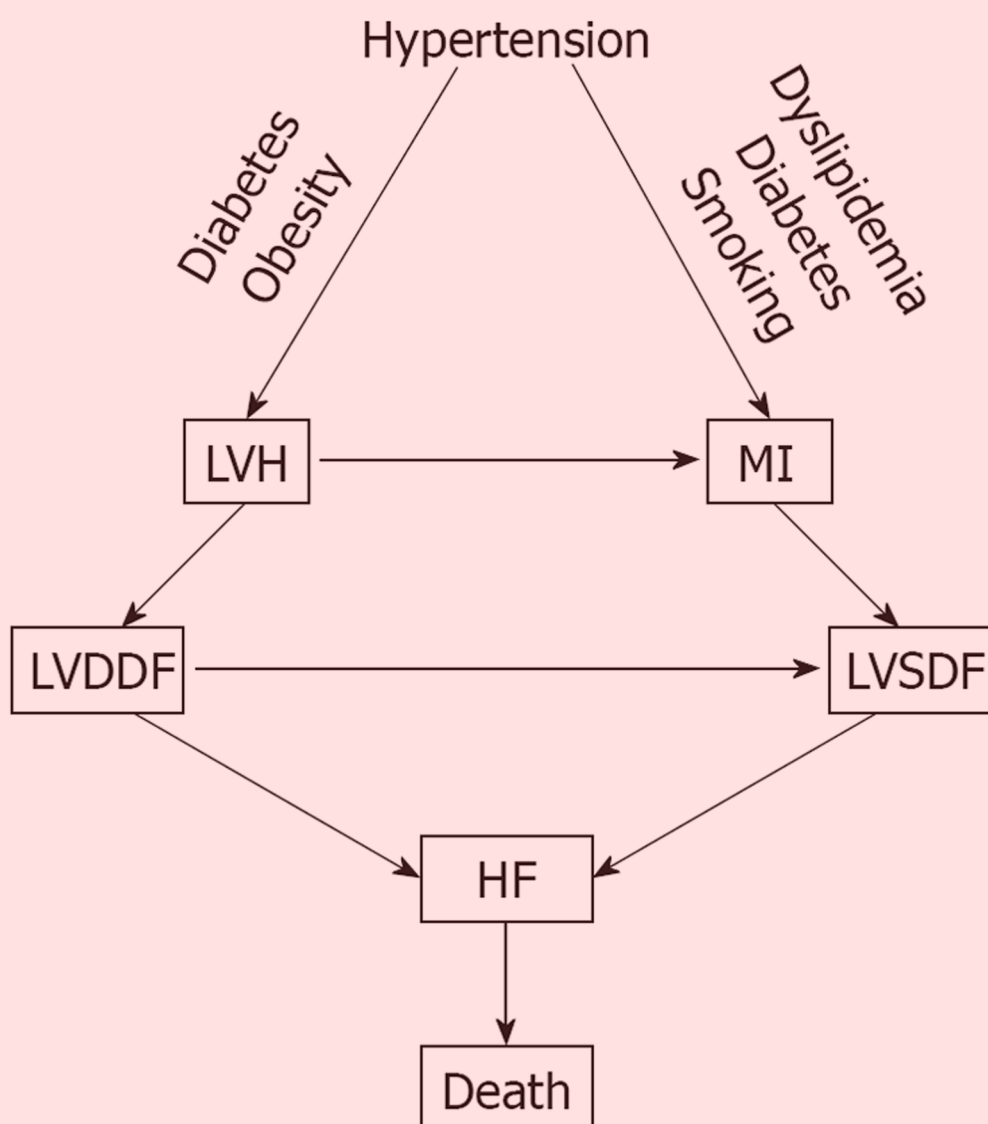


Pathophysiological mechanisms that lead to heart failure from hypertension.





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Stopping the cardiovascular disease continuum: Focus on prevention

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Abstract

The cardiovascular disease continuum (CVDC) is a sequence of events, which begins from a host of cardiovascular risk factors that consists of diabetes mellitus, dyslipidemia, hypertension, smoking and visceral obesity. If it is not intervened with early, it inexorably progresses to atherosclerosis, coronary artery disease, myocardial infarction, left ventricular hypertrophy, and left ventricular dilatation, which lead to left ventricular diastolic or systolic dysfunction and eventually end-stage heart failure and death. Treatment intervention at any stage during its course will either arrest or delay its progress. In this editorial, the cardiovascular risk factors that initiate and perpetuate the CVDC are briefly discussed, with an emphasis on their early prevention or aggressive treatment.

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Key words: Cardiovascular disease continuum; Dyslipidemia; Diabetes mellitus; Obesity; Hypertension; Smoking

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INTRODUCTION

The cardiovascular disease continuum (CVDC) was first conceived by Dzau *et al*^[1] in 1991; it is a chain of events precipitated by several cardiovascular risk factors, which if left untreated, inexorably culminate in end-stage heart failure (HF) and death. The major cardiovascular risk factors that lead to the CVDC are listed at the bottom of Figure 1 and consist of dyslipidemia, hypertension, diabetes, obesity and smoking^[2]. All these risk factors, with the exception of smoking, constitute the metabolic syndrome. The metabolic syndrome is defined by the coexistence of any three of the following risk factors: (1) increased waist circumference (≥ 102 cm in men, ≥ 88 cm in women); (2) high triglyceride levels (≥ 150 mg/dL, ≥ 1.68 mmol/L); (3) high-density lipoprotein cholesterol (HDL-C; < 40 mg/dL, < 1.03 mmol/L in men, or < 50 mg/dL, < 1.29 mmol/L in women); (4) blood pressure (BP; $\geq 130/85$ mmHg); and (5) glucose (≥ 100 mg/dL, ≥ 5.5 mmol/L); and is associated with high incidence of CVD^[3]. Since its introduction, the CVDC has been validated by several clinical trials and epidemiological studies, which have provided new insights into its underlying pathophysiology and the possible arrest of its progression by early intervention^[4].

Mounting evidence suggests that early intervention in managing the cardiovascular risk factors is more important than treating the CVD itself^[4]. CVD complications take years to develop, therefore, this affords ample time for early intervention and treatment of the various cardiovascular risk factors. In this editorial, the main CVD risk factors and their treatment are briefly reviewed.

DYSLIPIDEMIA

High cholesterol levels have long been considered an independent risk factor for CVD, and total cholesterol levels of 200 mg/dL (5.17 mmol/L) or higher and low-density lipoprotein cholesterol (LDL-C) levels of 130 mg/dL (3.36 mmol/L) or higher have been found in 50.7% and 45.8% of adult subjects, respectively^[5]. In addition, with the increase in obesity, total cholesterol levels > 200 mg/dL (5.17 mmol/L) have been found in 10% of children aged 12-19 years old, and of those screened, only 28.6% knew that high cholesterol is a risk factor for CVD. Also, a recent analysis of data for the United States, Finland and Australia^[6] has found that adolescents with dyslipidemia \geq 95th percentile have a higher incidence of increased carotid intima-media thickness in adulthood, which is a progenitor of coronary artery disease (CAD) in later life^[7]. These data suggest that obese adolescents with or without hypertension should be routinely screened for dyslipidemia and treated with lifestyle modification, or more aggressively, with cholesterol-lowering drugs. Adults with dyslipidemia and preexisting CAD should also be aggressively treated according to ATP III guidelines, to LDL-C < 130 mg/dL (3.36 mmol/L) for moderate CVD risk, to < 100 mg/dL (2.59 mmol/L) for high risk, and to < 70 mg/dL (1.81 mmol/L) for very high CVD risk^[8]. Several recent outcome trials have shown that aggressive treatment of LDL-C to < 70 mg/dL (1.81 mmol/L) with statins provides protection against recurrent CAD in high risk patients^[9-11]. However, despite aggressive LDL-C lowering, CVD continues to increase. According to the American Heart Association statistics, the incidence of CVD increased by 12% from 70.1 million in 2005 to 79.4 million in 2007^[12]. Therefore, besides LDL-C, other lipid subclasses have been considered as culprits for this increase in CVD, and recently, high non-HDL-C levels have been the focus for this increase, and have suggested that dyslipidemia is a multifactorial disease and should be treated with a combination of statins and other drugs^[13]. Also, the atherogenic phenotype that consists of small dense LDL-C particles, low HDL-C and increased triglyceride levels is also associated with high incidence of coronary heart disease^[14].

DIABETES MELLITUS

Diabetes mellitus, especially type 2, accounts for > 97% of the adult diabetic population and its prevalence has increased from 5% in 1988 to 6.5% in 2002, and is in

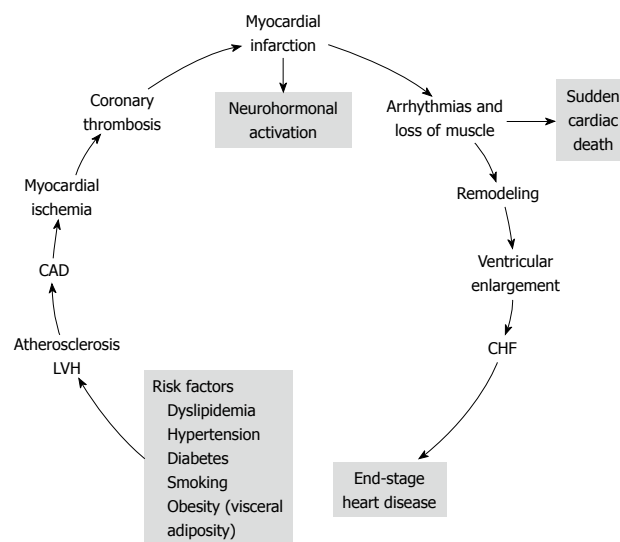


Figure 1 The various stages of the cardiovascular disease continuum (CVDC) and the different stages of intervention. CAD: Coronary artery disease; LVH: Left ventricular hypertrophy; CHF: Chronic heart failure. Reprinted with permission^[2].

line with the 6% estimate of global prevalence^[15]. This rise has been attributed to the increasing incidence of obesity and the aging of the population, which accounts for an annual incidence of 1.3 million Americans with new-onset type 2 diabetes and for the 18.2 million Americans with type 2 diabetes in 2002^[5]. The incidence of type 2 diabetes is also rising rapidly in Asian children and adults^[16]. Recent reports from China, Japan and the Pacific Islands indicate that > 70% of children are diagnosed with type 2 diabetes. In addition, a recent study from 10 Asian countries has suggested that Asian children are more susceptible in developing diabetes than Caucasian^[17]. Overt diabetes mellitus evolves from a pre-diabetic state that is characterized by insulin resistance, impaired glucose tolerance and fasting plasma glucose levels of 100-125 mg/dL (5.55-6.94 mmol/L). Several clinical trials have reported a significant improvement in the metabolic status, a delay in the progression of pre-diabetes to overt diabetes, and a decrease in the incidence of cardiovascular events with a combination of diet, exercise and anti-diabetic drugs, if necessary^[18-20]. Overt type 2 diabetes mellitus is a serious CVD risk factor and is presently considered a “cardiovascular risk equivalent”, thus conferring to diabetic patients the same risk for future cardiovascular complications as those who have already sustained a prior myocardial infarction (MI)^[21]. It is therefore critical that type 2 diabetes mellitus is treated aggressively with a combination of diet, exercise and anti-diabetic drugs, to a level of hemoglobin A_{1c} \leq 7% and BP < 130/80 mmHg, in order to prevent cardiovascular and renal complications^[22,23]. Three recently published studies have shown mixed results with respect to aggressive control of diabetes (hemoglobin A_{1c} < 7%). One study has shown a significant decrease in renal complications and no effect on cardiovascular and stroke complications by reducing hemoglobin A_{1c} to < 7%^[24]. Another

has shown an increased incidence in total mortality and no effect on cardiovascular events in the intensively treated compared to the standard treated group^[25]. A third study has shown no significant difference between the aggressively treated (hemoglobin A_{1c} < 7%) and the standard treated (hemoglobin A_{1c} > 7%) groups^[26]. In that study, LDL-C was decreased to 80 mg/dL (2.1 mmol/L). For the time being, it is prudent not to lower hemoglobin A_{1c} to < 7% in high-risk patients until new information becomes available. Also, it is recommended that LDL-C is lowered to < 100 mg/dL (< 2.59 mmol/L) in diabetic patients because they are considered to be high-risk patients^[22].

OVERWEIGHT AND OBESITY

Body overweight and obesity start from an early age. A large epidemiological study of 34 countries involving young persons aged 10-16 years old has shown that overweight and obesity are directly related to television viewing time, lack of exercise, and increased consumption of sweets and soft drinks, and decreased consumption of fruits and vegetables^[27]. Countries with the highest obesity rates are the United States, Canada, England and Southwest Europe^[27]. Other epidemiological studies have also shown that the percentage of Americans who are either overweight or obese has increased significantly over the past 25 years, and accounts for 64% and 30.5% of subjects age ≥ 20 years who are either overweight or obese, respectively^[28]. A rapid rise in obesity and the metabolic syndrome has also been noted in many Asian countries as a result of changes in nutrition and physical activity^[29]. This rise has resulted in increased incidence of diabetes and CVD^[29]. Excess body weight, besides being an independent risk factor for CVD, also contributes to other risk factors, such as type 2 diabetes mellitus, hypertension and dyslipidemia, which further increase the prevalence and severity of CVD^[28,30]. Central obesity is associated with insulin resistance and has been shown to be an independent risk factor for ischemic stroke, even after adjustments for body mass index and other risk factors^[31]. Because of these alarming trends in obesity increase, major medical societies have issued recent guidelines instructing healthcare professionals about how to stem the rise in this epidemic, by advising their patients about weight loss, diet, exercise, and pharmacological treatment, if necessary^[27,28,32,33].

SMOKING

Cigarette smoking is a well-established risk factor for the CVDC^[34,35], and is listed in the Framingham CVD risk factors^[36]. Long-term prospective studies have clearly demonstrated the considerable mortality risk reduction associated with smoking cessation^[35,37,38]. A 50-year follow-up of 34 439 male British physicians has shown that quitting cigarette smoking at any age is associated with prolongation of life expectancy^[35]. In that study,

physicians who stopped cigarette smoking at age 60, 50, 40 or 30 years, gained about 3, 6, 9, or 10 years in life expectancy, respectively^[35]. A recent study has also shown that subjects with CVD improve their survival^[39]. In 1521 patients aged ≤ 65 years with a first MI, who were followed for a mean 13.2 years, the odds of dying were 0.57 for never smokers, and 0.50 for pre-MI quitters compared to persistent smokers. In addition, among the persistent smokers, in those who reduced the number of cigarettes smoked, there was an 18% decline in mortality for every five-cigarette decrease in smoking^[39]. The mechanisms by which cigarette smoking exerts its cardiovascular damaging effects is not clearly delineated. The most plausible mechanisms include, lipid oxidation, inflammation and thrombosis, with lipid oxidation being the most dominant^[40]. Additional factors include vasospasm from nicotine and decreased oxygen delivery due to formation of carboxyhemoglobin. Quitting cigarette smoking is very difficult and recidivism is very high. According to a current American report, approximately 44% of smokers attempt to quit annually, but only 4%-7% succeed^[41]. The smoking cessation rate is a little higher in persons who suffer from CAD. It has been estimated that between 28% and 74% quit after an acute MI^[42,43]. However, about 40% of the quitters relapse and the major reason is post-MI depression^[42]. Medical intervention has resulted in a higher percentage of patients who quit smoking: 61% *vs* 42% of controls^[43]. Smoking cessation or abstinence altogether has been a major undertaking by many countries, by forbidding cigarette smoking in closed places or increasing the price of cigarettes. Family guidance and student education in schools about the health hazards of cigarette smoking will help stop young people from taking up cigarette smoking.

HYPERTENSION

Hypertension is one of the major cardiovascular risk factors for the CVDC and its incidence continues to rise. It increased by 10% between 2005 and 2007, from 65 million to 72 million^[12]. Hypertension evolves from a pre-hypertensive state, and this evolution can be delayed or prevented by treating pre-hypertension with diet, salt restriction or drugs^[44-48]. There is a linear and continuous relationship between BP level and cardiovascular morbidity and mortality, regardless of age or sex^[49], and its reduction is also directly related to the decreased incidence of cardiovascular and cerebrovascular complications^[50,51]. In addition, hypertension is one of the most common conditions that predispose to HF. A recent meta-analysis of clinical trials of 193 424 patients has found that 24 837 patients suffered major cardiovascular events^[52]. Of these, 7171 (28.9%) were cases of HF, 10 223 (41.1%) were cases of CAD, and 7443 (30.0%) were stroke cases. The incidence of HF was similar to that of stroke and was more prevalent in older persons (> 65 years), in blacks, and in diabetics. Other investigators have also reported that hypertension is a major risk

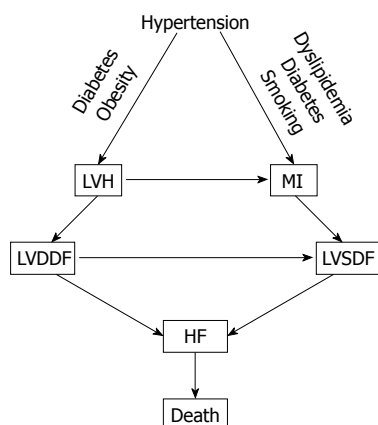


Figure 2 Pathophysiological mechanisms that lead to heart failure (HF) from hypertension. MI: Myocardial infarction; LVDDF: Left ventricular diastolic dysfunction; LVSDF: Left ventricular systolic dysfunction.

factor for HF^[53,54]. In a meta-analysis by Moser *et al*^[53], of 13 342 subjects with hypertension, 1493 (11.2%) from the control groups progressed from less severe to severe hypertension, compared with only 95 of 13 389 (0.17%) from the treated groups. The incidence of left ventricular hypertrophy (LVH) and HF was higher in the control (placebo) than in the treated groups^[53]. In the Framingham Heart Study, the association of baseline systolic, diastolic and pulse pressures was examined in 2040 subjects aged 50-79 years old who were free from HF at the baseline examination, and HF developed in 11.8% after 24 years of observation^[54]. All these studies point to a common pathophysiological mechanism for the development of HF. Untreated or poorly treated hypertension, alone or in combination with obesity and diabetes mellitus, eventually leads to cardiac remodeling, LVH, left ventricular diastolic dysfunction (LVDDF), HF and death. In addition, LVDDF may also lead to left ventricular systolic dysfunction, which also can arise from MI as a result of hypertension, dyslipidemia and diabetes. This eventually leads to HF and death as depicted in Figure 2. It is, therefore, prudent that instead of focusing on treating the end-stage disease, our attention should be directed to the early diagnosis and treatment of hypertension and other comorbid conditions. There are several options for the treatment of hypertension, including diet^[48], salt restriction^[47], or drug therapy with any class of antihypertensive drugs, but preferably with drugs that block the renin angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and direct renin inhibitors (DRIs). These drugs are more effective in preventing or regressing cardiac remodeling and LVH^[55-60].

CONCLUSION

From the evidence presented, it appears that early detection and treatment of the risk factors that initiate the CVDC could stop or greatly delay its further progression. The emphasis, therefore, should be based on preventing

the disease, instead of waiting for it to develop and then treat it. The new treatment paradigm is a shift to the left on the events that comprise the CVDC (Figure 1). On this theme, there have been several recent calls to practicing physicians by national scientific committees for proactive treatment of cardiovascular risk factors^[27,30,32]. There is an urgent need to stem the rising tide of obesity and the metabolic syndrome and their consequences by stressing weight loss through diet and exercise, starting from childhood and continuing through adult life. Pre-diabetes should be recognized and treated early to prevent its progression to overt diabetes. Overt diabetes should be treated aggressively to hemoglobin A_{1c} < 7%, with a combination of diet, exercise and anti-diabetic drugs. Caution should be exercised in older, high-risk patients to avoid serious hypoglycemia. High cholesterol level should also be recognized and treated early, and cigarette smoking should be discouraged through parental guidance and school education about the serious health problems that it can cause later in life. Above all, hypertension should be diagnosed and brought under control early, before it causes target organ damage that is difficult to repair. Whether to treat pre-hypertension pharmacologically, on a large scale, is a question that needs to be addressed soon. Preliminary studies have shown that treatment of pre-hypertension can delay or stop its progression to overt hypertension. Non pharmacological means such as weight loss, salt restriction and exercise should be tried first because they are known to work. Recent reports that aggressive treatment of hypertension is associated with higher cardiovascular complications concerns older, high-risk subjects with preexisting CAD^[61,62]. Aggressive control of uncomplicated hypertension is very important because it prevents target organ damage and the incidence of stroke, HF and renal failure. There are several classes of antihypertensive drugs to choose from because they are all effective in lowering BP^[63], but individualization of treatment may be necessary. Diuretics, although effective in lowering BP, may not be a good choice for hypertensive subjects with diabetes or the metabolic syndrome, because they increase blood glucose, which is associated with high incidence of cardiovascular morbidity and mortality^[64-66]. Drugs that block the RAS such as ACEIs, ARBs, and DRIs are preferable in such cases, because they interfere with the action of angiotensin II, which is responsible for cardiovascular remodeling, new-onset diabetes mellitus, and HF (Figure 2). In the Acute Decompensated Heart Failure National Registry (ADHERE), 91% of patients with HF and preserved ejection fraction had hypertension, CAD and diabetes^[67]. In the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT), control of BP was the most important factor in the reduction of hospitalization for HF^[68]. Since these comorbidities that are associated with hypertension greatly influence the patient's outcome, clinicians should try to identify and treat aggressively all these conditions associated with hypertension.

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Need for new materials, biofunctionalization and non-surgical heart valve technology

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INTRODUCTION

A number of recent reviews and original papers have demonstrated that transition from non-surgical heart valve defect repair from bench to bedside is a reality. Although this is also the case for atrioventricular valves, research and clinical applications are clearly prevalent among tubular system valves^[1]. In any case of new catheter-based technique, a precise imaging technique is essential (e.g. magnetic resonance imaging and/or transesophageal echocardiography).

VALVES PLACED WITHIN TUBULAR SYSTEMS

Bonhoeffer was the first to perform transcatheter implantation of a prosthetic valve into the pulmonary valve position in 2000^[2]. Cribier is credited with pioneering the concept of transcatheter aortic valve implantation (TAVI), with the first such procedure performed in 2002^[3]. Although TAVI has not gained worldwide acceptance, several thousands of these percutaneous prostheses have been implanted. Although there are several modifications, they are all bioprostheses with the dual components of a metallic carrier (i.e. the stent) and a prosthetic valve of animal origin. To date, almost 10 different designs of these prosthetic valves have been developed for catheter-based implantation. Of these, the CoreValve ReValving system has become the most widely used^[4]. Its design derives from original experiments by

Abstract

Transition from non-surgical heart valve defects repair from bench to bedside is a reality. Some biological material-based designs for transcatheter aortic valve implantation are ready for use. Their drawback, however is their unknown functional as well as structural durability. Moreover, research on new non-biological materials is essential to replace classical animal-derived sources of human heart valve prostheses.

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Key words: Biomaterials; Aortic valve; Non-biological materials; Heart valve prosthesis

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Andersen *et al*^[5] undertaken in 1992. The only difference is that the current valvular prostheses are self-expandable and do not use the hydraulic force of the balloon catheter to expand. The only justifiable indications include the impossibility of employing a standard heart surgery technique, or too high surgical or anesthesiology-related risks as determined by the hospital's institutional review board. Considering the fact that a target group of such patients no doubt exists, surgeons have sought to minimize the operating field by creating the transapical approach. However, it should be kept in mind that the conventional cardiac surgical procedure definitely serves as a gold standard. In terms of valve prosthesis durability, mechanical components are clearly superior to biological ones, even at the cost of risks associated with permanent anticoagulant therapy. As all biological materials including surgically implanted prostheses are subject to degeneration (e.g. leaflet thickening, calcium deposition or loss of physical properties), it is mostly elderly patients who are indicated for bioprosthesis implantation. With biological prostheses inserted using a catheter, emphasis is initially placed on increased mechanical trauma during the crimping process, and its subsequent catheter-based passage to the ultimate position. It was for this reason that all pilot studies enrolled patients of advanced age with limited life expectancy, which made it impossible to define valve durability clearly.

In conclusion, the design of current valves intended for placement in tubular structures has been refined and is functional and justified for a limited period of time. Moreover, there is no evidence of extensive randomized comparison between more valve designs, even if they have the same principle of action (i.e. Edwards Sapien *vs* CoreValve, when both are derived from Andersen's original model). The task in the years to come is to search for novel materials that are not prone to degeneration in the way that denatured tissues of animal origin are. These will most likely be polymers employed in the manufacture of biofunctional nanofibers. These materials are expected to offer prolonged durability compared with that seen in current biological valves, and feature all the possible attributes of the ideal implant in blood flow (biocompatibility, fatigue resistance, elimination of the risk of valve apparatus fracture, resistance of immunity-mediated processes, resistance to calcium deposition, and antithrombogenic surface). It would then be sufficient if the novel material possesses at least the properties identical to those seen in current components of mechanical valves^[6,7]. Several materials that have shown promise to meet these requirements are currently available^[8,9]. The introduction and widespread use of such materials will most likely change the position of bioprostheses, whatever their design, in the area of cardiac valve surgery, as well as TAVI. Efforts are also being made to miniaturize the biotechnology^[10] so that it could be combined with polymer engineering, thus giving additional biofunctionalization. The goal is thus set, the needs are defined, and the process is underway, but the product has not yet

been developed^[11]. However, it seems it is just a matter of time before one becomes available.

NON-TUBULAR SYSTEM VALVES: ATRIOVENTRICULAR VALVES

This issue is addressed here only for the sake of providing a comprehensive overview. Unlike tubular valves, those placed in between two moving compartments are much more complicated. Although the left heart is much more important than the right, the tricuspid valve is the most intricate structure (reduced wall thickness compared with the left heart, three papillary muscles, a larger annular area, different coaptation geometry). Still, it is the mitral valve that has long attracted more attention, both in experimental and clinical studies designed to manage valve repair non-surgically. Interest in balloon mitral commissurotomy, on the other hand, has waned completely as attention has mainly focused on defects with regurgitation. Also, major technical advances have been made in the mechanical, mostly metallic, components. It seems no progress has been made to date in the field of biomaterials. Non-surgical catheter-based techniques seem to be feasible *via* the left ventricular apical approach or the classical trans-vessel approach. The first approach has been attempted at mitral valve stabilization in the presence of papillary muscle rupture in a patient who developed cardiogenic shock after acute myocardial infarction^[12]. Other techniques that have found widespread use include those that connect both mitral leaflets using a clip or suture (Evalue edge-to-edge clip, and the Edwards MOBIUS system) and give rise to a double orifice mitral valve^[13,14]. Also relatively frequent are techniques that are designed to shift the anterior mitral leaflet towards the center of the annulus, thus making use of the deformation force of a body advanced into the coronary sinus. A number of modifications of the approach and a variety of devices have been reported; however, relative functionality has only been achieved in cases that do not involve annulus dilatation. Other catheter-based approaches are only of marginal importance and still under development, as are mini-surgical procedures. Although attempts at anchoring the bioprostheses in the stent carrier have been made, they are associated with excessive risks of stent migration, embolization, endoleak and interference with surrounding structures. Added to this are all the drawbacks of biomaterials listed in the section addressing the issue of bioprostheses placed within tubular structures.

The all-out effort within this exciting area of research, experiments, and initial clinical experience is far from being over. A true breakthrough will not come until a novel material is discovered that has the properties of biological tissue coupled with the durability of mechanical prosthetic valves currently used in cardiac surgery. This is as yet an unrealized goal for the coming years.

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Heart and HAART: Two sides of the coin for HIV-associated cardiology issues

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Abstract

The introduction of highly active antiretroviral therapy (HAART) has generated a contrast in the cardiac manifestations of acquired immunodeficiency syndrome. In developed countries, we have observed an approximately 30% reduction in the prevalence of human immunodeficiency virus (HIV)-associated cardiomyopathy, possibly related to a reduction of opportunistic infections and myocarditis. In developing countries, however, where the availability of HAART is limited and the pathogenic impact of nutritional factors is significant, we have observed an approximately 32% increase in the prevalence of HIV-associated cardiomyopathy and a related high mortality rate from congestive heart failure. Also, some HAART regimens in developed countries, especially those including protease inhibitors, have been shown to cause, in a high proportion of HIV-infected patients, an iatrogenic metabolic syndrome (HIV-lipodystrophy syndrome) that is associated with an increased risk of cardiovascular events related to a process of accelerated atherosclerosis, even in young HIV-infected people. Careful cardiac screening is warranted for patients who are being evaluated for, or who are receiving, HAART regimens, particularly for those with known underlying cardiovascular risk factors. A close collaboration between car-

diologists and infectious disease specialists is needed for decisions regarding the use of antiretrovirals, for a careful stratification of cardiovascular risk factors, and for cardiovascular monitoring of HIV-infected patients receiving HAART, according the most recent clinical guidelines.

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Key words: Human immunodeficiency virus; Acquired immunodeficiency syndrome; Cardiovascular disease; Lipodystrophy syndrome; Highly active antiretroviral therapy

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INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has significantly improved the clinical evolution of human immunodeficiency virus (HIV) disease, with increased survival of HIV-infected patients. How-

ever, this generated contrasting and intriguing issues in HIV-associated cardiovascular complications.

HIV-ASSOCIATED CARDIOLOGY ISSUES

HIV infection is recognized as an important cause of dilated cardiomyopathy. In developed countries, we have observed a reduction of 30% in the prevalence of HIV-associated cardiomyopathy, possibly related to the reduction of the incidence of opportunistic infections and myocarditis. On the other hand, in developing countries, with somewhat limited availability of HAART, and with a significant impact of nutritional factors, we have observed an increase in the prevalence of HIV-associated cardiomyopathy (about 32%)^[1], with a related high mortality rate for congestive heart failure. A similar trend has been observed for pericardial effusion, the prevalence of which was reduced by 30%-35% after the introduction of HAART in developed countries^[2], whereas in developing countries, the prevalence of pericardial effusion is increased by 35%-40%, mostly related to *Mycobacteria* infections^[3,4].

The prevalence of infective endocarditis does not vary in HIV-infected patients who use intravenous drugs after the introduction of HAART, even in developed countries^[5]. Estimates of infective endocarditis prevalence vary from 6.3% to 34% of HIV-infected patients who use intravenous drugs independently of HAART^[6]. Among intravenous drug addicts, the tricuspid valve is most frequently affected and the most frequent agents are *Staphylococcus aureus* (> 75% of cases), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*^[6]. Patients with HIV infection generally have similar presentations and survival (85% vs 93%) from infective endocarditis as those without HIV. However, patients with late-stage HIV disease have about 30% higher mortality with endocarditis than asymptomatic HIV-infected patients, which may be related to the degree of immunodeficiency^[7]. Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, had a prevalence of 3%-5% in acquired immunodeficiency syndrome (AIDS) patients, mostly in those with HIV-wasting syndrome, before the introduction of HAART^[6]. Marantic endocarditis is now more frequently observed in developing countries with a high incidence (10%-15%) and mortality for systemic embolization^[3,4].

The incidence of HIV-associated pulmonary hypertension increased after the introduction of HAART. It has been estimated at 1/200, which is much higher than 1/200 000 found in the general population^[8]. In this condition, a key pathogenetic role is played by pulmonary dendritic cells, which are not sensitive to HAART and may hold HIV-1 on their surfaces for extended time periods^[8]. The infection of these cells by HIV-1 cause chronic release of cytotoxic cytokines (e.g. endothelin-1, interleukin-6, interleukin-1 β and tumor necrosis factor- α), which contribute to vascular plexogenic le-

sions and progressive tissue damage, independently of opportunistic infections, stage of HIV disease and HAART regimens^[8]. Positive results have been reported with the use of bosentan, an endothelin-1 receptor antagonist, even in association with HAART, especially in the early stages of the disease^[9,10]. The efficacy of phosphodiesterase-5 inhibitors (e.g. sildenafil) is still debated because of their interaction with antiretroviral drugs, especially protease inhibitors (PIs).

The prevalence of cardiac Kaposi's sarcoma in AIDS patients ranges from 12% to 28% in retrospective autopsy studies performed before the introduction of HAART^[6]. Non-Hodgkin's lymphoma involving the heart is infrequent in AIDS^[6,11]. The introduction of HAART led to a reduction by about 50% in the overall incidence of cardiac involvement by Kaposi's sarcoma and non-Hodgkin's lymphoma, possibly related to an improved immunological state of the patients and to reduced prevalence of opportunistic infections (human herpes virus 8 and Epstein-Barr virus), which are known to play an etiological role in these neoplasms. On the contrary, an increased prevalence of cardiac involvement of AIDS-associated tumors may be observed in developing countries in relation to the scant availability of HAART^[3,5].

A wide range of inflammatory vascular diseases including polyarteritis nodosa, lupus-like syndrome, Henoch-Schönlein purpura, and drug-induced hypersensitivity vasculitis may develop in HIV-infected individuals. Kawasaki-like syndrome^[12-14] and Takayasu's arteritis^[15] have also been described. Drug-induced hypersensitivity vasculitis is common in HIV-infected patients who receive HAART^[13]. The vasculitis associated with drug reactions typically involves small vessels and has a lymphocytic or leukocytoclastic histopathology^[13]. Medical practitioners need to be especially aware of abacavir hypersensitivity reactions because of the potential for fatal outcomes. Hypersensitivity reactions of this type should always be considered as a possible etiology for a vasculitic syndrome in an HIV-infected patient^[13].

HIV-associated lipodystrophy or lipoatrophy, which were not reported before the introduction of HAART, was first described in 1998^[16]. It is characterized by the presence of a dorsocervical fat pad (also known as buffalo hump), increased abdominal girth and breast size, lipoatrophy of subcutaneous fat of the face, buttocks and limbs, and prominence of veins on the limbs. The overall prevalence of at least one physical abnormality is thought to be about 50% in otherwise healthy HIV-infected patients who are receiving HAART, although reported rates range from 18% to 83%^[17,18]. The pathogenesis of HAART-associated lipodystrophy is complex and a number of factors are involved, including direct effects of HAART on lipid metabolism, endothelial and adipocyte cell function, and mitochondrial dysfunction^[19]. As in genetic lipodystrophy syndromes, fat redistribution may precede the development of metabolic complications in HIV-infected patients who are receiving HAART. Among HIV-infected patients with lipodystro-

phy, increased serum total and low-density lipoprotein cholesterol and triglyceride levels have been observed in about 70%, whereas insulin resistance (elevated C-peptide and insulin) and type 2 diabetes mellitus have been observed in 8%-10%^[17-19].

The increased cardiovascular risk associated with lipodystrophy syndrome may be related to a specific action of antiretroviral drugs and to individual risk factors (e.g. smoking habit, and inherited metabolic disease). Some HAART regimens, such as those that include zidovudine, some non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz), and PIs disrupt endothelial cell junctions and cytoskeletal actin of the endothelial cells, which leads to endothelial dysfunction and damage^[20-22]. PIs may also reduce endothelial nitric oxide synthase expression and increase the levels of superoxide anion as expression of increased endothelial oxidative stress^[23].

According to most clinical studies, HAART should be considered a strong, independent predictor for the development of subclinical atherosclerosis in HIV-infected patients, as demonstrated by measurement of carotid intima-media thickness (cIMT), regardless of known major cardiovascular risk factors and atherogenic metabolic abnormalities induced by this therapy^[24-27]. The increased use of lipid-lowering agents and PI-free HAART regimens, and the reduction of smoking may decrease cIMT in HIV-infected patients over time^[28]. Markers of subclinical atherosclerosis should be carefully assessed in HIV-infected patients who are receiving HAART, especially in those with lipodystrophy syndrome.

HIV-associated endothelial dysfunction and injury, autoimmune reaction to viral infection (vasculitis), and renal disease have been hypothesized to play a role in the pathogenesis of HIV-associated hypertension. HIV-associated renal impairment can be caused directly or indirectly by HIV-1 and/or by drug-related effects that are directly nephrotoxic, or lead to changes in renal function by inducing metabolic vasculopathy and renal damage^[29]. Arterial hypertension, even in agreement with the Adult Treatment Panel-III guidelines^[30], is currently considered part of HAART-associated metabolic syndrome^[31]. It appears to be related to PI-induced lipodystrophy^[32] and metabolic disorders, especially to elevated fasting triglyceride and insulin resistance^[31,33].

Besides inherited disorders, HIV-infected patients who are receiving HAART, especially those with fat redistribution and insulin resistance, might develop coagulation abnormalities, including increased levels of fibrinogen, D-dimer, plasminogen activator inhibitor-1, and tissue-type plasminogen activator antigen, or deficiency of protein S^[34,35]. For instance, protein S deficiency has been reported in up to 73% of HIV-infected men^[34,35]. These abnormalities are associated with thromboses involving veins and arteries and seem to be related to HAART regimens that include PIs^[36]. Thrombocytosis has been reported in 9% of patients who are receiving HAART, with cardiovascular complications in up to 25% of cases^[37].

A debated issue concerns coronary artery disease. The association between viral infection (cytomegalovirus or HIV-1) and coronary artery lesions is not clear. HIV-1 sequences have been detected by *in situ* hybridization in the coronary vessels of an HIV-infected patient who died from acute myocardial infarction^[38]. Conflicting data still exist on the relationship between HAART and the incidence of acute coronary syndromes, such as unstable angina or myocardial infarction, among HIV-infected patients who are receiving PI-containing HAART^[39-43]. Differences in the study design, selection of patients, definition of the cardiovascular events and study endpoints, and statistical analyses might explain this disparity. However, longer exposure to HAART and/or PIs seems to increase the risk of myocardial infarction. The results of the Data Collection on Adverse Events of Anti-HIV Drugs study showed that HAART was associated with a 26% relative risk increase in the rate of myocardial infarction per year of HAART exposure^[44]. A recent analysis of the risk for myocardial infarction in relation to the exposure to specific antiretroviral drugs has shown that indinavir, lopinavir-ritonavir, didanosine and abacavir are associated with a more significant risk^[45]. However, as with any observational study, these findings must be interpreted with caution (given the potential for confounding) and in the context of the benefits that these drugs provide^[45].

For patients on HAART, it may be important to evaluate the traditional vascular risk factors and try to intervene in those that can be modified. Existing guidelines for the management of dyslipidemia in the general population, such as those of the National Cholesterol Education Program^[30], currently represent the basis for therapeutic recommendations in HIV-infected individuals, such as those reported by the HIV Medicine Association of the Infectious Disease Society of America and Adult AIDS Clinical Trial Groups and by the Pavia Consensus Statement^[46,47]. In the absence of specific trial data, HIV patients who present with acute coronary syndromes should be treated according to the international guidelines. Diet and exercise should not be overlooked, because both can be effective in managing these complications without causing further side effects. Fibric-acid derivatives and statins can lower HIV-associated cholesterol and triglyceride levels, although further data are needed on interactions between statins and PIs. Most statins are metabolized through the CYP3A4 pathway, which raises concern over potential interactions with PIs. The inhibition of CYP3A4 by PIs could potentially increase by several-fold the concentration of statins, thus increasing the risk of skeletal muscle or hepatic toxicity. Pravastatin, fluvastatin and rosuvastatin appear to be the safest agents at this time, since they are least influenced by the CYP3A4 metabolic pathway^[48]. Although further controlled clinical trials are needed, promising results have been reported with the administration of ezetimibe and omega-3 fatty acids^[48]. They do not interact with PIs and may be safely administered in combination with

low-dose statins. In treating hypertension in HIV-infected patients with metabolic syndrome, it may be important to remember that beta-blockers and diuretics may worsen the metabolic profile in these patients. Calcium channel blockers should be used with caution since they may interact with PIs. ACE inhibitors and angiotensin II receptor blockers may be recommended, but controlled clinical trials are still lacking in this subset of patients^[47]. Hypoglycemic agents may have some role in managing glucose abnormalities. Glitazones can be administered in combination with metformin. However, glitazones may interact with PIs and cannot be recommended for fat abnormalities alone, and metformin may cause lactic acidosis^[47].

New insights in defining the cardiometabolic risk in patients with HAART-associated metabolic syndrome have been recently provided by the echocardiographic measurement of the epicardial adipose tissue. Epicardial adipose tissue is the true visceral fat of the heart and is significantly correlated with both epicardial fat and abdominal visceral fat measured by magnetic resonance imaging^[49]. In patients with HIV-lipodystrophy syndrome, echocardiographic epicardial fat correlates with intra-abdominal visceral fat, cIMT, and clinical parameters of the metabolic syndrome (especially waist circumference, blood pressure, high-density lipoprotein cholesterol, fasting glucose and insulin), with adiponectin and with markers of fatty liver disease^[49-51]. These findings suggest that echocardiographic assessment of epicardial fat may have the potential to be a simple and reliable marker of visceral adiposity and increased cardiovascular risk in patients with HIV-lipodystrophy syndrome^[49,50].

CONCLUSION

The introduction of HAART has revealed two sides of the coin for HIV-associated cardiology issues. It has significantly reduced in developed countries the prevalence of HIV-associated cardiomyopathy, which heavily influenced the prognosis of HIV-infected patients living in these countries in the pre-HAART period, and still influences the prognosis of HIV-infected patients living in developing countries. However, HAART-associated lipodystrophy syndrome and related cardiovascular risks in developed countries is an increasingly recognized clinical entity. The multifactorial pathogenesis of HIV-associated lipodystrophy syndrome represents an intriguing field of future basic and clinical research. Careful cardiac screening for patients who are being evaluated for, or who are receiving, HAART regimens, is warranted according to the most recent clinical guidelines, with a close collaboration between cardiologists and infectious disease specialists.

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Advances in diastolic heart failure

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Abstract

More than 50% of people living with congestive heart failure have diastolic heart failure (DHF). Most of them are older than 70 years, and female. The prevalence of DHF has increased with time. DHF is caused by left ventricular (LV) diastolic dysfunction (DD) which is induced by diastolic dyssynchrony. Cardiac and extra-cardiac factors play important roles in the development of heart failure (HF) symptoms. The diagnosis of DHF is generally based on typical symptoms and signs of HF, preserved or normal LV ejection fraction, DD and no valvular abnormalities on examination, using non-invasive and invasive methodologies. The outcomes with pharmacological therapy in patients with DHF are frequently neutral in clinical trials, and prognosis still remains poor with a 5-year mortality of 42.3% after hospitalization for HF. Further trials are necessary.

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Key words: B-type natriuretic peptide; Diastolic dysfunction; Diastolic dyssynchrony normal ejection fraction; Diastolic heart failure; Echocardiography; Heart failure

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INTRODUCTION

The terms, systolic and diastolic heart failure (DHF), have been routinely used in clinical practice to establish categories of congestive heart failure (CHF). Ejection fraction (EF) as the preferred index of left ventricular (LV) systolic performance has been recognized. In addition, LVEF as an indicator of the LV pumping function allows the separation of patients with heart failure (HF) into grades of severity associated with different prognoses. In clinical practice, a group of patients with CHF characterized by normal or near-normal LVEF and absence of progressive LV dilatation, were classified as DHF by Kessler^[1]. This review highlights advances in the clinical and diagnostic aspects of DHF.

PREVALENCE OF DHF

CHF affects approximately six million people, and more than 550 000 new cases are diagnosed each year in the USA^[2,3]. Studies have demonstrated that more than 50% of people living with CHF have DHF^[3,4]. Most patients with DHF are older than 70 years, and are female. Patients with DHF are usually overweight and quite often are smokers^[5]. In another study, 69% of men and 90% of women with CHF had DHF, based on current HF symptoms and an LVEF > 45%^[6]. In the CHARM preserved trial of DHF, a total of 3025 patients with a mean age of 67 years and a mean LVEF of 54% were included, 40%

were women^[7]. In the PEP-CHF multicenter, randomized, placebo-controlled trial, 850 patients with DHF and a mean age of 76 years and a mean LVEF of 65% were enrolled, 55% were women^[8]. It is recognized that the prevalence of DHF has increased in accordance with a combination of factors, including an increase in the elderly population, the development of non-invasive diagnostic techniques for detecting heart function, such as echocardiography, cardiac magnetic resonance (CMR), positron emission tomography and single-photon emission computed tomography, as well as improvements in the treatment of coronary artery disease (CAD) and other cardiovascular diseases resulting in the preservation of LVEF. However, the prognosis of DHF still remains poor with a 5-year mortality of 42.3% after hospitalization for HF^[2].

PATHOPHYSIOLOGY OF DHF

DHF is caused by LV diastolic dysfunction (DD), leading to increased resistance to LV filling and finally resulting in HF syndrome. Diastolic dyssynchrony leading to DD is well supported by a number of studies^[9]. The pathophysiology of DHF is still not completely known, evidence suggests that cardiac and extracardiac factors play important roles in the development of HF symptoms. Elderly patients with DHF usually have systolic hypertension with a wide pulse pressure^[5] and have evidence of concentric LV hypertrophy or normal mass with increased wall thickness to cavity radius. Patients may also have complicating disorders, such as atrial fibrillation, CAD, anemia, diabetes, and renal failure.

Patients with DHF have normal or near-normal end-diastolic volumes with demonstrable DD that impairs primarily LV relaxation, followed by the development of an increased chamber stiffness^[9]. Cardiac relaxation is altered due to aging, pathological hypertrophy, increased afterload, ischemia and some neuro-hormonal factors such as the renin-angiotensin system. LV stiffness is mainly influenced by myocardial stiffness, which is altered by wall thickness, interstitial fibrosis, and incomplete relaxation, biventricular interaction, LV geometry, and pericardial constraint^[10]. In elderly and/or hypertensive patients, abnormalities of relaxation and stiffness are more common even without clinical findings of HF, which influence the effect of volume loading. What effect does left atrial (LA) function have in patients with DHF? A study showed that LA stiffness is the most accurate parameter in identifying patients with DHF^[11], and revealed that although asymptomatic hypertensive patients with LV hypertrophy and patients with normal LVEF and DHF had no differences in LV mass, LA volumes, or LA contraction function, DHF patients did have reduced LA strain and strain rate during LV systole, and increased LA stiffness index.

Diastole of the heart starts with isovolemic relaxation, which is an energy-dependent process, followed by

rapid ventricular filling, and eventually atrial contraction. Impairment in diastolic filling caused by DD leads to the development of an increase in pulmonary pressures and sequentially pulmonary congestion or edema, followed by the development of clinical symptoms and signs of DHF. DD can be induced by intrinsic or extrinsic factors, and intrinsic factors include impaired relaxation and/or increased stiffness. Active relaxation depends on the integrated process of the regulation of diastolic intracellular calcium levels and the uncoupling of the myofilament protein responsible for cellular contraction: Intracellular calcium control during diastole is mainly dependent on calcium uptake into the sarcoplasmic reticulum, mediated by the sarcoplasmic/endoplasmic reticulum calcium adenosine triphosphate (ATP)ase type 2^[12], and low sarcoplasmic/endoplasmic reticulum calcium ATPase type 2 is related to impaired relaxation^[13]. Activity of sarcoplasmic/endoplasmic reticulum calcium ATPase type 2 is regulated by the interacting protein, phospholamban, and is further controlled by phosphorylation^[12]. Extrinsic factors, such as pericardial restriction, can also induce DD^[14]. Pathological hypertrophy in the ventricle can increase ventricular stiffness and impair diastolic function. Concentric LV hypertrophy is common secondary to hypertension or aortic stenosis, resulting in disproportionate growth of the nonmyocardial extracellular matrix, which can also increase ventricular stiffness^[15], this change in the extracellular matrix, particularly in fibrillar collagen- α key component of the extracellular matrix, leads to ventricular hypertrophy and DD. This concentric LV hypertrophy may also decrease activity of the sarcoplasmic reticulum calcium ATPase and increase phospholamban which are caused by calcium removal from the cytosol due to ischemia^[16]. The hypertrophied heart can not completely relax, and thereby increases LV filling pressure^[17], influencing diastolic filling. Activation of the renin-angiotensin-aldosterone system is the key in developing myocardial fibrosis and stiffness, stimulating vasoconstriction, and maintaining sodium and water. Angiotensin II and aldosterone both stimulate collagen deposition, and aldosterone can also act in salt retention^[18].

LV rotation, twist, and torsion are important aspects of cardiac mechanics. The term "rotation" refers to rotation of the short-axis section of LV^[19]. LV twist is the net difference at isochronal time points between the apex and base in the rotation angle along the LV longitudinal axis, therefore LV torsion is LV twist indexed to the distance between LV apex and LV base (LV length)^[20]. The LV twist increases gradually from infancy to adulthood, increasing LV torsion and untwisting (clock-wise rotation) velocity with age. Untwisting normally starts in late systole and is complete before mitral valve opening. The LV untwisting rate has been evaluated as an index of myocardial relaxation. The LV untwisting rate correlates well with LV twist and with negative end-systolic volume regardless of LVEF.

Patients with DHF have delayed onset and delayed peak of untwisting, these patients have larger LA volumes and higher pulmonary artery pressure^[21]. One study has proposed that endocardial function is more likely to reduce with age due to greater susceptibility of the subendocardium to fibrosis and/or subclinical reduction in perfusion^[19]. The finding of increased torsion and reduced subendocardial function in the elderly results in the preservation of LVEF, and may explain why DHF is seen more often in elderly people. Studies have reported a significant correlation between LV twist and LVEF, or between dp/dt_{max} (an invasive unit for measuring LV contractility) and LV twist ($R^2 = 0.747$, $P < 0.001$). It is suggested that LV twist may be an index of systolic myocardial deformation, while LVEF simply reflects LV volume reduction during systole^[22].

DIAGNOSIS OF DHF

The diagnosis of DHF is generally based on the typical symptoms and signs of HF, preserved or normal LVEF, DD and no valvular abnormalities on examination (named HFNEF). The revised criteria for the diagnosis of HFNEF published by the European Society of Cardiology has to include all of the 3 following items: (1) Clinical symptoms or signs of HF; (2) Normal or mildly reduced LV systolic function and normal LV chamber size (LVEF $> 50\%$ and LVEDVI $< 97 \text{ mL/m}^2$); and (3) Evidence of abnormal LV relaxation, filling, diastolic distensibility and diastolic stiffness (including the following measurements: (a) PCWP $> 12 \text{ mmHg}$ or LVEDP $> 16 \text{ mmHg}$; (b) time constant of LV relaxation (τ) $> 48 \text{ msc}$; or (c) diastolic LV stiffness modulus > 0.27 , or (d) echocardiographic data alone or combined with biomarkers^[23]. The criteria of the National Heart, Lung, and Blood Institute's Framingham Heart Study, require all 3 of the following for the diagnosis of HFNEF: (1) Definite evidence of HF; (2) Normal LV systolic function (LVEF ≥ 0.50 within 72 h of the HF event); and (3) Evidence of abnormal LV relaxation, filling, distensibility indices on cardiac catheterization^[24]. Invasive criteria [as described in (a) of the European criteria] are more difficult to apply in the majority of patients, noninvasive modalities have recently had widespread clinical application.

Echocardiography can be used to reliably measure LV volumes, mass and EF. Tissue Doppler imaging of mitral annulus velocities is the most sensitive and reliable method for assessing LV relaxation and filling pressures in patients with DHF. Mitral annulus e' velocity relates significantly with the time constant of LV relaxation, and the ratio of mitral E velocity to mitral annulus e' velocity (E/e') correlates with LV filling pressure^[25]. The E/e' ratio also seems to reflect LV filling pressure during exercise. E/e' measured at the medial annulus was related to LVEDP both at rest and during exercise, but the r value during exercise ($= 0.570$) was worse than at rest ($= 0.67$)^[26]. Ommen *et al.*^[27] showed that the correlations between the E/e' ratio (e' measured at the medial mitral

annulus) and the mean LV diastolic pressure was 0.60 for patients with LVEF $< 50\%$ but only 0.47 for patients with LVEF $> 50\%$. All patients with an E/e' ratio > 15 had a mean diastolic LV pressure $> 12 \text{ mmHg}$. If the average of septal and lateral e' is used, an E/e' ratio < 8 identifies patients with normal filling pressure, a ratio > 13 identifies patients with elevated LV filling pressure^[28]. Therefore an E/e' ratio > 15 has been suggested for the diagnosis of HFNEF in patients with typical findings of HF and an LVEF $> 50\%$. An E/e' ratio between 8 and 15 was associated with a very wide range of mean LV diastolic pressure^[27]. CMR may be considered as the gold standard for LV and LA volume and LV mass measurements. In patients with suspected HFNEF, CMR can demonstrate preserved LV systolic function, normal LV volume, LV hypertrophy, and an enlarged LA volume^[29].

B-type natriuretic peptide (BNP), a cardiac neurohormone released by the ventricles in response to volume expansion and pressure overload, has a half-life of about 20 min, and the N-terminal part of its precursor peptide (NT-proBNP) has a longer half-life of approximately 1 to 2 h, leading to higher circulating levels and slower fluctuations compared with BNP, despite the 1:1 secretion. BNP and NT-proBNP levels were elevated in patients with LV DD and correlated with the severity of LV DD and LV filling pressure^[30]. Both BNP levels have been shown to correlate with invasive indices of LV DD, the time constant of relaxation, LV end-diastolic pressure, and LV stiffness^[31]. Investigators have suggested using NT-proBNP to distinguish a normal from a "pseudonormal" (elevated LVEDP) LV filling pattern^[30]. BNP levels are elevated in DHF and systolic heart failure (SHF), and mean BNP levels are 20 times greater in patients with DHF than in matched control normal subjects^[32]. Natriuretic peptide levels are clearly age- and gender-specific, the normal value in 90% of young, healthy adults is BNP $< 25 \text{ pg/mL}$ and NT-proBNP $\leq 70 \text{ pg/mL}$ ^[33]. The European criteria recommend that natriuretic peptide, when used for diagnostic purposes, should be implemented with echocardiographic indices of LV DD, but they can also be used for exclusion based on the high negative predictive value, which is 96% and 93% when using a cut-off value of 100 pg/mL for BNP and 120 pg/mL for NT-proBNP, respectively^[23].

TREATMENT OF DHF

Table 1 depicts the benefits of drugs in patients with DHF on the different studies. β blockers and slow-releasing calcium channel blockers are generally used in patients with DHF. These drugs can decrease blood pressure, afterload and increase the diastolic filling period. However, they may have an adverse effect on LV relaxation and negative chronotropic properties. Cardiac output will be reduced despite better filling when the heart rate is decreased significantly. An initial goal might be a heart rate of approximately 60 beats/min at rest. These drugs increase LV filling time to keep pulmonary

Table 1 The benefits of drugs in patients with DHF in different studies

	Diuretic	D + irbes	D + Ram	Digoxin	Candes	Perindo	Nebivo	irbes
<i>n</i>	50	56	45	492	3022	850	2128	4128
mean age (yr)	70	75	74	67	67	65	76	72
Female (%)	58	66	60	42	40	54	36	60
Mean LVEF (%)	69	66	65	50-71	54	65	36	59
Results								
(52 wk) LV mass (g)	-11	-8	-7					
QoL score	20.0-10.9	19.0-9.4	23.0-11.4					
6 MWT (meter)	1011-1048	950-1007	962-1028					
Benefits				No		No	No	
Death					No			No
CV or CHF hospital					Yes			No
Ref.	[36]	[36]	[36]	[35]	[7]	[8]	[34]	[42]

D: Diuretic; irbes: Irbesartan; Ram: Ramipril; Candes: Candesartan; Perindo: Perindopril; Nebivo: Nebivolol; QoL: Quality of life; 6 MWT: 6 min walk test.

artery pressure lower, but they also directly reduce the heart's ability to relax due to their effects at the cell level. Therefore, patients with DHF need very individualized treatment, and the final balance among all these effects determines the clinical response in a given patient. A new β blocker-Nebivolol has been investigated in an initial study^[34], and the main benefit of this agent is the blocking of β -1 without β -2 blocking as well as relaxing the arteries without the side effects of vasodilatation. Nebivolol also helps endothelial function and is a powerful anti-oxidant. The study showed that 43 HF patients (total 104 cases) with an LVEF < 36%, had reduced heart size and improved EF (5%), but no changes in patients with near-normal or normal LVEF (DHF) were observed after 1 year. In patients with HF and advanced systolic LV dysfunction, nebivolol reduces ventricular size and improves EF^[34]. A study revealed that digoxin is not helpful in treating patients with mild to moderate chronic DHF and normal sinus rhythm^[35]. In patients with signs of volume overload, diuretics are needed and appear to reduce symptoms and improve quality of life^[36], however, it is necessary to avoid an acute drop in LV stroke volume. Diuretic dose for DHF is usually much smaller than for SHF, whereas β blockers are titrated much more rapidly to moderate or high doses in DHF patients based on the clinical response^[37].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers can lead to regression of LV mass and interstitial fibrosis due partially to their favorable effect on LV stiffness^[38]. Initial therapy should begin with an ACEI when indicated. Studies have demonstrated that ACEIs can decrease LV hypertrophy, increase LV relaxation^[39], and significantly improve diastolic filling, exercise tolerance, LVEF and HF functional class^[40]. Losartan induced a greater reduction in LV mass from baseline than the β blocker atenolol in a study of patients with hypertensive LV hypertrophy^[41]. A multicenter, randomized, controlled trial^[36] indicated that irbesartan and ramipril in combination with diuretics could reduce LV mass, which become statistically significant only for irbesartan at 24 wk, with no differences

among the three groups at 1 year. A large multicenter placebo-controlled study of 4128 patients with a mean age of 72 years, of which 60% were female, showed the morbidity-mortality of DHF patients enrolled in the I (irbesartan)-PRESERVE trial, and demonstrated that irbesartan did not improve the outcomes of patients with HFNEF^[42]. Despite the use of similar drugs, outcomes in recent HF trials were frequently neutral in patients with HFNEF and positive in HF patients with reduced LVEF (HFREF). The neutral outcomes in HFNEF trials were often attributed to reduced HFNEF patient recruitment with inclusion of many HFREF or noncardiac patients^[43]. Further clinical trials are required to control the criteria and various cutoff points of the results.

CONCLUSION

More than 50% of people living with CHF have DHF. The prevalence of DHF has increased with time. The diagnosis of DHF is generally based on typical symptoms and signs of HF, preserved or normal LVEF, DD and no valvular abnormalities. The outcomes of pharmacological therapy in patients with DHF are frequently neutral in clinical trials. Further trials are necessary.

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Antithrombotic management of patients on oral anticoagulation undergoing coronary artery stenting

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Abstract

Patients on oral anticoagulation (OAC), who are referred for coronary artery stenting account for about 5% of the whole population undergoing percutaneous coronary intervention (PCI). Although relatively small, this patient subset poses particular problems owing to the need to balance carefully the risk of bleeding against the risk of stent thrombosis and thromboembolism. Triple therapy (TT) of OAC, aspirin and clopidogrel appears as the most effective for prevention of stent thrombosis and thromboembolism. However, an increased incidence of major bleeding is to be expected during follow-up. Therefore, TT should be prolonged for as short a time as possible, and implantation of drug-eluting stents avoided. Frequent monitoring of international normalized ratio is also warranted, and the intensity of OAC should be targeted at the lower limit of the therapeutic range. Gastric protection should also be considered for all patients on medium- to long-term TT, owing to the observed highest incidence of bleeding at the gastrointestinal site. Peri-procedural management is cumbersome, and a substantial incidence of in-hospital major bleeding has been reported. Since this latter is more related to procedural variables than to TT itself, choice of radial access, avoidance of glycoprotein II b/IIIa inhibitors, and preference for not interrupting

effective OAC should be implemented. However, the evidence on which the recommendations for managing this patient subset are based is limited and of relative poor quality. While waiting for the results of ongoing, large prospective studies that are aimed at conclusively determining optimal medium- to long-term antithrombotic treatment, the official recommendations issued by the Working Group on Thrombosis of the European Society of Cardiology on the management of patients on OAC undergoing PCI with stenting should followed.

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Key words: Anticoagulants; Warfarin; Aspirin; Clopidogrel; Stents; Percutaneous coronary intervention

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INTRODUCTION

Patients on oral anticoagulation (OAC), who are referred

for percutaneous coronary intervention with stent implantation (PCI-S) account for about 5% of the whole population undergoing PCI^[1-4]. Although relatively small, this patient subset is difficult to manage owing to the need to balance carefully the risk of bleeding against the risk of stent thrombosis and thromboembolism. The higher efficacy and safety of dual antiplatelet treatment (DAT) with aspirin and clopidogrel as compared to OAC after PCI-S has long been demonstrated^[5], as well as the superiority of OAC to DAT for conditions such as atrial fibrillation, prosthetic heart valve, or recent venous thromboembolism, for which OAC is indicated^[6,7]. Consistently, triple therapy (TT) of OAC, aspirin and clopidogrel appears as the optimal antithrombotic treatment following PCI-S in patients on OAC^[8].

SUMMARY OF THE EVIDENCE AND CURRENT RECOMMENDATIONS

The evidence on which the recommendations for how to manage patients on OAC undergoing PCI-S are based is limited and of relative poor quality. The first studies that have focused on this specific patient subset, which has been previously excluded from clinical trials, appeared only in 2004^[9-11]. Over the ensuing years, several contributions were published, and in 2008, the first consensus paper by a dedicated international working group that aimed at summarizing the evidence and giving practical information for the clinician was produced^[12]. In summary, TT is the most effective (i.e. the least incidence of stent thrombosis and stroke) compared to other antithrombotic combinations, although a higher incidence of major bleeding, which increases as the treatment prolongs, is to be expected during follow-up^[12]. Overall, these results have been confirmed by subsequent work^[3,13,14], and represented the base on which the first consensus document of an official Cardiology Society was built^[8]. According to this document, patients with atrial fibrillation (and probably also with other indications for OAC), who present with an acute coronary syndrome and/or who are undergoing PCI-S, should receive TT. Owing to the inherent risk of major bleeding, TT should be prolonged for as short a time as possible, and therefore the implantation of drug-eluting stents should be avoided. Whenever a drug-eluting stent is chosen in the light of a higher than expected benefit compared to bare metal stents, such as in long lesions, small vessels and diabetes, TT should be limited to the minimum, that is, 3 mo for a sirolimus, everolimus or tacrolimus-eluting stent and 6 mo for a paclitaxel-eluting stent. A longer duration, however, may be considered in selected patients with a low bleeding risk. In patients who are receiving a bare metal stent in the context of elective PCI-S, TT should be maintained for 1 mo, while a prolongation to 3-6 mo should be considered after an acute coronary syndrome. In order to limit the substantial incidence of peri-procedural/in-hospital bleeding, the radial approach is preferred for PCI-S, glycoprotein II b/IIIa inhibitors

should not be administered, and OAC should not be interrupted and bridged with heparin. Also, the intra-procedural dose of heparin should be adjusted to achieve an activated clotting time at the lower limit of the therapeutic range. During medium- to long-term treatment with TT, frequent (i.e. every 1-2 wk) monitoring of international normalized ratio (INR) is warranted and the intensity of OAC targeted at the lower limit of the therapeutic range (i.e. INR 2.0-2.5). Finally, gastric protection should be considered for all patients who receive medium- to long-term TT, because of the observed high incidence of bleeding at the gastrointestinal site. Proton-pump inhibitors, H2-receptor blockers or antacids can be used for that purpose, since the initial association of a negative interference of proton-pump inhibitors on the clinical efficacy of clopidogrel^[15] has been recently disproven by the analysis of two large, randomized trials^[16].

IS EVERYTHING CLEAR?

Although derived from the best of contemporary knowledge, the current recommendations appear to be essentially based on sound common sense rather than on objective data. The strength of available evidence in fact is heavily hampered by the limitations of most of the literature.

Most of the initial studies had a retrospective design, were carried out in a single institution, and were of limited size^[12]. The few prospective and large datasets actually represent a *post hoc* analysis of trials designed and conducted for other purposes, such as the CRUSADE, GRACE and BASKET trials^[3,17,18]. Also, in most cases, outcome comparisons are carried out between patients on TT against contemporary populations treated with DAT with no indication for OAC, rather than within individual populations with indications for OAC, who are receiving different antithrombotic regimens^[12]. The true incidence of bleeding associated with TT during follow-up is difficult to evaluate. This is because it is only in a minority of studies that the occurrence of in-hospital bleeding, which is more likely related to procedural variables, such as vascular access site, and use and dose of heparin or glycoprotein II b/IIIa inhibitors, rather than to TT itself, is reported separately, and because the antithrombotic treatment that is actually ongoing at the time of an event is documented only rarely. As it has been argued, it is unclear at present what is responsible for bleeding in patients on TT^[19,20], since hemorrhagic complications that occur weeks or months after treatment has been completed cannot plausibly be attributed to this regimen, even though the analysis is carried out according to the initially assigned treatment. The INR value at the time of bleeding is only rarely reported, while an over-therapeutic level might account in itself for a hemorrhagic complication, independently from the combined administration of antiplatelet agents. Finally, no valuable information is available on the concomitant use of gastric protection, which could actually be useful in limiting the incidence of bleeding in a population

like that which is receiving TT, in which hemorrhage has been shown to occur mostly at gastrointestinal sites.

Most recent work has focused on some specific aspects of the issue. The feasibility and safety of the radial approach during uninterrupted OAC has been prospectively evaluated in 50 patients at a single institution in France^[21]. At 1 mo follow-up, no thrombotic events or major bleeding were observed^[21]. In a Finnish multicenter database that included 377 atrial fibrillation patients on OAC who were undergoing PCI-S, the safety of glycoprotein II b/IIIa administration was retrospectively evaluated^[22]. A sixfold increase in major bleeding was found in patients treated with glycoprotein II b/IIIa inhibitors compared to those not receiving these agents^[22]. The in-hospital adverse cardiovascular event and bleeding rates were prospectively examined in 163 patients with an indication for OAC, who were enrolled in several centers in Italy and Spain^[2]. The overall major bleeding rate was about 4%, with the radial and femoral approach being of borderline significance as predictors of decreased and increased incidence of bleeding, respectively^[2].

When trying to determine the true hemorrhagic rate associated with medium- to long-term TT, the figure of about 4%, which is consistent with that observed in larger datasets^[3,14,17], should be subtracted from the 5%-10% occurrence of major bleeding reported for these patients after ≥ 12 mo follow-up^[8,12]. The remaining 1%-6% bleeding rate for medium- to long-term TT may actually be closer to the reality. Indeed, in a prospective randomized study of 515 patients on OAC, who were assigned to TT or DAT after PCI-S at a single center in Germany, the occurrence of major bleeding was as low as about 1.5%, and did not differ in the two groups^[23]. However, this is in contrast with the results of a recent large retrospective study in Spain of 604 atrial fibrillation patients undergoing PCI-S, in which the use of drug-eluting stents, and therefore of prolonged TT, was associated with an increased incidence of major bleeding over 4 years follow-up^[13]. It also contrasts with a recent retrospective analysis of 813 patients enrolled in the Swiss BASKET trial, in which patients on TT had a significantly higher incidence of major bleeding compared to those with DAT at 3 years, while no difference was present at discharge^[3]. Once again, however, some major flaws must be acknowledged. In the Spanish study, only 50% of patients that received a drug-eluting stent were discharged on TT, with no information as to whether subsequent bleeding occurred in this subset or in others treated with different antithrombotic regimens^[13]. Also, the duration of TT and whether it was ongoing at the time of bleeding was not reported^[13]. Out of the patients who experienced late major bleeding in the BASKET trial, only half of them were on TT, whereas the remaining half were receiving the combination of OAC and aspirin^[3]. Again, little information is given on the INR level at the time of the hemorrhagic complications^[3]. In patients on TT, successful maintenance of the INR level between 2.0 and 2.5 has been shown prospectively to be associated with bleeding that is comparable to that in

patients on DAT, while deviations above this level carry a definite increased risk of bleeding complications^[1].

CONCLUSION

The peri-procedural management of patients on OAC undergoing PCI-S is well substantiated by available evidence, and measures, such as choice of radial access, avoidance of glycoprotein II b/IIIa inhibitors, and preference for maintaining effective OAC with additional low doses of extra anticoagulants throughout the procedure, should definitively be implemented to limit the risk of major in-hospital bleeding. Owing to the well-recognized unfavorable prognostic role of bleeding and/or transfusion in patients with acute coronary syndromes^[24], meticulous attention to the above-mentioned technical and pharmacological aspects of PCI-S should be applied even more to patients at high risk of bleeding, such as those on OAC. More uncertain at present is the true risk of hemorrhagic complications associated with prolonged administration of TT. Since the occurrence of even minor bleeding has been shown to prompt the interruption of one or both antiplatelet agents^[25], which in turn is the major responsible factor for stent thrombosis^[26], it is mandatory to keep this risk as low as possible. Therefore, avoidance of drug-eluting stent implantation, careful maintenance of the INR level at the lower side of the therapeutic range, and extensive use of gastric protection should be applied during prolonged TT, which certainly represents the optimal antithrombotic treatment for OAC patients undergoing PCI-S. Large prospective studies are currently ongoing^[27-30] with the aim of conclusively defining the safety of prolonged TT and the safety and efficacy of combination of OAC and clopidogrel. This latter regimen has been proposed as an alternative to TT for patients at high risk of bleeding, especially after completion of an initial short period of TT^[8,12]. However, further data are needed before the combination of OAC and clopidogrel may be considered, since the initial evidence supporting comparable efficacy^[31] has been recently counterbalanced by the observation in a very large nationwide study of a safety profile no better than that of TT^[4].

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Long term combination treatment for severe idiopathic pulmonary arterial hypertension

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Abstract

We report the long-term follow-up of 3 cases of severe idiopathic pulmonary arterial hypertension, in whom tadalafil plus sitaxentan combination therapy improved the clinical condition and exercise performance without any relevant adverse event.

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Key words: Pulmonary hypertension; Tadalafil; Sitaxentan; Endothelin receptors

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating disease with a median life expectancy, without appropriate therapy, of 2.8 years from diagnosis^[1]. The better understanding of the pathologic processes responsible for the increase of pulmonary vascular resistance in PAH has led, in the past 10 years, to the development of new oral substances that have significantly improved the prognosis and the quality of life (QoL) of PAH patients^[2]. The 3 main mechanisms involved in the pathogenesis of PAH are vasoconstriction, proliferation and remodeling of the pulmonary arteries, and thrombosis. An imbalance among key neurohormonal mediators leads to the progression of the disease. Oral drugs are now available, targeting the different pathways involved in the pathobiology of PAH; it appears therefore likely that a prompt combination approach in the treatment of the disease may result in a synergistic action, with consequent slowing of disease progression and improvement of prognosis. However, the role and exact timing of initiation of multiple drug therapy are still debated.

Tadalafil is a long-acting phosphodiesterase type-5 inhibitor. By increasing the levels of cGMP, the final mediator in the nitric oxide pathway, tadalafil exerts vasodilatory and antiproliferative effects on pulmonary vascular smooth cells. Although only recently approved in Europe for PAH, tadalafil has proven to improve exercise capacity and QoL in patients^[3,4]. Endothelin-1 is a potent endothelium-derived vasoconstrictor peptide endowed with mitogenic properties. Its overexpression in PAH can be counteracted by endothelin receptor antagonists. Sitaxentan is an approved selective endothelin receptor antagonist that is selective for ET_A over ET_B.

Table 1 Parameters at baseline (T0), after 1 year of therapy with tadalafil 40 mg/d (T1) and after 6 (T2) and 12 mo (T3) of a combination of tadalafil 40 mg/d plus sitaxentan 100 mg/d

	Patient 1 F (74 yr)				Patient 2 F (44 yr)				Patient 3 F (45 yr)			
RHC PAP S/M/D (mmHg)	97/52/31				95/53/34				116/68/44			
RHC CI (L/min per m ²)	2.25				2.00				2.94			
RHC PVR (WU)	7.8				12.9				11.0			
Timepoint	T0	T1	T2	T3	T0	T1	T2	T3	T0	T1	T2	T3
WHO functional class	III-IV	III	III	III	III-IV	II-III	II-III	IV	III	II	I	I
6MWT (m)	251	276	305	330	245	285	311	90	316	456	462	470
Borg score	8	8.5	8	7	5	7	6	9	2	0.5	0	0.5
SF-36	83	89	93	91	82	96	100	n/a	91	107	119	115
PAP (mmHg)	97	94	70	75	110	80	80	75	118	97	60	70
NT-proBNP (pg/mL)	989	951	785	654	2094	1650	1812	2834	503	172	106	102
TLCO-SB (%)	23	41	42	46	60	68	68	n/a	58	74	68	70
VO2max (mL/min per kilogram)	n/a	n/a	n/a	n/a	n/a	10.0	11.1	n/a	10.6	16.8	16.9	15.3
FMD (%)	6.6	7.3	7.6	n/a	6.6	11.2	12.6	n/a	7.35	13.3	14.3	n/a

RHC: Right heart catheterization data at baseline; PAP: Pulmonary artery pressure (systolic/diastolic/mean); CI: Cardiac index; PVR: Pulmonary vascular resistance; WHO: World Health Organization; 6MWT: 6 min walking test; SF-36: Short Form-36 questionnaire; PAP: Doppler estimate of systolic pulmonary arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; TLCO-SB: Transfer factor of the lung for carbon monoxide; VO2max: Peak oxygen consumption on cardiopulmonary exercise testing; FMD: Flow mediated dilation.

receptors and has about a 6000-fold higher affinity than non-selective endothelin receptor antagonists. It is also associated with a lower incidence of hepatic abnormalities, and with a comparable improvement in the 6-min walking test^[5].

As a result of their long half lives, both tadalafil and sitaxentan can be administered once a day. In addition, they are not associated with the pharmacokinetic interactions reported with other combinations of the same drug classes^[6].

CASE REPORT

Three patients with severe idiopathic PAH, assessed by right heart catheterization (baseline data shown in Table 1), had been treated for 1 year with tadalafil 40 mg/d. Subsequently, an oral dose of sitaxentan 100 mg was added to the therapy. All patients had negative coronary angiograms and no segmental defects on a lung perfusion scan. While patient 1 had longstanding disease, both patients 2 and 3 had been diagnosed within 1 year of the start of tadalafil therapy.

Clinical status, exercise capacity, QoL, vascular reactivity [measured by flow-mediated dilation (FMD)], diffusion capacity of the lung (DLCO), Doppler PA pressure estimates and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were assessed at baseline (T0), after 1 year of therapy with tadalafil alone (T1), after 6 mo of treatment with a combination of tadalafil plus sitaxentan (T2) and after 12 mo follow-up of combined therapy (T3). Liver function tests and hemoglobin were evaluated monthly. Patients also received supportive therapy, as indicated, including warfarin, digoxin, furosemide, and supplemental O₂. Adverse events were monitored throughout the period.

After 1 year of treatment with tadalafil, the 3 patients showed a clear improvement in their clinical condition,

exercise capacity and QoL (Table 1). Subsequently, sitaxentan (100 mg/d) was added to the tadalafil treatment, despite the stable clinical conditions and the improvement of pulmonary pressure. The combination was well tolerated and, after 6 mo, there was an additional improvement in the patients' clinical status, exercise capacity, DLCO, FMD, WHO functional class, QoL, NT-proBNP levels and estimated PA pressure (Table 1). After 12 mo, patient 2 deteriorated to WHO class IV and was promptly started on epoprostenol therapy, with good clinical and hemodynamic response. In this patient, sitaxentan was withheld, while tadalafil therapy was continued. Patient 3 improved further, whereas patient 1 remained stable. No adverse event and no hemoglobin or liver enzyme abnormalities were recorded. As recommended, when initiating sitaxentan, doses of warfarin were halved in all 3 patients.

Invasive follow-up of hemodynamics was not performed because of objective and subjective symptomatic improvement and satisfactory Doppler-echocardiographic measurements, in a "clinical strategy" approach. Interestingly, measurements of vascular reactivity by means of FMD correlated well with clinical benefit and changes in NT-proBNP in the 3 subjects.

DISCUSSION

The results obtained in our 3 patients affected by severe idiopathic PAH show that an *ab initio* combination treatment strategy might be effective, well tolerated and safe in the long-term. To our knowledge, only one case series has been published to date on this combination therapy^[7]. In fact, the combination of tadalafil and sitaxentan improved QoL and exercise capacity in these patients, and, because of the simple dose schedule, the compliance was very good, and no side effects were recorded.

There is an ongoing debate as to whether to initiate patients with PAH directly on combined therapy or to wait for clinical deterioration. The recent guidelines from the 4th World Conference on Pulmonary Hypertension report that a combinative approach may be proposed only when the clinical response to monotherapy is not adequate^[8]. However, clinical studies suggest that delaying the start of therapy may lead to a loss of efficacy with respect to prompt therapy, and, probably, this could be considered particularly true in a combination strategy^[9]. We believe that early treatment with a combination of 2 or more drugs, acting on different pathologic pathways at the base of the disease, could prevent or slow the further progression, limiting the costs in terms of clinical worsening; we look forward to the results of large controlled trials exploring this intriguing hypothesis with a more powerful study design.

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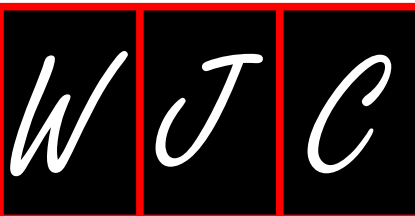
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Meetings

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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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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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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Write as mean \pm SD or mean \pm SE.

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