has been essentially conceived as a "man's disease", and the influence of gender on CHD has been misunderstood and underestimated. Really, mortality due to CHD has not decreased in women as it has in men in the last 20 years, with most women dying suddenly from cardiovascular disease (CVD) without previous symptoms, but with a high prevalence of risk factors for CHD[2].

Generally, the risk for women is misperceived because of the strong conviction that females are "protected" against CVD. This conviction rises from the fact that women are effectively at lower risk of cardiovascular events with respect to men during their first decades of life, being protected by estrogen action in their premenopausal life (Figure 1). However, the onset of menopause marks a crucial point in the woman with important implications also for the cardiovascular system. It is well known that the incidence of CVD is significantly higher in postmenopausal women when compared to those in the same age range who are still fertile[3]. To note, life expectancy for women is greatly increased, and women spend up to one third of their life in their menopause status. Thus, according to the increased possibility of experiencing cardiovascular events, which rapidly rises after the menopause, the advantage gap for

women becomes progressively smaller until it is overcome by that of men in advanced age (Figure 2)[2,4].

Aspects related to pathogenesis, clinical presentation and outcome of the CHD have not been as extensively studied in women as in men. For a long time, the percentage of women included in CVD trials was always too low[5]. Consequently, most current indications for the prevention, diagnosis and therapy are deduced from cohort trials essentially conducted in men, and often result in inappropriate treatment.

However, the deepening of these issues is of particular interest because much evidence indicated that elderly women have even higher mortality and morbidity than men after cardiovascular events. Interestingly, some recent trials on the prevalence of normal or nonobstructive coronary arteries by gender assessed by early angiography after an acute coronary event showed a 20% or greater excess of normal or nonobstructive arteries in women *vs* men[6]. The women with nonobstructive coronary artery disease appeared to have an even higher rate of subsequent adverse events, as indicated by the Women's Ischemia Syndrome Evaluation study[7].

Obviously, if many aspects of CVD are similar in both men and women, some differences concerning physiopathology, risk profile, symptoms, age of onset and response to medical treatments are emerging[8]. These differences demonstrate the need of more attention by physicians to address gender disparities[9]. Thus, new insights into women's cardiovascular physiopathology are essential in order to assess more accurately and target more specific prevention strategies to reduce CHD risk in female subjects, as well as in men.

GENDER DIFFERENCES AND CARDIOVASCULAR RISK FACTORS

The studies focused on the possible gender-related role of different cardiovascular (CV) risk factors, have shown important differences (Table 1)[8]. Naturally, hormonal status represents a specific and unique risk factor for women. Moreover, in addition to traditional risk factors, cardiometabolic risk is an important determinant in women[10]. It is known from examining the lipid profile that total cholesterol, triglycerides, low-density lipoprotein (LDL) and lipoprotein [Lp(a)] increase sharply within 6 mo of menopause onset, while high-density lipoprotein (HDL) gradually declines[10]. However, HDL-C is always significantly higher in women than in men; this may be considered a gender-specific protective factor[10]. Nonetheless, it has been determined that low HDL-C, rather than high total and LDL-C, represented a more important predictor of CHD in women[10].

Other gender-related differences emerged in a meta-analysis of 17 studies (including 46 000 men and 11 000 women), which indicated elevated triglycerides as a greater predictor of CV events for women than for men, even after adjustment for HDL-C and other risk factors[11].

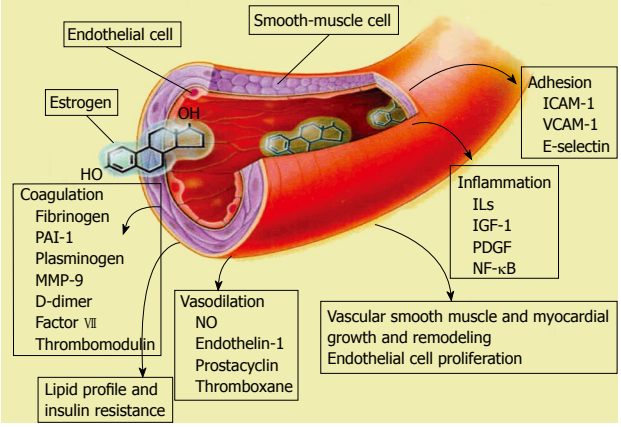

Figure 1 Multiple effects of estrogen on the cardiovascular system. Available from: URL: http://www.ehealthspan.com.

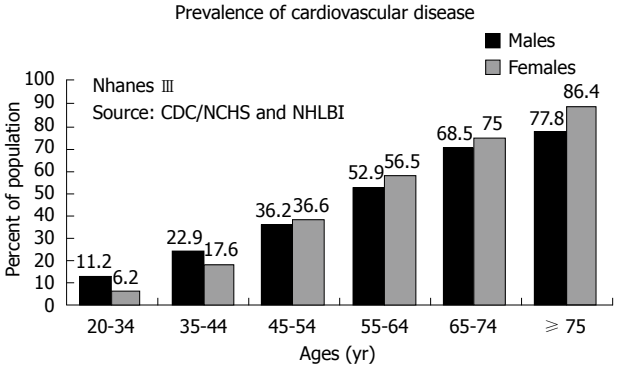

Figure 2 Prevalence of cardiovascular disease in males and females during their lifespan. From: Nhanes Ⅲ: 1999-2002. Source: Center for Disease Control (CDC)/National Center for Health Statistics (NCHS), National Heart, Lung and Blood Institute (NHLBI).

Moreover, high levels of Lp(a)were associated with increased CV risk, particularly in women with high levels of LDL-C[12].

Among the inflammatory biomarkers, the addition of C-reactive protein to the Framingham risk score improved the global CV risk prediction in women, especially in those at low-to-intermediate risk[13].

THE ROLE OF OXIDATIVE STRESS FOR CV RISK IN WOMEN

Many risk factors that promote CVD have been identified, including hypertension, hypercholesterolemia, diabetes, decreased estrogen in post-menopausal women, increased homocysteine, and cigarette smoking[14]. A mechanism common to all these risk factors is the elevation of the oxidative stress status[15]. In particular, oxidative stress phenomena occur during the progressive step that characterizes an atherosclerotic lesion from the onset, during its development until the events that induce clinical manifestation of the CVD[15]. Consequently, oxidative stress biomarkers have been found by us and others to be associated with the presence and severity of the CVD, and to

Table 1 Risk factors for cardiovascular disease in men and women

Risk factor	Men	Women
Total cholesterol	+++	+++
LDL	+++	+++
HDL	++	(+++)
Triglycerides	+	(++)
Apo A- I	+++	+++
Apo B	+++	+++
Apo (a)	++	+(+)
Smoking	++	(++(+))
Diabetes	++	(+++)
Body mass index	++	++
WHR	+++	+++
Hypertension	++	++
Family history	++	(++(+))
Hormones		(+++)
Homocysteine	+	+
Fibrinogen	++	++
Inflammation (PCR)	+	(++)
Psychosocial factors	+	+

Modified from Ref. 8.

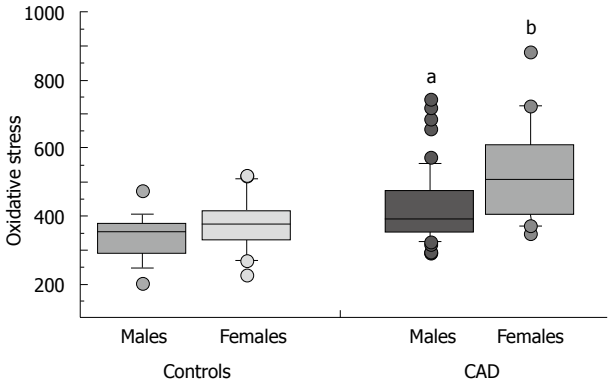

Figure 3 Levels of an oxidative stress biomarker by coronary artery disease (CAD) and gender. Modified from: Vassalle C, Maffei S, Boni C, Zucchelli GC. Gender-related differences in oxidative stress levels among elderly patients with coronary artery disease. *Fertil Steril* 2008; 89: 608-613. [a]$P < 0.05$ *vs* males; [b]$P < 0.001$ *vs* both control groups (males and females).

the presence and number of risk factors[16,17]. However, few studies evaluating the risk of CVD in women also included markers of oxidative stress[18].

It is known that young women during their fertile life are at lower risk of cardiovascular events compared with men, being protected by estrogen action and that oxidative stress is generally higher in men than in premenopausal women[19,20]. However, after menopause the risk of experiencing cardiovascular events rapidly rises in women, in conjunction with a parallel increase in oxidative stress biomarkers[19,21,22]. Recent data showed higher levels of biomarkers of inflammation and higher oxidative stress levels in elderly women than in elderly men[23]. Oxidative stress has been found elevated in post-menopausal women when compared to pre-menopausal women, and recent data has shown that oxidative stress plays a major role in different conditions which often accompany menopause, such as hot flashes and osteoporosis[24-26]. Moreover, although oxidative stress results are lower in females compared to males during the first decades of life, this difference decreases until the age range which corresponds to the onset of menopause for women, while for elderly people the tendency is even inverted[27].

Although many *in vitro* data showed the antioxidant properties of estradiol, the role of hormone replacement therapy (HRT) on oxidative stress levels remains still to be demonstrated[28]. However, most of the studies suggested possible beneficial effects or lack of adverse consequences of different doses and formulations of estradiol on the oxidative status in postmenopausal women treated with HRT[29,30]. Nonetheless, future studies are needed in this field to better clarify the role of different HRT regimens and doses on the oxidative stress balance.

Interestingly, data conducted in patients with neurodegenerative disease showed that female patients presented with higher levels of oxidative stress compared to affected males, suggesting a higher susceptibility to oxidative injury in such female subjects[31,32]. However, there is a dearth of reliable information on oxidative stress in women in the field of CVD[18]. We have recently evaluated whether gender-related differences in oxidative stress levels in aged patients with coronary artery disease (CAD) exist. Data obtained showed a higher oxidative stress status in elderly women with respect to men, whereas elevated oxidative stress levels represented the only strong independent risk factor for CAD in elderly women (Figure 3)[33]. At the moment, molecular mechanisms for the overwhelming gender disparity concerning oxidative stress in CAD are unknown, but they are probably related to hormonal status and likely associated with the loss of estrogen-dependent antioxidant effects[34,35]. Nonetheless, the estimation and correction of levels of oxidative stress might represent a crucial issue in elderly female patients.

With regard to antioxidant vitamin supplementation to prevent CVD, actual guidelines did not recommend its use although folic acid supplementation is advised for high-risk women with high levels of homocysteine[36,37]. Moreover, two recent trials (Norwegian Vitamin and Heart Outcomes Prevention Evaluation 2) have demonstrated the lack of efficacy of combined supplementation of folic acid and vitamins B12 and B6 in preventing CVD[38,39]. Conversely, data from the Women's Health Study suggested that vitamin E failed to provide benefits for either major CV events or myocardial infarction except in women > 65 years of age, where it significantly reduced the risk of major CV events[40].

CONCLUSION

Emerging data have suggested significant gender-based differences in CVD. In particular, menopausal status appears to enhance the development of CVD through several unfavourable changes in metabolism and hemodynamic parameters. Exploration of these aspects of CVD will provide a basis for clinical strategies directed to improve the outcome for women and consequently

lead to the discovery and adaptation of different approaches to prevention, diagnosis and management of CVD in women when appropriate.

In particular, recent data on the role of oxidative stress suggested that the estimation of oxidative stress, central to cardiovascular physiopathology, could represent a useful biomarker for cardiovascular risk estimation particularly relevant in elderly female subjects.

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REVIEW

Atherosclerosis, inflammation and *Chlamydia pneumoniae*

Giovanni Fazio, Maria Giovino, Alessandro Gullotti, Daniela Bacarella, Giuseppina Novo, Salvatore Novo

Giovanni Fazio, Maria Giovino, Alessandro Gullotti, Daniela Bacarella, Giuseppina Novo, Salvatore Novo, Division of Cardiology, University of Palermo, 90100, Palermo, Italy
Author contributions: All authors participated in the literature research and wrote the article.
Correspondence to: Dr. Fazio Giovanni, Division of Cardiology, University of Palermo, 90100, Palermo, Italy. giovanni.fazio-aaaa@poste.it
Telephone: +39-333-4439962 Fax: +39-91-5501809
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Abstract

Coronary heart disease is the single most common cause of illness and death in the developed world. Coronary atherosclerosis is by far the most frequent cause of ischemic heart disease, and plaque disruption with superimposed thrombosis is the main cause of the acute coronary syndromes of unstable angina, myocardial infarction, and sudden death. Atherosclerosis is the result of a complex interaction between blood elements, disturbed flow, and vessel wall abnormality, involving several pathological processes: inflammation, with increased endothelial permeability, endothelial activation, and monocyte recruitment; growth, with smooth muscle cell proliferation, migration, and matrix synthesis; degeneration, with lipid accumulation; necrosis, possibly related to the cytotoxic effect of oxidized lipid; calcification/ossification, which may represent an active rather than a dystrophic process; and thrombosis, with platelet recruitment and fibrin formation. In this review we discuss these processes and the possible pathological effects of *Chlamydia* infection and the ensuing phlogosis.

Key words: *Chlamydia*; Coronary heart disease; Coronary atherosclerosis; Phlogosis

Peer reviewer: Wei-Chuan Tsai, MD, Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng-Li Road, Tainan 704, Taiwan, China

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INTRODUCTION

Approximately one third of patients with coronary artery disease (CAD) do not have traditional risk factors. New evidence shows that systemic markers of inflammation are a strong predictor of cardiovascular events, adding independently to traditional risk factors. Inflammation systemically or locally within an atherosclerotic plaque is believed to play a major role in the initiation and progression of CAD and the precipitation of acute coronary events. Cardiovascular events may most commonly arise from sites of "nonsignificant" stenosis, suggesting that plaque instability rather than the degree of stenosis is the key risk factor. This plaque instability is believed related to inflammation within the plaque, with activated macrophages releasing inflammatory mediators, activating matrix metalloproteinases (MMP), and breaking down the protective fibrous cap. Sources of this inflammation may include non-infectious triggers [e.g. oxidized low-density lipoprotein (LDL), oxidation products of smoking, endothelial injury, genetics, *etc.*] or a number of proposed infectious triggers[1-9].

Currently, it is known that local and systemic inflammatory processes play an important role in the genesis and development of atherosclerotic lesions and in the pathophysiology of acute coronary syndromes. This hypothesis is supported by findings of elevated parameters of the inflammatory reaction in the blood of atherosclerotic patients as well as findings of histopathological characteristics of unstable plaques (thin fibrous cap,

large necrotic core, less smooth muscle cells and abundant foamy cells and lymphocytes). Furthermore, several studies have demonstrated that inflammation has a determining role in the rupture of the coronary plaque, and investigations have been carried out to identify the etiopathogenetic basis of the inflammation itself, trying to correlate coronary atherosclerosis and its development with some infectious agents[7-12].

Potentially, acute or chronic infections could initiate and promote CAD in the absence of traditional risk factors. More likely, infections act to augment CAD risk in the presence of other risk factors. A number of mechanisms have been proposed which could link infection to atherosclerosis[10].

Understanding the pathogenesis of atherosclerosis and the role of inflammation first requires some knowledge of the structure and biology of the normal artery and its indigenous cell types.

ANATOMY

Normal arteries have a well-developed trilaminar structure. The innermost layer, the tunica intima, is a monolayer of endothelial cells abutting directly on a basal lamina and constitutes the crucial contact surface with blood. Arterial endothelial cells possess many highly regulated mechanisms of capital importance for vascular homeostasis that often go awry during the pathogenesis of arterial diseases. The internal elastic membrane serves as the border between the intimal layer and the underlying tunica media[8-12]. The media of elastic arteries such as the aorta have well-developed concentric layers of smooth muscle cells, interleaved with layers of elastin-rich extracellular matrix. This structure appears well adapted for the storage of the kinetic energy of left ventricular systole by the walls of great arteries. The lamellar structure also doubtless contributes to the structural integrity of the arterial trunks. In the media of smaller muscular arteries there are usually smooth muscle cells residing within the surrounding matrix in a more continuous manner than in lamellar array. In the normal artery the smooth muscle cells are generally quiescent from the standpoint of growth control and there is a state of homeostasis of extracellular matrix. The external elastic lamina forms a border with the adventitial layer. The adventitia contains collagen fibrils and a cellular population such as fibroblasts and mast cells. Vasa vasorum and nerve endings localize in this outermost layer of the arterial wall[12-15].

PATHOPHYSIOLOGY

The pathogenesis of atherogenesis and of its development remain largely conjectural. One of the first ultrastructural alterations is an accumulation of small lipoprotein particles (LDL) in the intima, where binding of lipoproteins to proteoglycan occurs which tends to coalesce into aggregates. This process is supported by permeability of the endothelial monolayer. Lipoprotein particles bound to proteoglycan appear to exhibit increased susceptibility to oxidative or other chemical modifications such as enzymatic processing and glycation which can modify LDL in the intima. The second morphologically definable event in the initiation of atheroma is leukocyte recruitment and accumulation; these adhere to the endothelium by means of adhesion molecules, and diapedese between endothelial cell junctions to enter the intima, where they begin to accumulate lipids and transform into foam cells. In addition to the monocytes, T lymphocytes also tend to accumulate in early atherosclerotic lesions. The current concept of directed migration of leukocytes involves the action of protein molecules known as chemoattractant cytokines, or chemokines, produced by the endothelium and smooth muscle in response to oxidized lipoprotein and other stimuli[16-19].

Until now the natural history of the atherosclerotic process has not been totally understood. Some researchers have invoked a multicentric origin hypothesis of atherogenesis, positing that atheromas arise as benign leiomyomas of the artery wall. However, the location of sites of lesion predilection at proximal portions of arteries after branch points or bifurcations at flow dividers suggests a hydrodynamic basis for early lesion development. Locally disturbed flow could induce alterations that promote the steps of early atherogenesis; alternatively, the laminar flow may elicit antiatherogenic homeostatic mechanisms (atheroprotective functions). This hypothesis is supported by *in vitro* data suggesting that laminar shear stress can augment the expression of genes that may protect against atherosclerosis, including forms of the enzymes superoxide dismutase (which reduces oxidative stress by catabolizing the reactive and injurious superoxide anion) or nitric oxide synthase (which produces nitric oxide, an endogenous vasodilator and anti-inflammatory agent)[19,20].

Whereas the early events in atheroma initiation involve primarily altered endothelial function and recruitment and accumulation of leukocytes, the subsequent evolution of atheroma into more complex plaques additionally involves smooth muscle cells. Some smooth muscle cells likely migrate from the underlying media into the intima, attracted by molecules such as platelet-derived growth factor, secreted by activated macrophages and overexpressed in atherosclerosis. These smooth muscle cells begin to replication themselves; furthermore, death of these cells may also participate in complications of the atherosclerotic plaque. The vascular smooth muscle cell produces extracellular matrix molecules which make up much of the volume of an advanced atherosclerotic plaque. This matrix is catalyzed in part by enzymes known as MMP. This dissolution also likely plays a role in the arterial remodeling that accompanies lesion growth. During the first part of the life

history of an atheromatous lesion, growth of the plaque is outward, in an abluminal direction, rather than inward. The smooth muscle cell is not alone in its proliferation and migration within the evolving atherosclerotic plaque. Endothelial cell migration and replication also occur as plaques develop in microcirculation, characterized by plexuses of newly formed vessels. The microvascularization of plaques may also allow growth of the plaque, overcoming diffusion limitations on oxygen and nutrient supply. Finally, the plaque microvessels may be friable and prone to rupture. Hemorrhage and thrombosis *in situ* could promote a local cycle of smooth muscle cell proliferation and matrix accumulation in the area immediately adjacent to the microvascular disruption. Plaques often develop areas of calcification as they evolve[21-23].

The process of initiation and evolution of the atherosclerotic plaque generally takes place over many years, during which the affected person often has no symptoms. After the plaque burden exceeds the capacity of the artery to remodel outward, encroachment on the arterial lumen begins. Eventually the stenosis may progress to a degree that impedes blood flow through the artery. The development of chronic stable angina pectoris or intermittent claudication on increased demand is a common presentation of this type of atherosclerotic disease. However, several kinds of clinical observation suggest that most myocardial infarctions result not from critical blockages but from lesions that produce stenoses which do not limit flow. Instead of progressive growth of the intimal lesion to a critical stenosis, we now recognize that thrombosis, complicating a not necessarily occlusive plaque, most often causes episodes of unstable angina or acute myocardial infarction. Thrombosis is the consequence of a fracture of the plaque's fibrous cap, or of a superficial erosion of the intima[24-28].

RISK FACTORS

The "risk factor" is a characteristic or feature of an individual or population that is present early in life which is associated with an increased risk of developing future cardiovascular disease. The risk factor of interest may be a behavior (e.g. smoking), an inherited trait (e.g. family history), or a laboratory measurement (e.g. cholesterol). Features can be classified as conventional atherosclerotic risk factors such as hyperlipidemia, smoking, hypertension, insulin resistance and diabetes, physical activity, obesity, and hormone status; or novel atherosclerotic risk factors, including levels of homocysteine, fibrinogen, lipoprotein(a) [Lp(a)], as well as infective agents, markers of inflammation [e.g. high-sensitivity C-reactive protein (CRP)], indices of fibrinolytic function [e.g. tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor 1 (PAI-1)][10,14,25].

Dyslipidemia

Dyslipidemia encompasses disorders that include high average total plasma cholesterol levels, particularly LDL, but low high-density lipoproteins (HDL). Several studies point out the relationship between LDL and possibly very LDL and CAD. The role of HDL as a protective fraction has also emerged. Cholesterol (C) plays an important role in the atherosclerotic process, as it actually is a main constituent of the plaque. Furthermore, the presence of small, dense LDL particles may be related to features of the "metabolic syndrome", characterized by the presence of abdominal obesity, peripheral insulin resistance, high blood pressure, and a dyslipoproteinemia with elevated plasma triglycerides and reduced HDL-C levels[21-26].

Smoking

Cigarette consumption constitutes the single most important modifiable risk factor for CAD. Smoking affects atherothrombosis *via* several mechanisms. In addition to accelerating atherosclerotic progression, long-term smoking may enhance oxidation of LDL-C and reduce levels of HDL-C. Smoking also impairs endothelium-dependent coronary artery vasodilation and has multiple adverse hemostatic effects; it actually increases inflammatory markers such as CRP, soluble intercellular adhesion molecule (ICAM-1), and fibrinogen, causes spontaneous platelet aggregation and increases monocyte adhesion to endothelial cells[26].

Hypertension

Hypertension is often a silent cardiovascular risk factor. The risk increases in the presence of other cardiovascular risk factors such as insulin resistance and obesity. This cluster of metabolic and cardiovascular risk factors is named "Metabolic Syndrome" and also includes dyslipidemia, prothrombotic state and inflammatory state[27].

Insulin resistance and diabetes

Diabetic patients have a greater atherosclerotic burden both in the major arteries and in the microvascular circulation. Insulin resistance also produces a prothrombotic state due to increased levels of PAI-1 and fibrinogen. In addition to these systemic metabolic abnormalities, hyperglycemia causes accumulation of advanced glycation end products inculpated in vascular damage. Furthermore, diabetic patients have markedly impaired endothelial and smooth muscle function and appear to have increased leukocyte adhesion to vascular endothelium, a critical early step in atherogenesis[28].

Exercise and obesity

Regular physical exercise reduces myocardial oxygen demand and increases exercise capacity, both of which are associated with lower levels of coronary risk. The mechanisms by which exercise lowers cardiovascular risk remain uncertain but likely include favorable effects on blood pressure, weight control, lipid profiles, and improved glucose tolerance. Exercise also improves

endothelial function, enhances fibrinolysis, reduces platelet reactivity, and reduces propensity for *in situ* thrombosis.

Controversy remains as to whether obesity itself is a true risk factor for cardiovascular disease or whether its impact on vascular risk is mediated solely through interrelations with glucose intolerance, insulin resistance, hypertension, physical inactivity, and dyslipidemia[28,29].

Mental stress

The adrenergic stimulation of mental stress can clearly augment myocardial oxygen requirements, can cause coronary vasoconstriction, particularly in atherosclerotic coronary arteries, and hence can also influence myocardial oxygen supply. Catecholamines can also promote alterations in thrombosis[30].

Estrogen status

Before the menopause, women have lower age-adjusted incidence and mortality rates for coronary heart disease than men. This effect results from the beneficial actions of estrogen on lipid fractions, but is also due to direct vascular mechanisms such as improved endothelial-dependent vasomotion, reduced LDL oxidation, altered adhesion molecule levels, increased fibrinolytic capacity, and enhanced glucose metabolism.

Despite these facts, exogenous estrogen use among young women as a form of oral contraception is associated with increased rates of intravascular thrombosis; these effects are particularly prominent among smokers[28-31].

Several novel markers of atherothrombotic risk have emerged from epidemiological studies and might prove useful clinically.

Homocysteine

Hyperhomocystinemia is linked to atherosclerosis. The mechanisms that account for these effects remain uncertain but may include endothelial toxicity, accelerated oxidation of LDL-C, impairment of endothelial-derived relaxing factor, and reduced flow-mediated arterial vasodilation[32].

Fibrinogen

Plasma fibrinogen critically influences platelet aggregation and blood viscosity, interacts with plasminogen binding, and in combination with thrombin mediates the final step in clot formation. In addition, fibrinogen associates positively with age, obesity, smoking, diabetes, and LDL-C and inversely with HDL-C, alcohol use, physical activity, and exercise level. Several studies consider fibrinogen an independent marker of risk for coronary heart disease[33-35].

Lp(a)

The normal function of Lp(a) is unknown; the close homology between Lp(a) and plasminogen has raised the possibility that this unusual lipoprotein may inhibit endogenous fibrinolysis by competing with plasminogen for binding on the endothelial surface. More recent data demonstrate accumulation of Lp(a) and co-localization with fibrin within atherosclerotic lesions, both in stable patients and among those with unstable angina pectoris. Apo(a) may also induce monocyte chemotactic activity in the vascular endothelium, whereas Lp(a) may increase release of PAI. Thus, several mechanisms may contribute to a role for Lp(a) in atherothrombosis. As yet, many studies have not established the importance of Lp(a) as a marker for all future cardiovascular events or whether an increased risk is restricted to those with the highest levels or with an absence of other traditional risk factors[34-36].

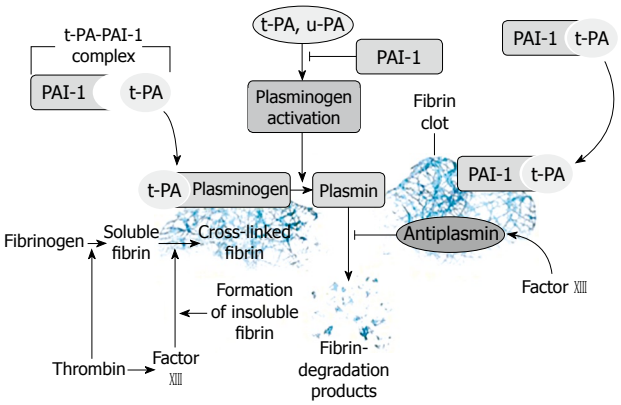

Figure 1 Relationship of the fibrinolytic factors in humans.

Markers of fibrinolytic function

A role for either t-PA or PAI-1 in the development of venous thrombosis remains controversial. In contrast, a highly consistent series of studies have linked abnormalities of fibrinolysis to increased risk of arterial thrombosis. Finally, several studies indicate that levels of D-dimer also predict myocardial infarction, peripheral atherothrombosis, and recurrent coronary events. Despite these data, the clinical use of fibrinolytic markers to determine coronary risk may offer little marginal value (Figure 1)[37,38].

Markers of inflammation and infection

Recently, interest has increased in the possibility that infections, and perhaps chronic infection, may cause atherosclerosis. Inflammation characterizes all phases of atherosclerosis from foam cell formation to plaque progression and rupture.

In fact, there are a lot of data related to this issue; atherosclerotic lesions are heavily infiltrated by cellular components associated with inflammation, especially lymphocytes [T cells of both the helper (CD4+) type and cytotoxic/suppressor (CD8+) immunologically activated type], macrophages, and foam cells. It is evident that plaque complexities, especially intraplaque hemorrhages, are connected with the intensity of inflammation. Several studies have shown a link between baseline

elevations of CRP, or other acute phase proteins, and the risk of future cardiac events, and the evaluation of this marker of infection and inflammation may be of importance for an effective prevention of cardiovascular events[21-28].

However, the potential mechanisms for infection-induced atherosclerosis remain speculative.

Inflammation may promote the process by acting both directly and indirectly. Infection could indirectly influence this process without infiltrating the artery wall. Host defenses to extravascular infections usually elicit proinflammatory cytokines and stimulate increased expression of cellular adhesion molecules, enhancing leukocyte adhesion. These cytokines could promote a second wave or "echo" from inflammatory cells already at sites of atherogenesis, such as arterial wall cells or macrophages. Circulating microbial products such as endotoxin can also produce an echo. Similarly, cytokines induced by extravascular infection [specifically interleukin (IL)-6] characteristically elicit hepatic synthesis of acute-phase reactants, some of which might promote atheromata complicated by thrombosis. Accordingly, levels of the acute-phase reactant fibrinogen correlate prospectively with risk for coronary events, and plasminogen activator inhibitor can promote clot stability by interfering with fibrinolysis. However, direct infection of the arterial wall could promote evolution of atherosclerotic lesions or precipitate acute cardiovascular events as suggested by histological findings in unstable coronary plaques, evidence of systemic release of thromboxanes and leukotrienes, and the presence of activated circulating leucocyte[15,39].

The earliest lesions of atherogenesis, consisting of altered endothelial permeability (endothelial dysfunction), can be induced by hemodynamic forces, by a variety of vasoactive substances, by mediators from blood cells, and directly from risk factors for atherosclerosis, with resulting arterial intimal accumulations of leukocytes, foam cells (primarily lipid-laden macrophages) and T lymphocytes intermixed with smooth muscle cells. After crossing the surface of the endothelium, the leukocytes accumulate within the intima. As the process continues, monocytes are converted to activated macrophages and take up oxidized LDL particles, thus becoming foam cells. The formation and accumulation of foam cells within the intima create the fatty streaks of atherosclerotic lesions. If the precipitating risk factors or offending agents are not removed, this process continues and leads to complex lesions. These complex lesions contain layers of smooth muscle, connective tissues, macrophages, and T lymphocytes. The presence of activated T lymphocytes in the atherosclerotic plaque suggests a local immune response, and it has been postulated that such a response may be directed against local antigens in the plaque. Activated T lymphocytes secrete growth factors and cytokines that may affect other cell types and the process of atherosclerosis. Interleukins, complement factor fragments, and tumour necrosis factors (TNF) can enhance monocyte adhesiveness and chemotaxis and so form an amplification mechanism for recruitment of further monocytes into the lesion. Following endothelial adhesion and transmigration into the arterial intima, these cells express markers of activation. Furthermore, released mitogens, such as macrophage derived growth factor, may play a key role in smooth muscle cell migration and subsequent proliferation and hence the progression of plaques. Activation of circulating leucocytes may be facilitated at the endothelium covering an atherosclerotic plaque, with upregulation of adhesion molecules and tethering of circulating cells. These inflammatory responses may further promote the infiltration of activated leucocytes into the atherosclerotic lesion, which in turn may directly activate smooth muscle cells, macrophages, and T cells inside the vessel wall. Lesional macrophages produce proteolytic enzymes, including members of the metalloproteinase family, which contribute to weakness of the protective fibrous cap of the plaque and hence promote the propensity of those plaques to rupture and trigger thrombosis. Over time, fibrous caps, consisting of smooth muscle, collagen, and elastic fibers, form to cover the complex lesions and intrude into the arterial wall. Along with impeding blood flow in the lumen, these fibrous plaques may rupture, causing thrombus formation, plaque progression, or death.

Raised concentrations of LDL and possibly Lp(a) may attract monocytes to adhere to endothelium and induce their transformation into macrophages. The proinflammatory effects of oxidised LDL involve peroxides and other reactive oxygen intermediates generated by the oxidation of LDL. These molecules activate nuclear transcription factor κB (NF-κB), which plays a key role in the orchestration of inflammatory and immune responses by controlling the transcription of the genes encoding several of the adhesion molecules, ILs, TNFα, class Ⅱ antigen, and antibodies. NF-κB recognises various activators, among which are the proinflammatory cytokines and CRP[38-41].

Most important is the role of cytokines such as TNFα or IL-1 isoforms, which can stimulate the expression of IL-6, IL-8, and leucocyte-platelet adhesion molecules such as ICAM-1. These cytokines are produced by neutrophils and macrophages which are located in atheromatous plaques. They may be derived from non-vascular sources and reflect generalised inflammatory states, such as chronic infection, which have been linked to atherogenesis and its clinical manifestations. The contribution of vascular and extravascular sources of inflammatory cytokines may vary between individuals. Primary cytokines (TNFα, IL-1) stimulate the production, by endothelial and other cells, of adhesion molecules, procoagulants, and other mediators that may be released in soluble form into circulating blood. Primary cytokines also stimulate the production of messenger cytokine, IL-6, which induces expression of hepatic genes encoding acute phase reactants found in the

blood, including CRP and serum amyloid A. Moreover, CRP may activate complement and thus participate in sustaining inflammation. Serum amyloid A can bind to HDL particles, perhaps rendering them less protective against vascular inflammation[1-12].

Inflammatory cytokines modulate the homeostatic properties of the endothelium. The local effects of inflammatory cells on digestion of the fibrous cap lead to plaque disruption and thrombus formation. Tissue factor is normally expressed in exposed intima and activates factor Ⅶ which in turn activates factors Ⅸ and Ⅹ. Collagen in exposed intima binds von Willebrand factor, which mediates platelet adherence by binding to the glycoprotein Ⅰb/Ⅴ/Ⅸ platelet surface receptor complex under high shear stress conditions. Von Willebrand factor itself is the carrier protein for factor Ⅷ, an essential component of the amplifying mechanism of the factor Ⅹ-Ⅹa conversion. Furthermore, platelets activated by adhesion then adhere to other platelets through the glycoprotein Ⅱb/Ⅲa receptor and its ligand, von Willebrand factor and fibrinogen. Such activated platelets release PAI-1, which locally inhibits the fibrinolytic mechanism[39,40].

Inflammation may promote thrombosis by acting both locally and systemically. Local mechanisms include the cytokine-stimulated expression of tissue factor by endothelial cells and macrophages. Indirectly, inflammation may act locally to induce thrombosis by weakening the fibrous cap of the atheromatous plaque, leading to plaque rupture. However, this role of inflammation, and specifically the role of macrophages, remains controversial. Inflammation can affect systemic hemostatic activity *via* IL-6-mediated stimulation of hepatocytes to produce acute phase reactants. These include certain coagulation factors, such as increased levels of fibrinogen and PAI-1, which induce a prothrombotic state. An enhanced CD40L-CD40 interaction also promotes thrombotic activity by enhancing tissue factor expression in macrophages and through the direct regulation of endothelium procoagulant activity. Intravascular fibrinolysis induced by tissue type plasminogen activator may contribute to atherosclerosis by inducing P-selectin and platelet activating factor, as well as contributing to plaque rupture by activating metalloproteinases. Oxidised LDL also induces tissue factor expression in macrophages and decreases the anticoagulant activity of the endothelium by interfering with thrombomodulin expression and inactivating tissue factor pathway inhibitor. Its expression is upregulated in circulating and endothelium adherent monocytes, and tissue factor has been found to be increased in coronary tissue of the culprit lesion from patients with unstable angina.

It is also now accepted that platelets may promote inflammatory responses. Studies have shown that activated platelets may mediate the homing of leucocytes by interaction with the subendothelial matrix under shear stresses that do not allow neutrophil adhesion. They may also contribute to the oxidative modification of LDL, provide a source of lipids for foam cell generation, and contribute to smooth muscle cell proliferation[40].

It is now known that acute cardiovascular events are linked with a non-stenotic, but a vulnerable plaque. The difference between the mature and the unstable plaque is related to both core and fibrous cap. The former consist of two main components, a soft lipid-rich atheromatous "gruel" and hard collagen-rich sclerotic tissue. The latter contain a core of soft atheromatous gruel that is separated from the vascular lumen by a thin cap of fibrous tissue. The fibrous cap is infiltrated by foam cells indicating ongoing disease activity. Such a thin and macrophage-infiltrated cap is probably very weak and vulnerable, and it can indeed be disrupted nearby, explaining why erythrocytes can be seen in the gruel just beneath the macrophage-infiltrated cap. Sclerosis is relatively innocuous because fibrous tissue appears to stabilize plaques, protecting them against disruption. In contrast, the usually less voluminous atheromatous component is the more dangerous component, because the soft atheromatous gruel destabilizes plaques, making them vulnerable to rupture, whereby the highly thrombogenic gruel is exposed to the flowing blood, leading to thrombosis - a potentially life-threatening event.

The risk of plaque disruption is related to intrinsic properties of individual plaques (their vulnerability) and extrinsic forces acting on plaques (rupture triggers). Plaque disruption occurs most frequently where the fibrous cap is thinnest, most heavily infiltrated by foam cells, and therefore weakest. The vulnerability to rupture depends on size and consistency of the atheromatous core, thickness and collagen content of the fibrous cap covering the core, inflammation within the cap and the cap "fatigue" caused by cyclic stretching, compression, bending, flexion, shear, and pressure fluctuations. Regarding the cap during inflammation, macrophages play an important role as they are capable of degrading extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and a family of MMPs such as collagenases, gelatinases, and stromelysins that may weaken the fibrous cap, predisposing it to rupture, and also promoting thrombin generation and luminal thrombosis through the tissue factor pathway. Neutrophils are also capable of destroying tissue by secreting proteolytic enzymes, but neutrophils are rare in intact plaques. They may occasionally be found in disrupted plaques beneath coronary thrombi, probably entering these plaques shortly after disruption, and neutrophils may also migrate into the arterial wall shortly after reperfusion of occluded arteries in response to ischemia/reperfusion. The rupture of a cap is linked, presumably, with digestion by macrophages but also with senescense or apoptosis of smooth muscle cells caused by inflammatory cytokines.

Coronary plaques are constantly stressed by a variety of biomechanical and hemodynamic forces that may

precipitate or "trigger" disruption of vulnerable plaques. The circumferential wall tension (tensile stress) caused by the blood pressure establishes a stress which is redistributed to adjacent structures and may be concentrated at critical points. The consistency of the gruel may be important for this stress redistribution, as indeed are the characteristics of the cap; the thinner the fibrous cap, the higher the stress that develops within it. Furthermore, mechanical shear stresses may develop in plaques at the interface between tissues of different stiffness, resulting, for example, in shear failure, calcified plates and adjacent noncalcified tissue[29,30].

Plaque disruption may occur when there are increases in the intraplaque pressure, caused by vasospasm, bleeding from vasa vasorum, plaque edema, and/or collapse of compliant stenoses. Vasospasm reduces the circumferential tension in fibrous caps by narrowing the lumen (Laplace's law). Nevertheless, spasm could theoretically rupture plaques by compressing the atheromatous core, "blowing" the fibrous cap out into the lumen. Bleeding and/or transudation (edema) into plaques from the thin-walled new vessels originating from vasa vasorum and frequently found at the plaque base could theoretically increase the intraplaque pressure, with resultant cap rupture from the inside. High-grade stenosis may be subjected to strong compressive forces due to the accelerated velocities in the throat. Collapse of severe but compliant stenoses due to negative transmural pressures may produce highly concentrated compressive stresses from buckling of the wall with bending deformation, preferentially involving plaque edges, and theoretically, this could contribute to plaque disruption.

Another factor important for the rupture is the propagating pulse wave during the cardiac cycle that causes changes in lumen size and shape with deformation and bending of plaques, and particularly of eccentric plaques[12-15].

Onset of acute coronary syndromes does not occur at random; in fact, a large fraction appear to be triggered by external factors or conditions such as emotional stress, vigorous exercise or cold. The pathophysiological mechanisms responsible for the nonrandom and (apparently often) triggered onset of infarction are unknown but probably related to (1) plaque disruption, most likely caused by surges in sympathetic activity with a sudden increase in blood pressure, pulse rate, heart contraction, and coronary blood flow; (2) thrombosis, occurring on previously disrupted or intact plaques when the systemic thrombotic tendency is high because of platelet hyperaggregability, hypercoagulability, and/or impaired fibrinolysis; and (3) vasoconstriction, occurring locally around a coronary plaque or generalized[23-25].

The possibility that various microbial agents may trigger a cascade of reactions leading to inflammation, atherogenesis, and thrombotic events in the vascular system has been raised in the last two decades. Chronic infection with various agents, both bacteria and viruses, such as *Chlamydia pneumoniae* (*C. pneumoniae*), *Cytomegalovirus* (CMV), HSV, *Helicobacter pylori* (*H. pylori*), *Mycoplasma pneumoniae*, anaerobic periodontal organisms, *etc*., has been implicated in the pathogenesis of CAD. Specific agents have been proposed as direct initiators or accelerators of atherosclerosis, through nonspecific stimulation of the inflammatory cascade. However, the role of these infection agents must be proven; there are often confounding factors which should be carefully considered, although it is quite plausible that infections may potentiate the action of traditional risk factors.

C. pneumoniae

C. pneumoniae is an important respiratory pathogen associated with 5% to 10% of community-acquired cases of pneumonia, pharyngitis, bronchitis, and sinusitis. It is an obligatory intracellular bacterium that has the tendency to cause persistent infection, and may drive a chronic inflammatory reaction in coronary vasculature or other tissues. *C. pneumoniae* has been proposed as an etiologic factor for atherosclerosis, contributing either directly or indirectly, by modifying traditional risk factors[34-40].

In particular, cytokines produced by *C. pneumoniae*-infected macrophages, located in coronary atherosclerotic plaques, may trigger an ongoing inflammatory response, and thus an increased prothrombotic state and smooth muscle cell proliferation, all of which favor atherothrombotic complications and restenosis after stenting. Lines of evidence associating *C. pneumoniae* with atherosclerosis include seroepidemiologic studies, direct detection of bacterial components in atherosclerotic lesions by polymerase chain reaction or electron microscopic studies, occasional isolation of viable organisms from coronary and carotid atheromatous tissue, and *in vitro* and animal experiments. The strongest evidence associating *C. pneumoniae* with atherosclerotic cardiovascular disease has been detection of bacterial components in atherosclerotic lesions. *C. pneumoniae* appears to have a tropism for atheromata. In addition, it is rarely found in normal arteries[34-40].

C. pneumoniae may infect circulatory components, which may attach to the endothelium and smooth muscle cells and kill them by apoptosis. The probable molecular mechanism of atherosclerosis pathogenesis can be explained by up-regulation of expression of heat shock protein 60 (HSP-60) by *C. pneumoniae* infection, which induces production of cytokines such as TNF-α, IL-1β and IL-6, and MMPs by macrophages. Furthermore, *C. pneumoniae* could lead to elevation of CRP and contribute to instability or progression of atherosclerotic plaques. The bacterium replicates in endothelial and smooth muscle cells and macrophages, and it can activate CD4+ and CD8+ T lymphocytes. *C. pneumoniae* initiates inflammatory activation *via* the NF-κB pathway, resulting in increased expression of vascular cell adhesion molecule-1, enhanced recruitment of inflammatory leukocytes to the vessel wall, impaired

activity of endothelial nitric oxide, increased platelet adhesion to endothelial cells and procoagulant activity in endothelial cells, as well as causing oxidation of LDL-C. Therefore, chronic infection may contribute to the risk of CHD by initiating a high level of immunologic activity, by raising triglyceride levels and decreasing HDL levels, and by increasing the concentrations of acute-phase reactants such as fibrinogen, CRP, and sialic acid.

Specific microbial products such as lipopolysaccharides, heat-shock proteins, or other virulence factors might act locally at the level of the artery wall to potentiate atherosclerosis in infected lesions. Extravascular infection might also influence the development of atheromatous lesions and provoke their complication. For example, circulating endotoxin or cytokines produced in response to a remote infection can act locally at the level of the artery wall to promote the activation of vascular cells and of leukocytes in pre-existing lesions, producing an "echo" at the level of the artery wall of a remote infection. Also, the acute phase response to an infection in a nonvascular site might affect the incidence of thrombotic complications of atherosclerosis by increasing fibrinogen or PAI-1 levels or otherwise altering the balance between coagulation and fibrinolysis. Such disturbance in the prevailing prothrombotic/fibrinolytic balance may critically influence whether a given plaque disruption will produce a clinically inapparent, transient or nonocclusive thrombus, or sustained and occlusive thrombi that could cause an acute coronary event. Acute infections might also produce hemodynamic alterations that could trigger coronary events such as tachycardia; increased metabolic demands of fever could augment the oxygen requirements of the heart, precipitating ischemia in an otherwise compensated individual. Infectious processes, either local in the atheroma or extravascular, might aggravate atherogenesis, particularly in preexisting lesions or in concert with traditional risk factors.

The presence of *C. pneumoniae* in atherosclerotic lesions raises the possibility that antibiotic treatment might have a favourable effect on the course of CAD. However, a few large randomized antibiotic trials have not shown any beneficial effect of long term antibiotic therapy (azithromycin and rifampin) suggesting that large randomized antibiotic trials may not show clinical benefit in patients with established acute or chronic CAD. After failure of antibiotic trials, it was postulated that *C. pneumoniae* has a pathogenetic role in the early development of atherosclerosis. It is possible, therefore, that infection with *C. pneumoniae* plays a part in the initiation of atherosclerosis early on in life; however, once plaque and inflammation are established, antichlamydial antibiotics cannot alter the progression of coronary disease[34-42].

Other infectious agents

Specific infectious agents other than *C. pneumoniae* have the potential to play a role in atherosclerosis as demonstrated by experimental models, the presence of organisms within plaques and inflammatory cells, and by seroepidemiologic associations.

Several investigators suggested a role for other bacteria and viruses in cardiovascular disease such as oral infections caused by *Porphyromonas gingivalis*, *Bacteroides forsythus*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Treponema spp*., and *Prevotella species*. Like *C. pneumoniae*, oral bacteria might affect atherosclerosis through direct invasion of vascular endothelial cells or indirectly through products that stimulate proinflammatory and prothrombotic functions of vascular cells.

The literature linking *H. pylori*, HIV, HSV-1, and HSV-2 to atherogenesis is less extensive than for *C. pneumoniae* or CMV[12]. CMV, a herpes-family DNA virus, is a common human pathogen and a candidate atherogenic organism. CMV can also accelerate atherosclerosis in animal models. Infection may induce a systemic inflammatory response that promotes atherosclerosis. CMV may contribute to CAD by several mechanisms, including impaired fibrinolysis, increased Lp(a), enhanced procoagulant activity, and upregulation of the macrophage oxidized LDL scavenger receptor. CMV can inactivate p53, an apoptosis-related protein, facilitating excessive proliferation of vascular smooth muscle cells[38].

The presence of any chronic bacterial infection (e.g. respiratory, urinary, dental, or other) increases considerably the risk of developing atherosclerosis[17]. *H. pylori*, the etiologic organism of peptic ulcer disease, has also received attention as a potential pathogen in atherosclerosis, although the early positive serologic associations have not been confirmed. *H. pylori* organisms have not been demonstrated in atherosclerotic plaques, nor have animal models demonstrated a pathologic role. However, *H. pylori* infection can increase CRP and fibrinogen levels and promote platelet aggregation. Thus, a role for *H. pylori* in atherogenesis also remains to be established[39,40].

CONCLUSION

The best way to prevent cardiovascular disease is the prevention of atherosclerosis and its development through removal of risk factors. Statins are the best therapeutic option to modulate inflammation, in fact several studies have demonstrated their anti-inflammatory, antioxidant and plaque-stabilizing effects in addition to their cholesterol-lowering effects. Statin treatment for global cardiovascular risk prevention is indicated and must be proposed in high risk patients. In addition, treatments for hypertension, diabetes, weight loss, exercise and smoking cessation are vitally important measures for cardiovascular risk reduction.

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REVIEW

Key questions resulting from the JUPITER trial assessing cardiovascular disease intervention with rosuvastatin

Shirya Rashid

Shirya Rashid, Department of Medicine, McMaster University, Henderson Research Centre, Hamilton, Ontario, L8V 1C3, Canada
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Supported by Grants from Hamilton Health Sciences, the Canadian Institutes of Health, AstraZeneca and Merck Frosst Schering, A Department of Medicine McMaster University Internal Career Award
Correspondence to: Dr. Shirya Rashid, PhD, Department of Medicine, McMaster University, Henderson Research Centre, Room 206, G-Wing, 711 Concession Street, Hamilton, Ontario, L8V 1C3, Canada. srashid@thrombosis.hhscr.org
Telephone: +1-905-5272299-43780 Fax: +1-905-5752646
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Abstract

This paper presents an analysis of the recently published Justification for the Use of statins in Prevention (JUPITER: an intervention trial evaluating rosuvastatin) trial, which tested the statin rosuvastatin in apparently healthy individuals with no prior cardiovascular (CVD) disease and with normal plasma low density lipoprotein (LDL) cholesterol concentrations but with raised plasma high sensitivity C-reactive protein (hsCRP) levels. The rate of the combined primary CVD endpoint was significantly reduced in the treatment arm after a median of under 2 years. The JUPITER trial is distinct from previous studies examining statin use in primary prevention groups because the target group for drug therapy was apparently healthy men and women at low or intermediate risk for developing CVD. On the basis of JUPITER's findings, there are key questions that should be assessed on the therapeutic intervention of CVD regarding: the primary prevention groups that should be targeted for statin therapy, the utility of targets in addition to plasma LDL cholesterol levels, and the need to consider the metabolic state of individuals targeted for therapy (including the presence of obesity and inflammation). The conclusion from the current analysis is that the JUPITER results warrant further LDL cholesterol lowering than is currently targeted in primary prevention groups that have a pre-existing condition or lifestyle that elevates CVD risk but still do not have a high global CVD risk (as assessed with current algorithms). This group is not captured in current widely used CVD risk calculations, however, with the identification of useful biomarkers, such as hsCRP, this group can be better identified and targeted for intervention.

Key words: Statin; C-Reactive Protein; Low density lipoprotein cholesterol; Inflammation; Cardiovascular diseases

Peer reviewer: JJ Brugts, MD, PhD, MSc, Department of Cardiology, Erasmus MC Thoraxcenter, Kralinger esch 266, 3063NB Rotterdam, Zuid-Holland, The Netherlands

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INTRODUCTION

The recently published Justification for the Use of statins in Prevention (JUPITER: an intervention trial evaluating rosuvastatin) trial by Ridker *et al*[1] has been received with much fanfare. The JUPITER trial tested the statin rosuvastatin in 17 802 apparently healthy individuals with no prior cardiovascular (CVD) disease and with normal plasma low density lipoprotein (LDL) cholesterol concentrations but with raised plasma high sensitivity C-reactive protein (hsCRP) levels. The key

findings of the study were that: (1) rosuvastatin reduced LDL cholesterol levels by 50% in the target group; (2) rosuvastatin reduced hsCRP by 37% in the group; and (3) the rate of the combined primary CVD endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from CVD causes was significantly reduced in the treatment arm after a median of under 2 years.

Currently, the established guidelines, including the most recent Adult Treatment Panel Guidelines (ATP Ⅲ) recommendations[2] and the Canadian Cardiovascular Society position statement on statin treatment[3,4], are based mainly on large randomly controlled clinical studies using statin intervention in the secondary prevention of CVD endpoints after a CVD event has already taken place (including myocardial infarction, ischemic heart disease, and heart failure). The JUPITER trial target group adds to the growing list of primary prevention groups, either proposed or directed (those with diabetes, with hypertension, with elevated LDL cholesterol levels, or at high global risk for CVD) for statin usage by the medical community.

While statins are known to be effective in the secondary prevention of CVD in patients with established CVD, whether the benefits apply to primary prevention have not been definitely shown due to ambiguous results of statin studies in relatively small numbers of primary prevention individuals. A recent meta-analyses by Brugts *et al*[5] was carried out on 10 randomised trials (including the JUPITER trial) that focused on whether statin use in primary prevention is justified to reduce all cause mortality and the incidence of major coronary and cerebrovascular events in people without established CVD but with cardiovascular risk factors. The data from 70 388 individuals showed Statin therapy was associated with significant risk reductions in all cause mortality, in major coronary events, and in major cerebrovascular events[5]. These results are in line with those previously published on the effects of statins in secondary prevention[6]. The efficacy of statins in subgroups of people aged more than 65, women, and those with diabetes mellitus has also been debated; the Brugts *et al*[5] meta-analyses also showed that statins improve survival and the risk of major CVD in these primary prevention groups as well.

The JUPITER trial is distinct, however, from previous studies examining statin use in primary prevention groups precisely because the target group for drug therapy is apparently healthy men and women at low or intermediate risk (using established factors for risk assessment) for developing CVD. The JUPITER trial results are important in the assessment of CVD risk and the assessment of individuals targeted for statin therapy for three reasons; it demonstrates: (1) the benefit of targeting a population at apparently low or moderate risk for developing CVD for statin use; (2) the potential of hsCRP as a CVD biomarker; and (3) the suitability of targeting individuals with inflammation but no other obvious CVD risks for statin use. On the basis of JUPITER's findings, there are four questions that I, and most likely others in the CVD medical and research community, would like to ask to ascertain the impact of the study.

SHOULD WE BE TARGETING A WIDER PRIMARY PREVENTION POPULATION FOR THERAPEUTIC CVD RISK LOWERING THERAPY

In general, statin therapy in primary prevention has been limited to groups at high risk for CVD, currently characterized as individuals with diabetes, hyperlipidemia, a family history of premature vascular disease, or those at high global risk of developing CVD. However, this group only comprises a small percentage of the population CVD burden (in Canada, it is approximately 10% when combined with the high-risk secondary prevention group)[3-7]. With the high health, social and economic burden of CVD (accounting for approximately 30% of deaths in Canada)[8], approaches to decrease the population CVD burden are urgently required. Targeting a broader proportion of the population could result in a substantial decrease in clinical disease incidence and the population burden of CVD. Both lifestyle modification and, when needed, pharmacological interventions should be included as therapeutic options for such individuals.

The current characterization of high-risk primary prevention groups does not capture all of the individuals without a prior CVD event who are at high risk of CVD. The number of individuals targeted for therapy in the primary prevention group is expected to increase as more reliable CVD biomarkers are identified (which may be plasma hsCRP or normal, Western plasma LDL cholesterol levels, which may be too high in certain primary prevention groups).

Furthermore, as the composition of the population in Canada and globally continues to change, including greater numbers of individuals at higher risk of CVD - particularly, overweight and obese individuals and individuals with metabolic syndrome - risk factors that capture these higher risk metabolic conditions (again these may include hsCRP or normal, Western plasma LDL cholesterol levels, which may be too high in certain primary prevention groups) should be incorporated in calculations of CVD risk and individual physician decisions on whether to treat or not to treat.

DO WE NEED OTHER TREATMENT TARGETS FOR THERAPEUTIC CHOLESTEROL-LOWERING INTERVENTION?

In the JUPITER trial, in the treatment arm, Crestor reduced CRP by 37% and lowered LDL cholesterol by

50% in individuals with normal (a mean of 100 mg/dL) cholesterol, with a subsequent highly significant reduction in myocardial infarction and stroke of approximately half and a 20% reduction in mortality. The question is whether the marked reduction in LDL cholesterol in any targeted group for statin therapy should be the sole focus of therapy. LDL cholesterol reduction with statin therapy alone reduces heart attacks by up to 40% in 5-year statin trials, regardless of the presence of other risk factors[9]. Moreover, analysis of the large-scale, randomized, placebo-controlled statin trials showed that the decrease in coronary events was best predicted by the absolute decrease in plasma LDL cholesterol concentrations[9]. Thus, it is concurred in the medical community that in individuals with either elevated plasma LDL cholesterol levels or at high CVD risk (which were the key cohorts studied in the large statin trials), LDL cholesterol reduction is likely a sufficient target of the therapy, regardless of other measurable biochemical risk factors.

A more debated question is whether individuals with normal plasma LDL cholesterol levels exhibiting adverse metabolic states (e.g. obesity or the metabolic syndrome) or lifestyles (e.g. smoking), in whom hsCRP levels are elevated, should be targeted for cholesterol reduction therapy. The current evidence indicates that this mode of therapy may be warranted. The lifetime CVD risk is quite high in "healthy" men and women by age 40, even with "normal" Western LDL-C levels[4]. This is in contrast to populations with much lower LDL-C levels (less than 70 mg/dL), due to diet and lifestyle, that have an absence of the earlier indications of chronic disease seen in the young and atherosclerosis in older people in Western populations[10,11]. Other evidence of the potentially beneficial effects of lower-than-normal LDL cholesterol concentrations comes from studies in individuals with a functional mutation in the gene for the serine protease *PCSK9*[12]. The resulting inactive protein results in decreased serum LDL cholesterol levels in affected individuals (28% in blacks and 15% in whites) with concomitant very large reductions in CVD risk (88% and 50% reductions in the coronary event rate, respectively)[12]. The resultant large reductions in CVD risk for the relatively modest decreases in LDL cholesterol, below normal, underscores the potentially large reductions in CVD risk achievable in healthy populations if therapy is initiated early enough, before LDL cholesterol levels reach normal, Western levels.

SHOULD ALL INDIVIDUALS WITH NORMAL LDL CHOLESTEROL LEVELS BE TARGETED FOR STATIN THERAPY?

The majority of individuals recruited into the JUPITER study and in whom CVD and mortality benefits were demonstrated were either obese, had the metabolic syndrome, or were smokers. Beyond these sets of patients, in whom hsCRP levels are elevated, there is not currently justification for statin use. While the cost-benefit analyses for individuals with normal, Western LDL cholesterol levels and who are neither obese, have the metabolic syndrome nor smoke has not been calculated, it would be expected that the numbers needed to treat to decrease the CVD rate and mortality and the economic cost of drug intervention in such large numbers of individuals would be too high. Furthermore, because of a lower baseline CVD risk, overall mortality benefits, it would be expected, would be more difficult to demonstrate. Finally, there is the issue of adverse effects, which might result in significant numbers of total affected individuals in the clinic, due to the large numbers in this primary prevention group.

By targeting individuals for treatment in the subset of individuals with normal, Western LDL cholesterol levels that are obese, have the metabolic syndrome, smoke or that have elevated hsCRP, we may be targeting individuals with functionally abnormal LDL particles. Elevated hsCRP is associated with increased insulin resistance and dysglycemic conditions[13]. These are conditions in which LDL particles increasingly become oxidized, glycosylated and become small and dense[14,15]. Oxidation of LDL plays a critical role in the early development of atherosclerosis[15], through the recruitment of monocyte-derived macrophages into the arterial wall and by stimulating the incorporation of cholesterol within macrophages, which results in foam cell formation and the resulting fatty streak in the arterial wall. CRP is known to form complexes with oxidized LDL[16] and thus may serve as a biomarker of oxidized LDL. In fact this may be identified by elevated hsCRP plasma levels. In this regard, the Jupiter trial may not have yielded beneficial outcome results of statin preventive intervention if smokers and obese individuals had been excluded. Despite this limitation, the Jupiter trial raises an important issue whether CRP plasma levels could be useful in the primary cardiovascular risk stratification. Rosuvastatin's beneficial CVD effects in the JUPITER trial may thus be explained both by LDL cholesterol lowering and its known pleiotropic effects, including its favourable effects on oxidized LDL and vascular remodelling[17].

SHOULD THE PRESENCE OF AN ELEVATED INFLAMMATORY STATE BE INCORPORATED IN GLOBAL CALCULATIONS OF CVD RISK, OR BE SUFFICIENT TO JUSTIFY ALTERATIONS IN LIFESTYLE OR THERAPEUTIC INTERVENTION?

CRP is a sensitive marker of inflammation and this may also be a reason that declines in CRP levels with rosuvastatin reduced CVD endpoints[1]. There is an increasing consensus that inflammation plays a key role

in advancing the atherosclerotic process in arterial walls. How does this occur? Pro-inflammatory stimulators upregulate vascular cell adhesion molecule expression by cells in the arterial wall[18,19]. This leads to the recruitment of T cells, leukocytes and macrophages to the arterial wall[18,19]. These cells, in turn, play a pathogenic role in atherosclerosis by producing pro-inflammatory cytokines and chemokines[18,19]. In animal studies, the development of atherosclerotic lesions were reduced in *ApoE* knock-out mice when specific cytokines (e.g. TNF-α)[20] and chemokines (*MCP-1* action *via* knockout of its receptor *CCR-2*)[21] were also knocked out. These studies indicated the importance of the above inflammatory cells and their secretory products in the initiation and development of atherosclerosis. The above recruited inflammatory cells also contribute to the formation of vulnerable plaques, which are prone to rupture[22]. This is because the cells contribute to the production of thrombogenic and matrix-degrading substances. Indeed, atherosclerotic plaques from unstable symptomatic patients exhibit significant infiltration by leukocytes[23]. This process results in subsequent clinical events, such as acute coronary syndromes (unstable angina, myocardial infarction and sudden death)[23].

The increased inflammation in the vasculature may be reflected in the systemic circulation by factors such as CRP. CRP levels increase in conditions with increased inflammation, including lupus, inflammatory bowel syndrome, smoking, insulin resistance and obesity[24-28]. While a direct role for CRP in mediating inflammation and atherosclerosis progression has not been conclusively established, CRP is a marker for inflammatory factors that may themselves be directly affecting CVD health since they have a known functional/enzymatic role. CRP correlates both with mediators of increased and decreased inflammation which decrease and increase, respectively, as CRP levels are reduced. Factors that are correlated with CRP and stimulate inflammation include secretory phospholipase A2, serum amyloid A (SAA) and oxidized LDL[29]. Those that are inversely correlated with CRP and decrease inflammation include HDL and its components apolipoprotein A-1 (apoA-1) and paraoxonase 1 (PON1)[29]. For example, *in vitro* and animal experiments have found that SAA can enhance inflammation by inducing the expression of proteinases thought to degrade the extracellular matrix[29]. It can also act as a chemoattractant for inflammatory cells such as monocytes, polymorphonuclear leukocytes, and T-lymphocytes[29]. Conversely, PON1 inhibits the oxidation of LDL[29,30], thereby inhibiting the effects of oxidized LDL in forming lipid-filled foam cells from macrophages, (which forms the fatty streak in atherosclerotic lesions) and activating macrophages to secrete cytokines and chemokines. The above factors that have a direct role in inflammation and affect CVD risk should be assessed for their relative utility in predicting CVD events. In the meantime, measurement of plasma hsCRP has been found to be a sensitive and reproducible marker of inflammation. This fact is highlighted in the Reynolds Score, which incorporates CRP in CVD risk calculations, and has been shown to be superior to some other CVD global risk calculations in predicting CVD events[30]. The findings of the utility of hsCRP in the JUPITER trial also suggests that incorporating plasma levels of inflammatory markers when other CVD risk factors are present (e.g. the presence of obesity) can strengthen a case for and further justify therapeutic intervention in an individual. Conversely, a convincing case has not been made for therapeutic intervention in individuals solely on elevated plasma hsCRP or other inflammatory markers. Rosuvastatin does decrease the levels of some of these factors, which have known inflammatory effects (e.g. SAA)[17], and increases others that have known benefits (HDL apoA-1)[31], while others have not been tested (e.g. PON1).

CONCLUSION

The JUPITER trial demonstrated the utility of targeting a larger primary prevention population group for therapeutic intervention than is currently targeted. Although apparently "healthy" individuals were part of the study cohorts, the majority of these individuals had at least one underlying condition or lifestyle habit, in addition to an elevated hsCRP, that is known to elevate CVD risk; e.g. the presence of obesity and smoking. While LDL cholesterol lowering alone, which was substantial in the study cohort that was administered rosuvastatin, is known to decrease CVD risk markedly, regardless of an individual's baseline plasma LDL cholesterol level, the costs for such an approach would likely be too high. Thus, pharmaceutical intervention is not warranted currently for such a broad group. The JUPITER results do indicate, however, that further LDL cholesterol lowering in primary prevention groups that have a pre-existing condition or lifestyle that elevates CVD risk but still do not have a high global CVD risk (as assessed with current algorithms) should be considered for therapeutic intervention. This group is not captured in current widely used CVD risk calculations, however, with the identification of useful biomarkers such as hsCRP, this group can be better identified and targeted for intervention.

Lifestyle changes, including cessation of smoking, exercise intervention, dietary changes and normalisation of body weight should be achieved first before considering preventive statin therapy according to CRP plasma levels.

The aim here is to decrease the high population burden of CVD and to begin therapy in individuals early enough such that their high lifetime burden of disease is lowered. As more of these biomarkers, in addition to hsCRP, are indentified and evaluated for their utility, more primary prevention groups can be rationally targeted. Just as with an elevated hsCRP, inflammation on its own is not a sufficient CVD risk factor for therapeutic intervention, but combined with other risk factors, it can

move an individual over the boundaries of who should and should not be targeted for therapy. Future directions of study on CRP include determining the direct effects of CRP in plaque progression, lesion advancement and unstable plaque formation *via* targeted CRP antisense combined with IVUS and other imaging modalities. This should help in determining the true role of CRP in atherosclerosis. Meanwhile, both lifestyle interventions and pharmaceutical treatments should be considered for individuals with elevated hsCRP that have sufficently elevated CVD risk due to the presence of other CVD risk factors, currently considered insufficient for therapeutic intervention.

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BRIEF ARTICLE

Serum oxidizability potential of ischemic heart disease patients is associated with exercise test results and disease severity

Allah Shanati, Yelena Rivlin, Sergei Shnizer, Uri Rosenschein, Ehud Goldhammer

Allah Shanati, Yelena Rivlin, Sergei Shnizer, Uri Rosenschein, Ehud Goldhammer, Department of Cardiology and Cardiac Rehabilitation, Bnai Zion Medical Center, and the Faculty of Medicine, Technion, Haifa 31048, Israel
Author contributions: Shanati A provided database and performed the research; Rivlin Y performed exercise test procedures and provided database; Shnizer S performed laboratory procedures; Rosenschein U wrote the paper; Goldhammer E designed and performed this research, analyzed the data and wrote the paper.
Correspondence to: Ehud Goldhammer, Professor, MD, FESC, Department of Cardiology and Cardiac Rehabilitation, Bnai Zion Medical Center, and the Faculty of Medicine, Technion, 47, Golomb Str., Haifa 31048, Israel. egoldh@netvision.net.il
Telephone: +972-4-8359225 Fax: +972-4-8359702
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Abstract

AIM: To find out whether serum oxidizability potential correlates with exercise test (EXT) parameters and predicts their results in chronic ischemic heart disease (IHD) patients.

METHODS: Oxidizability potential was determined in a group of chronic IHD patients who underwent a symptom limited EXT upon initiation of a cardiac rehabilitation program. The thermo-chemiluminescence (TCL) assay was used to assess serum oxidizability potential. This assay is based on heat-induced oxidation of serum, leading to the formation of electronically excited species in the form of unstable carbonyls, which further decompose into stable carbonyls and light energy (low chemiluminescence). Measured photons emission is represented by a kinetic curve which is described by its amplitude and slope (= ratio). We assessed the correlations of TCL ratio with exercise duration, metabolic equivalents (METS), maximal heart rate (mHR), maximal systolic BP, > 1 mm S-T depression, diabetes, hypertension, smoking, left ventricular ejection fraction (LVEF) > or < 40%, previous myocardial infarction, and aorto-coronary by-pass surgery and compared to the TCL ratio measured in a group of healthy controls.

RESULTS: A high TCL ratio (%) correlated well with METS (r = 0.84), with mHR (r = 0.79) and with exercise induced S-T segment shift (r = 0.87, P < 0.05). A lower serum oxidizability potential, expressed as a low TCL ratio, thus suggestive of a previous high oxidative stress, was found in IHD patients compared to healthy controls, and, in particular, in patients with low LVEF%. The TCL ratio (%) in IHD patients was 193 ± 21, compared to 215 ± 13 in controls (P < 0.05), and was 188 ± 14.7 in patients with LVEF < 40% as compared to 200 ± 11.9 in those with LVEF > 40% (P < 0.01). A trend for lower TCL ratio (%) was found in diabetic, hypertensive, and post-coronary bypass surgery patients. A paradoxically low TCL ratio (low oxidizability potential) was observed in patients without S-T depression compared to patients with S-T depression (189 ± 22 *vs* 201 ± 15, P = NS), due to the fact these patients had a much lower LVEF% and a lower exercise capacity.

CONCLUSION: Serum oxidizability potential is associated with EXT parameters, results, and IHD severity. TCL ratio is an "easy-to-measure marker" that might be incorporated into risk assessment and prediction in chronic IHD patients.

Key words: Oxidative stress; Exercise test; Ischemic heart disease

Peer reviewers: Raul Moreno, MD, Director of Interventional Cardiology, University Hospital La Paz, Paseo la Castellana, 261,

28046 Madrid, Spain; Antony Leslie Innasimuthu, MD, MRCP, Presbyterian-Shadyside Program, University of Pittsburgh Medical Center, Pittsburgh, 5230 Center Ave, Pittsburgh, PA 15232, United States

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INTRODUCTION

Oxidative stress reflects a condition in which the balance between reactive oxygen species (ROS) production and the subsequent response of the antioxidant defense system is lost, becoming skewed in favor of free radical expression[1-3]. Although a multitude of free radicals exists (hydrogen atoms, transition metal ions, carbon-centered radicals, sulfur-centered radicals *etc.*), those derived from oxygen are referred to as ROS. ROS are highly reactive and very unstable molecules, which tend to initiate chain reactions resulting in irreversible chemical changes of lipids and proteins. These potentially deleterious reactions can result in profound cellular dysfunction and even cytotoxicity[4].

Recent data imply that measurement of oxidizability is a key to kinetic evaluation of oxidative processes of LDL, blood serum and other body fluids, and can be used for monitoring the oxidative stress in different diseases and antioxidant drug therapy[5-9]. The oxidizability of a biological sample is a measure of its susceptibility to oxidation.

Growing evidence indicates that chronic and acute overproduction of ROS under pathophysiologic conditions is important for the development of cardiovascular diseases (CVD). ROS mediate various signaling pathways that underlie vascular inflammation in atherogenesis: from the initiation of fatty streak development through lesion progression to ultimate plaque rupture. Oxidative stress is the unifying mechanism for many CVD risk factors, which additionally supports its central role in CVD[10].

Evidence for increased oxidative stress has been found in plasma of patients with ischemic and nonischemic dilated cardiomyopathy and correlates directly with the severity and chronicity of symptoms, and inversely with left ventricular ejection fraction (LVEF)[11,12].

Free radical injury has also been implicated in the pathogenesis, evolution and progression of heart failure[9,13-15]. Furthermore, with the evolution of heart failure, there is a progressive increase in free radical injury and reduction of antioxidant reserves, which impacts significantly on prognosis.

Single bouts of aerobic and anaerobic exercise can induce an acute state of oxidative stress. This is indicated by an increased presence of oxidized molecules in a variety of tissues. Exercise mode, intensity and duration, as well as the kind of population under study, can impact on the extent of oxidation[16-22]. Exercise-induced oxidative stress has been investigated during and after exercise in chronic heart disease and chronic heart failure patients[13,23,24]. Most studies have shown an increased oxidative stress pre- and post-exercise However, no study has assessed the relationship between pre-exercise test (EXT) oxidizability potential, the EXT parameters and their results.

MATERIALS AND METHODS

Selection of patients

Fifty-four chronic ischemic heart disease (IHD) patients (13 females and 41 males, age 63 ± 5 years) and 11 healthy, age-matched controls were included. In the IHD group, Forty-seven patients (87%) had a previous myocardial infarction, 19 (35.2%) had an aorto-coronary bypass surgery (CABG), and 35 (64.8%) had a previous percutaneous intervention (PCI). Fifteen patients (27.7%) had diabetes mellitus (DM), 31 (57.4%) had hypertension, and 34 (62.9%) had dyslipidemia. Thirty-nine patients (72.2%) were in New York Heart Association (NYHA) class Ⅰ-Ⅱ, and 15 (27.8%) in class Ⅲ; patients in NYHA class Ⅳ were not included. Twenty-eight patients (51.8%) had LVEF < 40%, and 26 (48.2%) had an EF > 40%, including 4 patients who had normal EF (≥ 55%).

Patients with an acute or recent febrile illness, significant liver dysfunction, or renal failure (serum creatinine ≥ 2.0 mgr%) were excluded from the study. Subjects regularly using anti-oxidant supplements (vitamins A, C, E, or Co-Enzyme Q-10) or drugs with presumed anti-oxidant properties (statins, carvedilol) were required to stop these medications 7 d prior to the test.

All subjects underwent a symptom limited EXT upon initiation of a cardiac rehabilitation program; prior to the EXT, a 2 mL venous blood sample was drawn for thermo-chemiluminescence (TCL) assay.

Determination of TCL and oxidizability potential

Photons emission during heating was measured by TCL Analyzer (manufactured by Lumitest Ltd., Caesarea, Israel) using a photomultiplier model R265P (Hamamatsu Photonics Co. Ltd. Ichino-cho, Higashi-ku, Hamamatsu City, Japan) with a spectral response range of 280-650 nm. The computer program of the device has two main functions: (1) analysis of the sample preparation (0.05 mL of serum required for the test); and (2) data processing, display and storage. The serum under exam was spread over the surface of aluminum tray (a kind of miniature Petri dish) inside the sample preparation block and then was vacuum-dried. Then, the dish was mounted on a constant heater with heating temperature 80 ± 0.5℃ in the analysis block and the photons emission was measured each second for 300 s. The obtained TCL curve was described mathematically as the amplitude of the kinetic curve of the photons emission

Table 1 Demographic, clinical and TCL data *n* (%)

	IHD group	Control group
Males	41	9
Females	13	2
Age (yr)	63 ± 5	57 ± 3
Previous M.I.	47 (87)	0
Previous ACBG	19 (35.2)	0
Previous PCI	35 (64.8)	0
Diabetes	15 (27.7)	0
Hypertension	31 (57.4)	0
Current Smokers	9 (16.6)	3 (27.3)
Dyslipidemia	34 (62.9)	0
S-T depression > 1 mm ↓	21 (38.8)	0
METS	6.4 ± 0.5	10.9 ± 0.6
Exercise duration (min)	6.5 ± 0.8	11.2 ± 1.1
Max Systolic BP (mmHg)	137 ± 11	178 ± 10
Max HR (bpm)	133 ± 9	159 ± 11
EF% < 40	28 (51.8)	0
EF% > 40	26 (48.2)	0
Normal EF% (> 55%)	4	11
F.C. Ⅰ-Ⅱ	39 (72.2)	0
F.C. Ⅲ	15 (27.8)	0

and slope of the curve. The obtained curve is described mathematically as the amplitude of the kinetic curve and its slope (= ratio), which reflects the heat-induced susceptibility to oxidative modification of the tested sample, i.e. the residual oxidative capacity due to prior *in vivo* molecular oxidation. Thus, a lower curve slope suggests a lower oxidative potential, indicating higher oxidative activity before test.

Statistical analysis

Statistical analysis was performed using SPSS v15.0 (Chicago, IL, USA) and data were presented as means ± SD. Student's *t*-test was used, due to the normal distribution of results, and correlations were determined by Pearson's coefficient. Associations were considered statistically significant when the *P* value was < 0.05. Regression analysis was performed in order to find out the independent variables with the most evident impact on TCL ratio.

RESULTS

A lower serum oxidizability potential, expressed as a low TCL ratio, suggestive of a previous, high oxidative stress, was found in patients with IHD compared to normal controls, and in particular among patients with low LVEF% (please see examples in Table 1, Figures 1 and 2).

The TCL ratio (%) in IHD patients was 193 ± 21 compared to 215 ± 13 in the control group ($P < 0.05$) and was 188 ± 14.7 in patients with low LVEF (< 40%) compared to 200 ± 11.9 in patients with a better LVEF (> 40%) ($P < 0.01$). The TCL ratio correlated well with exercise tolerance expressed in metabolic equivalents as well with exercise duration ($r = 0.89$ and 0.91, $P < 0.01$, respectively). Similarly, TCL ratio correlated with exercise maximal heart rate ($r = 0.79$) and with exercise-induced ≥ 1 mm ST segment shift ($r = 0.77$).

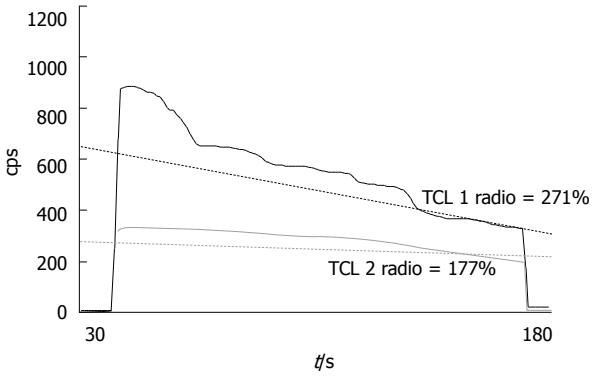

Figure 1 TCL ratios (and trend lines) of a normal subject (TCL 1) and of a patient suffering from congestive heart failure (TCL 2).

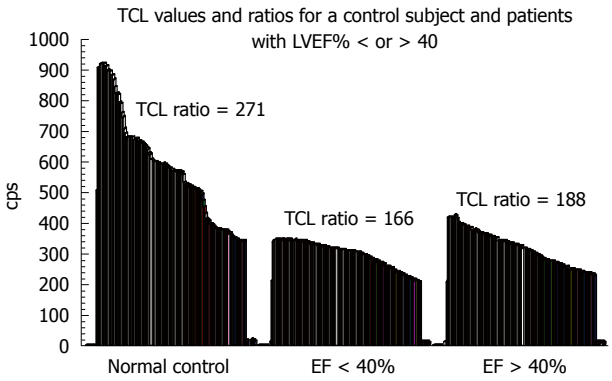

Figure 2 TCL ratio of a normal control, a patient with EF < 40%, and a patient with EF > 40%.

A trend for lower TCL ratio (%) was found in diabetic, hypertensive, and post-CABG patients (194 ± 13, 195 ± 17, and 197 ± 13, respectively, *P* = NS).

A paradoxically low TCL ratio (low oxidizability potential) was observed in patients without S-T depression compared to patients with S-T depression (189 ± 22 *vs* 201 ± 15, *P* = NS), due to the fact that these patients had a much lower LVEF% and a lower exercise capacity.

Regression analysis showed that left ventricular EF% was the best independent predictor of the TCL ratio [$R^2 = 0.87208$, $R = 0.9338$, St Err = 17.76, Adj $F = 0.87118$, ($n = 144$), $P < 0.001$].

DISCUSSION

Oxidative stress, which may result in oxidative tissue damage, occurs when there is an imbalance between ROS production and antioxidant defenses, i.e. either increased ROS production and/or impaired defense mechanisms. The net result may be assessed by the oxidizability potential.

The TCL assay used in our study is one among the accepted, validated and reproducible methods[7-9] for measurement of oxidative stress and serum oxidizability potential. This assay is based on the heat-induced oxidation

of a sample leading to the formation of electronically excited species (in particular of triplet excited carbonyls) and of light-energy, low-level chemiluminescence.

It is well known that atherosclerosis and IHD are associated with increased lipid peroxidation, and exaggerated free radical production is often observed in patients with congestive heart failure (CHF). Increased ROS production has been shown to impair endothelium-dependent vasorelaxation, to cause myocyte apoptosis, to increase monocyte adhesion and inflammatory gene expression, thus contributing to myocardial and skeletal muscle contractile dysfunction and deterioration in CHF patients[13].

In most studies involving chronic IHD and CHF patients, a significant increase in exercise-induced plasma oxidative stress was found. Exercise mode, intensity, and duration, as well as the subject population tested, all can certainly impact the extent of oxidation[16-21,25]. However, these studies disagree when pre-exercise oxidative status is examined. Sayar *et al*[13] failed to find a significant difference in resting plasma oxidative stress in CHF patients as compared with controls, the likely reason for these unexpected findings being that the control group contained patients with many cardiovascular risk factors rather than healthy controls. Thus, it was suggested that the underlying risk factors may be associated with an increase in resting pre-exercise plasma malondealdehyde levels. Díaz-Vélez *et al*[26] have reported similar findings concerning the resting plasma oxidative stress in symptomatic CHF patients (LVEF < 40%), and in asymptomatic patients with LVEF > 40% without clinical evidence of CHF but with hypertension, DM or a history of myocardial infarction. On the other hand, in the study of Belch *et al*[27], there was a significant, negative correlation between LVEF and oxidative stress.

Our findings suggest that previous, chronic or recurrent oxidative stress in IHD patients practically reduces and depletes residual oxidative capacity. In other words, residual oxidative capacity is decreased due to prior recurrent *in vivo* molecular oxidation in chronic IHD patients.

No study so far has addressed the question whether the pre-exercise oxidative status may have an impact on EXT results or whether it can contribute to the risk assessment of these patients. The findings of our study show that the sicker the patient is, with lower EF and lower exercise capacity, the lower is his serum oxidizability potential, as reflected by the lower TCL ratio. Thus, assessment of TCL ratio at resting conditions may predict EXT results and, therefore, support risk assessment in chronic IHD patients. Oxidizability potential assessment may have clinical applications in the routine follow-up of the atherosclerotic disease in obese, diabetic, and hypertensive patients, as well as in patients treated with drugs, vitamins, and food supplements with alleged or proved anti-atherogenic or pro-atherogenic properties.

COMMENTS

Background

Exercise-induced oxidative stress has been investigated during and after exercise in chronic heart disease and chronic heart failure patients. Oxidizability potential is a key to kinetic evaluation of oxidative processes of LDL, blood serum and other body fluids, and can be used for monitoring the oxidative stress.

Research frontiers

Most studies have shown an increased oxidative stress pre- and post-exercise, however, no study has assessed the relationship between pre-exercise test oxidizability potential, exercise test parameters and their results.

Innovations and breakthroughs

Study findings suggest that oxidative capacity is decreased due to prior recurrent *in vivo* molecular oxidation, thus, the sicker the patient is, with lower LVEF%, and lower exercise capacity, the lower is the serum oxidizability potential, as reflected by the lower TCL ratio.

Applications

Oxidizability potential assessment may have clinical applications in the routine follow-up of the atherosclerotic disease in obese, diabetic, hypertensive patients, in patients treated with drugs, vitamins, and food supplements with alleged or proved anti-atherogenic or pro-atherogenic properties. Measurment at resting conditions may predict exercise test results, therefore, supporting risk assessment in these patients.

Peer review

The paper is interesting, though there are small number of patients and control and they were poorly matched, the study is interesting and this should be taken as a concept of proof study. It will be a nice and interesting paper to publish.

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S- Editor Cheng JX **L- Editor** Negro F **E- Editor** Zheng XM

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Filippo Cademartiri, MD, PhD, Department of Radiology - c/o Piastra Tecnica - Piano 0, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci, 14-43100 Parma, Italy

Wayne Grant Carter, Biomedical Sciences, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, United Kingdom

Jun R Chiong, MD, MPH, FACC, FCCP, Associate Professor of Medicine, Director, Advanced Heart Failure Program, Loma Linda University, 11234 Anderson Street, Suite 4404, Loma Linda, CA 92354, United States

Alberto Cuocolo, MD, Professor, Department of Biomorphological and Functional Sciences, University Federico II, Via Pansini 5, 80131 Napoli, Italy

Alberto Dominguez-Rodriguez, MD, PhD, FESC, Department of Cardiology, University Hospital of Canarias, Ofra s/n La Cuesta, La Laguna, E-38320, Tenerife, Spain

Serafino Fazio, Associate Professor of Internal Medicine, Department of Internal Medicine, Cardiovascular and Immunologic Sciences, University Federico II, Via S. Pansini 5, 80131 Naples, Italy

Ming-Jui Hung, MD, Cardiology Section, Department of Medicine,Chang Gung Memorial Hospital at Keelung,Chang Gung University College of Medicine, 222 Mai-Chin Road, Keelung City 20401, Taiwan, China

Antony Leslie Innasimuthu, MD, MRCP, Presbyterian-Shadyside Program, University of Pittsburgh Medical Center, Pittsburgh, 5230 Center Ave, Pittsburgh, PA 15232, United States

Klaus Kettering, MD, Department of Cardiology, University of Mainz, Langenbeckstrasse 1, D-55131 Mainz, Germany

Antigone Lazou, Professor of Physiology, Lab of Animal Physiology, Sch of Biology, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

Sang-Hak Lee, Associate Professor, Cardiology Division, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul, 120-752, South Korea

Veselin Mitrovic, MD, Professor, Department of Cardiology, Kerckhoff-Klinik GmbH, Benekestrasse 2-8, 61231 Bad Nauheim, Germany

Raul Moreno, MD, Director of Interventional Cardiology, University Hospital La Paz, Paseo la Castellana, 261, 28046 Madrid, Spain

Mehmet Ozaydin, Associate Professor, Sevket Demirel Kalp Merkezi, 32100, Isparta, Turkey

Boris Z Simkhovich, MD, PhD, The Heart Institute, Good Samaritan Hospital, 1225 Wilshire Boulevard, Los Angeles, CA 90017, United States

Jonathan S Steinberg, MD, Chief, Division of Cardiology, Al-Sabah Endowed Director, Arrhythmia Institute, St. Luke's and Roosevelt Hospitals, Professor of Medicine, Columbia University College of Physicians & Surgeons, 1111 Amsterdam Ave, New York, NY 10025, United States

Wei-Chuan Tsai, MD, Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng-Li Road, Tainan 704, Taiwan, China

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Meetings

Events Calendar 2010

January 12-13
Riyadh, Saudi Arabia
1st International Cardiovascular Pharmacotherapy Conference

January 17-21
Hollywood, United States
22nd Annual International Symposium on Endovascular Therapy

January 20-23
Sao Paulo, Brazil
World Cardiology, Metabolism and Thrombosis Congress

January 21-24
Phoenix, United States
13th Society for Cardiovascular Magnetic Resonance Annual Scientific Sessions

January 28-30
Brussels, Belgium
29th Belgian Society of Cardiology Annual Scientific Meeting

January 28-31
Nashville, United States
31st Annual Meeting of The American Academy of Cardiovascular Perfusion

February 3-6
Snowbird, United States
35th Annual Cardiovascular Conference at Snowbird

February 4-5
Leuven, Belgium
Leuven Symposium on Myocardial Velocity and Deformation Imaging

February 6-9
St. Petersburg, United States
10th Annual International Symposium on Congenital Heart Disease

February 8-10
Tel Aviv, Israel
10th International Dead Sea Symposium on Cardiac Arrhythmias and Device Therapy

February 11-12
London, United Kingdom
2nd National Chronic Heart Failure and Hypertension

February 18-21
Istanbul, Turkey
The 2nd World Congress on Controversies in Cardiovascular Disease (C-Care)

February 22-25
Maui, United States
Arrhythmias & the Heart Symposium

February 22-26
Cancun, Mexico
15th Annual Cardiology at Cancun-Advances in Clinical Cardiology and Multi-Modality Imaging

February 25-28
Valencia, Spain
First International Meeting on Cardiac Problems in Pregnancy

February 26-28
Hong Kong, China
International Congress of Cardiology

February 28-March 4
Scottsdale, United States
International Congress XXIII on Endovascular Interventions

February 28-March 5
Keystone, United States
Keystone Symposia: Cardiovascular Development and Repair (X2)

March 3-5
Kish Island, Iran
Islamic Republic of 4th Middle East Cardiovascular Congress

March 4-7
Newport Beach, United States
30th Annual CREF: Cardiothoracic Surgery Symposium

March 7-12
Snowmass Village, United States
Interventional Cardiology 2010: 25th Annual International Symposium

March 14-16
Atlanta, United States
American College of Cardiology 59th Annual Scientific Session

March 18-20
Rome, Italy
VIII Congress of the Italian Society of Cardiovascular Prevention

March 18-20
Prague, Czech Republic
XI International Forum for the Evaluation of Cardiovascular Care

March 24-25
Jeddah, Saudi Arabia
12th KFAFH Cardiovascular Conference: A balanced approach to treatment of cardiovascular diseases

April 8-11
Guangzhou, China
The 12th South China International Congress of Cardiology

April 14-15
Tel Aviv, Israel
The 57th Annual Congress of the Israel Heart Society in Association with The Israel Society of Cardiothoracic Surgery

April 15-18
Izmir, Turkey
59th European Society for Cardiovascular Surgery International Congress

May 5-7
Prague, Czech Republic
EuroPRevent 2010-Cardiovascular Prevention: a Lifelong Challenge

May 8-9
St. Paul, United States
Controversies in Cardiovascular Disease: Practical Approaches to Complex Problems: Medical and Surgical

May 12-16
Marrakesh, Morocco
7th Metabolic Syndrome, type II Diabetes and Atherosclerosis Congress

May 17-20
Whistler, Canada
6th IAS-Sponsored HDL Workshop on High Density Lipoproteins

May 21-22
Sydney, Australia
3rd Cardiovascular CT, Concord Conference 2010

May 29-June 1
Berlin, Germany
Heart Failure Congress 2010

June 1-4
Seoul, Korea, Republic of
9th Asian-Pacific Congress of Cardiovascular & Interventional Radiology (APCCVIR 2010)

June 16-19
Beijing, China
World Congress of Cardiology Scientific Sessions

June 17-19
Port El Kantaoui, Tunisia
The 7th Tunisian and Europeans Days of Cardiology Practice

July 1-3
Singapore, Singapore
6th Asian Interventional Cardiovascular Therapeutics Congress

July 16-19
Berlin, Germany
Frontiers in CardioVascular Biology 2010-1st Meeting of the CBCS of the ESC

July 24-27
Vancouver, Canada
15th World Congress on Heart Disease, Annual Scientific Sessions 2010

August 13-15
Krabi, Thailand
East Meets West Cardiology 2010

September 16-18
Athens, Greece
5th International Meeting of the Onassis Cardiac Surgery Center

September 25-29
Belo Horizonte, Brazil
65th Brazilian Congress of Cardiology

September 30-October 2
Berlin, Germany
5th International Symposium on Integrated Biomarkers in Cardiovascular Diseases

October 10-13
Rochester, United States
26th Annual Echocardiography in Pediatric and Adult Congenital Heart Disease Symposium

October 16-19
Copenhagen, Denmark
Acute Cardiac Care 2010

October 20-23
Boston, United States
2010 Cardiometabolic Health Congress

November 25-26
London, United Kingdom
13th British Society for Heart Failure Annual Meeting

December 9-11
Lisbon, Portugal
Heart, Vessels & Diabetes-The European Conference

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Instructions to authors

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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