

# World Journal of *Cardiology*

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## Management dilemmas in patients with mechanical heart valves and warfarin-induced major bleeding

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### Abstract

Management of warfarin-induced major bleeding in patients with mechanical heart valves is challenging. There is vast controversy and confusion in the type of treatment required to reverse anticoagulation and stop bleeding as well as the ideal time to restart warfarin therapy safely without recurrence of bleeding and/or thromboembolism. Presently, the treatments available to reverse warfarin-induced bleeding are vitamin K, fresh frozen plasma, prothrombin complex concentrates and recombinant activated factor VIIa. Currently, vitamin K and fresh frozen plasma are the recommended treatments in patients with mechanical heart valves and warfarin-induced major bleeding. The safe use of prothrombin complex concentrates and recombinant activated factor VIIa in patients with mechanical heart valves is controversial and needs well-designed clinical studies. With regard to restarting anticoagulation in patients with warfarin-induced major bleeding and mechanical heart valves, the safe period varies from 7-14 d after the onset of bleeding for patients with intracranial bleed and 48-72 h for patients with

extra-cranial bleed. In this review article, we present relevant literature about these controversies and suggest recommendations for management of patients with warfarin-induced bleeding and a mechanical heart valve. Furthermore, there is an urgent need for separate specific guidelines from major associations/professional societies with regard to mechanical heart valves and warfarin-induced bleeding.

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**Key words:** Warfarin; Major bleeding; Mechanical heart valve; Thromboembolism; Vitamin K; Fresh frozen plasma; Prothrombin complex concentrate; Recombinant activated factor VIIa

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### INTRODUCTION

Warfarin acts by inhibiting the enzymes involved in the formation of a reduced form of vitamin K, which is essential for  $\gamma$ -carboxylation of glutamate residues at the amino terminus of coagulation factors II, VII, IX and X and anticoagulant factors protein C and S. This results in production of partially carboxylated, biologically inactive clotting factors. Unlike older mechanical heart valves (MHV), the newer valve design with very low thrombogenicity has reduced markedly the rate of valve thrombosis and thromboembolism events (TEs), along with the required level of anticoagulation [ $< 3.5$  international

normalized ratio (INR)], which has led to use of a lower dosage of warfarin as well as bleeding complications<sup>[1]</sup>. Despite this trend, patients with MHV on warfarin therapy develop major bleeding complications due to a narrow therapeutic index of warfarin, an unpredictable biological response (including genetic polymorphisms in warfarin metabolism) and multiple interactions with concomitant drugs/food and other patient-related factors. Furthermore, management of warfarin-induced major bleeding in patients with MHV is challenging and controversial.

## INCIDENCE OF MAJOR BLEEDING AND THROMBOEMBOLISM IN PATIENTS WITH MECHANICAL HEART VALVE AND WARFARIN

In recent studies, the incidence of major bleeding complications in patients with MHV and taking oral anticoagulants has varied from 0.34% to 1.32% per patient-year<sup>[2-4]</sup>. The International Society on Thrombosis and Hemostasis in 2005<sup>[5]</sup>, defined major bleeding in non-surgical patients as: (1) fatal bleeding; and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular (iliopsoas) with compartment syndrome; and/or (3) bleeding causing a fall in hemoglobin level of 2 gm% or more, or leading to transfusion of two or more units of whole blood or red cells.

Among the factors increasing warfarin-induced major bleeding, an INR level over the therapeutic range is the most important risk factor, independent of the indication for therapy, with the risk increasing dramatically with INR > 4.5<sup>[6,7]</sup>. Other risk factors which can increase major bleeding in patients on oral anticoagulation include age > 75 years, hypertension, previous stroke, concomitant antiplatelet agents, and a previous history of bleeding<sup>[6,7]</sup>. Overall, in clinical studies associated with careful monitoring of INR, treatment with oral anticoagulants increases the risk of major bleeding by 0.3%-0.5% per year and the risk of intracerebral hemorrhage (ICH) by approximately 0.2% per year compared to controls<sup>[6]</sup>.

In an earlier study, the incidence of prosthetic valve thrombosis in patients not anticoagulated or taking antiplatelet drugs was 1.8% per patient-year (95% CI: 0.9-3.0)<sup>[8]</sup>. The incidence of TE resulting in death, stroke, or peripheral ischemia requiring surgery was 4% per patient-year (95% CI: 2.9-5.2). This was reduced to 2.2% by antiplatelet drugs and 1.0% per patient-year with warfarin<sup>[8]</sup>. In the German Experience With Low-Intensity Anticoagulation study involving > 2000 patients with MHV, the annual incidence of major and minor TE on various levels of therapeutic anticoagulation was 0.75% with 0.32% per patient-year minor, 0.15% per patient-year moderate and 0.28% per patient-year severe events<sup>[2]</sup>. TEs following aortic valve replacement were significantly lower than mitral valve replacement

(0.53% per patient-year *vs* 1.64% per patient-year)<sup>[2]</sup>.

## MORTALITY AND MORBIDITY ASSOCIATED WITH WARFARIN-INDUCED BLEEDING

The common sites of major bleeding related to warfarin are the gastrointestinal tract (40%-60%) and urinary tract (15%) followed by ICH/subdural hematoma and retroperitoneal bleed/abdominal compartment syndrome<sup>[9-11]</sup>. Of all bleeding episodes, nearly 50% are major bleeds<sup>[10]</sup>. Warfarin-related bleeding results in significant morbidity related to transfusion and hospitalization. Approximately 1 in 10 major bleeds are fatal, and 1 in 12 patients will re-bleed after warfarin resumption<sup>[10]</sup>. Among those who develop warfarin-related major bleeds, the fatality rate may be as high as 9.5%-13.4%<sup>[10,11]</sup>.

## TREATMENT OF WARFARIN INDUCED MAJOR BLEED

Currently, the treatments available to reverse warfarin-induced bleeding in combination with cessation of oral anticoagulant therapy are vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC) and recombinant activated factor VIIa (rFVIIa)<sup>[12-14]</sup>. The American College of Chest Physicians (2008) guidelines recommends oral doses of vitamin K 1-2.5 mg for an INR between 5 and 9 and 2.5-5 mg for all patients with an INR ≥ 9, but with no significant bleeding<sup>[12]</sup>. In patients with serious bleeding and elevated INR, regardless of the magnitude of the elevation, 10 mg vitamin K is recommended by slow IV infusion supplemented with FFP, PCC, or rFVIIa, depending on the urgency of the situation. Repeat vitamin K administration every 12 h is also recommended for persistent INR elevation<sup>[12]</sup>.

### Vitamin K

Historically, vitamin K and FFP are well-known standard therapies to reverse warfarin anticoagulation. However, neither of them is ideal during a major bleed, specifically when emergency surgical intervention or urgent invasive diagnostic intervention is needed, as they take a long time to act, when INR levels of < 1.5 (< 1.2 for neurosurgery) are desirable<sup>[9]</sup>. Administration of vitamin K (10 mg intravenously at an infusion rate of 1 mg/min, diluted in dextrose 5% in water or dextrose 5% in normal saline) alone will require 12-24 h (reversal begins within 6 h) to reverse warfarin-induced coagulopathy<sup>[14-17]</sup>. A dose of 5-10 mg may be repeated every 12 h, up to a total dose of 25 mg<sup>[14]</sup>. The advantage of vitamin K injection is the ease of administration, wide availability, promotion of the formation of factor II, VII, IX and X in the liver and an effect that lasts beyond the relatively short half lives of FFP and PCC, hence producing a well sustained correction of the coagulopathy<sup>[17]</sup>. The disadvantages of vitamin K are risk of development of anaphylaxis which is thought to be due to the castor oil in the dilu-



ent and a state of “warfarin resistance”<sup>[13-15,17]</sup>. To avoid anaphylactic reactions (an estimated 3/100 000 risk of anaphylaxis), a few authors advise vitamin K to be mixed in a minimum of 50 mL of intravenous fluid and administered using an infusion pump, over a minimum of 30 min<sup>[15,16]</sup>. The oral route of vitamin K is used if reversal is warranted over 24 h in patients with high INR without bleeding, but this is of no benefit in patients with a major bleed. Subcutaneous administration is unreliable and may take up to 72 h to reverse the INR<sup>[14,15,17]</sup>. Intramuscular administration of vitamin K can cause hematoma and response is unpredictable<sup>[15]</sup>.

American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that high-dose (10 mg) vitamin K must not be used routinely in patients with MHV as this may create a hypercoagulable state with risk of valve thrombosis and TE<sup>[18]</sup>. In addition, high dose vitamin K may lead to “warfarin resistance” (up to 3%; for 1 wk or more) due to accumulation of vitamin K in the liver, necessitating use of higher doses of warfarin later to achieve therapeutic INR levels and increasing the risk of TE<sup>[18]</sup> during this period. However, vitamin K does not affect subsequent use of heparin which is commonly used in MHV with warfarin overlap. Furthermore, ACC/AHA guidelines recommend that FFP is preferable to high-dose vitamin K in patients with MHV. Alternatively, low-dose vitamin K (e.g., 1-2 mg intravenous) with FFP may be appropriate.

### Fresh frozen plasma

FFP contains vitamin K-dependent clotting factors and consists of the fluid portion of 1 unit of human blood, frozen within 8 h after collection and used within 12 mo<sup>[16,19]</sup>. The suggested dose is 15 mL/kg infusion (range 10-30 mL/kg), about 3-4 units of plasma in the average-sized adult (one unit = 250 mL), but optimal dose is unknown<sup>[14,15,17]</sup>. Time to effect of FFP is 10 min, but it takes a few hours for partial reversal and at least 9 hours for complete reversal of INR (INR < 1.5)<sup>[13,17]</sup>. Other limitations in using FFP include fluid overload and transfusion-related acute lung injury, and it carries a minimal risk of infection<sup>[13,16,17,19]</sup>. In addition, since the plasma is frozen, it has to be thawed and blood type-matched, which will cause delay in administration, but in emergency situations AB Rh D FFP can be used without previous blood typing<sup>[16,17]</sup>.

### Prothrombin complex concentrate

Although FFP is commonly used, as it is widely available and costs less, PCC has been noted to have significant benefits over FFP and according to a few authors it is the “gold standard” therapy<sup>[14,15,17,20]</sup>. This is because of the concentration of clotting factors in PCCs being approximately 25 times higher than in FFP and because FFP contains an inadequate concentration of factor IX<sup>[20-22]</sup>. Approximately 60 mL of PCC corresponds to 1500 mL of FFP leading to a minimal risk of volume overload<sup>[17]</sup>. PCC is pooled from donor plasma, reconstituted for clotting factor replacement; virus inactivated and is available

from the pharmacy in powder form<sup>[17]</sup>. Four-factor PCC includes coagulation factors II, VII, IX and X, and anticoagulant proteins C and S. The typical recommended dose is 25 to 50 U/kg<sup>[20,21]</sup>. After initial infusion of 500-1000 IU at a rate of 100 IU/min, subsequent infusion should be at 25 IU/min or less<sup>[14,20,21]</sup>. Some have safely infused higher doses (3500 IU) over 10 min<sup>[21]</sup>. The advantages of PCC are rapid preparation (time taken getting PCC 15 min *vs* 1-2 h for FFP), and complete reversal of warfarin effect within 10-30 min of administration<sup>[9,14,17,20-22]</sup>. INR should be measured within 30 min of PCC administration. If it remains  $\geq 1.5$ , a further PCC dose should be administered<sup>[9]</sup>. The INR must be measured again after 6 to 8 h and then daily while the situation remains critical. The major issues that have limited the use of PCC in patients with a major bleed are the fear of thrombotic complications (around 0%-7%, mean of 2.3%), and limited availability of these products<sup>[15,16]</sup>. One suggested cause of PCC-associated thrombotic risk is a high level of factor II in the PCC (relative to the other factors), which is known to increase thrombin generation<sup>[20]</sup>. If either FFP or PCCs are administered without vitamin K, initially there will be rapid normalization of the INR with a “rebound” increase 12-24 h later; this phenomenon is commonly seen when vitamin K is not given simultaneously with FFP or PCC or an inadequate dose of vitamin K is administered. This is because the half-life of warfarin far exceeds the half-life of the administered coagulation factor complexes (FFP T<sub>1/2</sub>: 1.5 h-2 d; PCC T<sub>1/2</sub>: 6-8 h; Warfarin T<sub>1/2</sub>: 20-60 h)<sup>[14,16]</sup>.

### Recombinant activated factor VIIa

Recombinant FVIIa (used in hemophilia patients), is also effective in reversing elevated INR at doses of 10-40 µg/kg bolus dose<sup>[14-16,23-25]</sup>. It should be reconstituted with sterile water for injection and used within 3 h of reconstitution. Recombinant FVIIa gives a rapid and complete biochemical reversal of INR within 10 min, but has a short half-life of < 1 h<sup>[17]</sup>. The disadvantage of rFVIIa is that it does not replace all clotting factors and even though INR is reduced immediately, clotting may not be restored *in vivo*. Hence, repeat infusions are necessary unless vitamin K and FFP are used concomitantly. In a recent large meta-analysis of rFVIIa use involving > 4000 patients, 11.1% developed TE<sup>[24]</sup>. Hence, the most recent guidelines on management of these patients advise against use of rFVIIa in the treatment of warfarin-associated bleeding/ICH or limit its use only if PCC or FFP are not available<sup>[9,26]</sup>. In general, most of the guidelines recommended use of PCC over FFP, but they do not comment specifically whether PCC can be used in MHV patients<sup>[6,9,25-29]</sup>.

## DO CURRENT TREATMENT MODALITIES APPLY TO PATIENTS WITH MECHANICAL VALVES?

Currently, there is limited information, especially case

reports, about the use and safety of giving either PCC or rFVIIa in patients with mechanical valve replacement and warfarin-induced bleeding<sup>[22,30-33]</sup>. Hence they cannot be routinely recommended in this group of patients. In addition both PCC and rFVIIa potentially produce thrombotic complications which may restrict their use by physicians in MHV as there is a chance of valve thrombosis which can be catastrophic. Hence, in patients with MHV and major bleeding, ACC/AHA guidelines should be followed by using FFP and vitamin K intravenous injection. The predominant concern is the need for large quantities of FFP to bring down the INR within a few hours. In patients who cannot tolerate a large volume of FFP, adjunctive use of diuretics may be needed or cautious use of PCC may be considered. Even though high dose intravenous vitamin K is not routinely advised in patients with mechanical valves, in emergency situations with major bleed and hemorrhagic shock or need for emergency surgery, higher doses can be used to bring the INR down fast and prevent rebound anticoagulation. In these situations the risk of death from major bleeding far exceeds the risk of death from TEs<sup>[15]</sup>. In a case series, 7 patients with MHV and subdural hematoma were treated with 10 mg intravenous vitamin K and FFP to reverse INR completely and were off any anticoagulation for a mean of 20 d without any TEs<sup>[13]</sup>. Whether PCC/rFVIIa can be used safely in patients with MHV needs further study.

## HOW LONG CAN YOU STOP WARFARIN? WHEN TO RESTART WARFARIN AFTER A MAJOR BLEED

In patients with MHV, stopping warfarin and reversing anticoagulation therapy with the ensuing risk of valve thrombosis/TEs must be weighed against the risk of continued bleeding. No large prospective trials have evaluated the issue of when to restart anticoagulation after warfarin-induced major bleed. The publications report withholding all anticoagulation for 1 to 2 wk<sup>[34,35]</sup>, 4 to 6 wk<sup>[36]</sup> or advise the use of bridging therapy with intravenous unfractionated heparin (UFH)/subcutaneous low-molecular weight heparin (LMWH) immediately after the INR is corrected to normal<sup>[37,38]</sup>. In an earlier study, Phan *et al*<sup>[34]</sup> reported withholding of anticoagulation for mean of 10 d in patients with ICH, but the 30-d TE rate estimated was high at 3% for those with prosthetic valves. In another study, involving patients with MHV and ICH, anticoagulation therapy was discontinued from 2 d to 3 mo (median, 8 d) and there were no TEs. They concluded that for most patients, discontinuation for 1 to 2 wk should be sufficient to observe the evolution of a parenchymal hematoma to prevent its expansion, to clip or coil a ruptured aneurysm, or to evacuate an acute subdural hematoma<sup>[35]</sup>. Butler *et al*<sup>[38]</sup> reported withholding anticoagulation in MHV patients with ICH with the INR remaining < 2.0 for 0-19 d (median 7) with no

short-term TEs.

It has been observed that the presumed risk of TEs with a MHV is generally overestimated. Crawley *et al*<sup>[36]</sup> reporting on MHV patients off anticoagulation observed that if the risk of embolism from MHV resulting in major stroke or death is 4% a year and the risk of valve thrombosis is 1.8% a year<sup>[8]</sup>, the daily risk can be estimated to be 0.016%. Thus stopping anticoagulation for 6 wk is associated with a risk of major stroke or death of 0.67% and suggested that with such low risk of TEs, the use of heparin as a bridging therapy cannot be recommended in patients with major warfarin-induced bleeding<sup>[36]</sup>. In another study, among patients with prosthetic heart valves and major hemorrhage, the mean duration of anticoagulation withholding was  $15 \pm 4$  d with no episodes of TE during hospitalization and at 6 mo, but on re-starting warfarin, the patients with gastrointestinal bleed were at high risk of re-bleed<sup>[39]</sup>. In one large prospective study, 1300 cases (in 1024 patients, 10% with MHV) of warfarin interruption (80% < 5 d) before an invasive procedure were examined<sup>[40]</sup>. Only 0.7% patients had a post procedure TE within 30 d of the procedure and none of these patients received bridging therapy. Nearly 60% of the patients had periprocedural bleeding and all of them were on bridging heparin therapy<sup>[40]</sup>. In a similar study from The Mayo Clinic<sup>[41]</sup>, 556 MHV patients off warfarin therapy for 5 d, undergoing surgery underwent bridging therapy with UFH or LMWH with very low TEs of 0.9% over 3 mo with 3.6% major bleeding episodes. It was concluded that post-procedural heparin use must be reserved for patients with the highest thromboembolic risk (mitral MHV, multiple MHVs, and MHV with prior stroke or atrial fibrillation) waiting at least 48 h before initiating treatment. Even though these two studies involved MHV patients without a major bleed, they indicate that the incidence of TEs off warfarin therapy with or without bridging therapy is very low at 0.7% to 0.9%, respectively and even for very high risk patients among MHVs, a minimum 48 h with no bridging therapy should be given<sup>[41]</sup>. In addition, TE risk is high during the first 6 mo of MHV implantation<sup>[42]</sup>.

In an analysis, Aguilar *et al*<sup>[14]</sup> reported that, overall, the data (8 studies involving 132 patients) suggest a low risk of TE complications between 7 and 14 d after anticoagulation reversal in patients with warfarin-associated ICH and prosthetic valves. In a recent systematic review of the literature on the management of oral anticoagulant therapy after an ICH in patients with a mechanical heart valve, stopping anticoagulant therapy for few days (7-14 d) after ICH was found to be safe<sup>[43]</sup>. The risk of TE in a patient with a MHV during 7 d without anticoagulation can be estimated between 1 in 1300 and 1 in 240, assuming an annual incidence of between 4% and 22%<sup>[38]</sup>. Romualdi *et al*<sup>[43]</sup> estimated that in the worst-case scenario, the incidence of TEs without anticoagulation in patients with MHV is 22 per 100 patient-years which is a high risk on a yearly basis, but this corresponds to a 0.06% daily risk (i.e., 6 in 10 000 patients).

Therefore, they concluded that short interruption of anticoagulation may not be as dangerous as is often presumed. The risk of damage to organs by bleeding when anticoagulation is not fully interrupted is probably much higher in these situations. The European Stroke Initiative recommends that patients with very high risk for TE should be restarted on warfarin after 10 to 14 d, and the AHA recommends 7 to 10 d after ICH<sup>[26,44,45]</sup>. The most recent French guidelines recommend holding any anticoagulation for 1-2 wk in MHV patients with intracranial bleed and for 48-72 h for extra cranial major bleed<sup>[9]</sup>.

## CONCLUSION

After reviewing the available literature, we suggest the following treatment strategies in patients with MHV and warfarin-induced major bleeding: (1) high dose vitamin K therapy (5-10 mg) should be administered immediately by slow intravenous infusion over 10-30 min, and a repeat dose should be considered at 12 h; (2) large volume of type-specific FFP (initially, emergency-released AB plasma = universal plasma donors, maximum 4 units) should be infused as tolerated according to desired INR levels as well as to stop bleeding. Caution is needed during large volume FFP infusion and diuretic therapy should be used when needed. Four hourly INR needs to be checked for the first 24 h, if INR is not to the desired level, repeat FFP infusion; (3) PCC should be reserved for patients who are allergic or intolerant to FFP and in those who cannot tolerate a large volume of FFP such as patients with heart failure in view of its potential thrombotic complications till further data prove that it is safe to be used routinely in MHV patients; (4) recombinant FVIIa should not be used in patients with MHV in view of its high incidence of thrombotic complications till further studies prove its safety in MHV patients; and (5) with regard to restarting any anticoagulation in patients with warfarin-induced major bleeding and MHV (especially in patients with high risk MHV = mitral MHV, multiple MHVs, MHV with prior stroke or atrial fibrillation, and MHV implanted within 6 mo), any anticoagulation should be withheld (or safe to re-start) for 7-14 d in patients with intracranial bleed and 48-72 h for patients with extra cranial bleed.

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## Acupuncture for paroxysmal and persistent atrial fibrillation: An effective non-pharmacological tool?

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### Abstract

In Traditional Chinese Medicine, stimulation of the Neiguan spot has been utilized to treat palpitations and symptoms related to different cardiovascular diseases. We evaluated whether acupuncture might exert an antiarrhythmic effect on patients with paroxysmal or persistent atrial fibrillation (AF). Two sets of data are reviewed. The first included patients with persistent AF who underwent electrical cardioversion to restore sinus rhythm. The second included patients with symptomatic paroxysmal AF. All subjects had normal ventricular function. Acupuncture treatment consisted of 10 acupuncture sessions on a once a week basis with puncturing of the Neiguan, Shenmen and Xinshu spots. In patients with persistent AF, the recurrence rate after acupuncture treatment was similar to that observed in patients on amiodarone, but significantly smaller than that measured after sham acupuncture treatment or in the absence of any antiarrhythmic drugs. In a small group of patients with paroxysmal AF, acupuncture resulted in a significant reduction in the number and duration of symptomatic AF episodes. In conclusion,

we observed that acupuncture of the Neiguan spot was associated with an antiarrhythmic effect, which was evident in patients with both persistent and paroxysmal AF. These preliminary data, observed in 2 small groups of AF patients, need to be validated in a larger population but strongly suggest that acupuncture may be an effective non-invasive and safe antiarrhythmic tool in the management of these patients.

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**Key words:** Chinese medicine; Antiarrhythmic drugs; Autonomic mechanisms; Atrial arrhythmias

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### INTRODUCTION

Atrial fibrillation (AF) is the most common clinical arrhythmia with a relevant socioeconomic impact. Patients with AF have symptoms such as palpitations and shortness of breath; they have reduced exercise capacity and are subject to a higher risk of thromboembolic events<sup>[1-3]</sup>. AF diagnosis is relatively simple when a permanent form is present, but is much more complicated when it is paroxysmal. Indeed, up to 25% of cryptogenic strokes may be due to paroxysmal or undiagnosed AF. Management of AF patients is also difficult because of uncertainties about the optimal therapeutic strategy<sup>[4]</sup>, and the limited efficacy and safety of the most common antiarrhythmic drugs<sup>[3,5]</sup>. More recent approaches, such as the use of ra-

diofrequency ablation of pulmonary vein firing to reduce arrhythmia triggering or angiotensin-converting enzyme inhibitor therapy targeting the atrial substrate, remain controversial because of the uncertainty of patient selection criteria and the limited efficacy in controlled trials<sup>[6-9]</sup>.

In the last 20 years<sup>[1-3]</sup>, a general consensus has been reached on the fact that AF is not only a simple electrocardiographic diagnosis but rather a clinical disorder in which different factors act as triggers or substrate modifiers and affect the medical history of AF patients (Figure 1).

The complexity of the picture and the interaction among different factors may therefore explain the difficulty in managing AF patients and the need for new or alternative therapeutic options<sup>[10]</sup>. In traditional Chinese medicine<sup>[11]</sup>, stimulation of the Neiguan spot on the meridian of the Minister of the Heart has been extensively used to treat nausea and vomiting. It is also considered to be an essential point in the treatment of cardiovascular pathologies, specifically with regard to disorders of rhythm as well as of the coronary blood flow. Recently also in Western literature, reports have been published supporting the clinical efficacy of acupuncture to treat arterial hypertension<sup>[12]</sup> and to reduce chest pain<sup>[13,14]</sup>.

We have previously reported<sup>[15]</sup> that acupuncture might prevent the recurrence in patients with persistent AF. In the present review we also report the antiarrhythmic effects of Chinese acupuncture therapy in patients with paroxysmal or persistent AF.

## PATIENT POPULATIONS

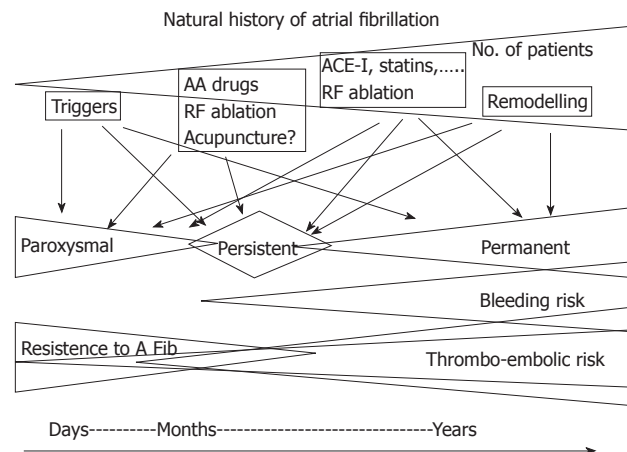
From our outpatient arrhythmia clinic, we enrolled 2 sets of patients. All had preserved ventricular function (defined as left ventricular ejection fraction > 45%). Subjects with ischemic, dilated or valvular cardiomyopathy, New York Heart Association functional class III-IV, signs of acute or chronic inflammatory disease, malignancies, significant renal or hepatic failure and thyrotoxicosis were excluded.

The first set<sup>[15]</sup> consisted of patients with persistent AF who underwent electrical cardioversion to restore sinus rhythm. All were on anticoagulant therapy and were randomized to acupuncture, sham acupuncture and no antiarrhythmic therapy. A group of patients on amiodarone was considered as a reference group. The second set of patients consisted of 31 subjects with frequent symptomatic paroxysmal AF episodes present for at least a 6-mo period. Most received antiarrhythmic drugs (Table 1). At enrolment, patients were given a chart to annotate the occurrence and duration of paroxysmal symptomatic episodes. All patients of this latter group as well as patients with persistent AF randomized to acupuncture underwent 10 acupuncture sessions of 15-20 min duration on a once a week basis in the following spots (Figure 2): PC-6 (Neiguan in modern Chinese language), which is reported to have a modulating effect on the autonomic nervous system, with a mainly vagomimetic and sympatholytic action<sup>[16-18]</sup>; HT-7 (Shenmen in modern Chi-

**Table 1 Clinical characteristics of patients with symptomatic paroxysmal atrial fibrillation**

Sex (M/F) (%M)	17/14 (55)
Age (yr)	32-78
LVEF (%)	54 (52-64)
LA diameter	37 (35-42)
Duration AF (yr)	7 (2-12)
Hypertension (%)	18 (58)
Diabetes (%)	9 (29)
Medication (%)	
None	7 (23)
Flecainide	7 (23)
Amiodarone	3 (10)
Propiophenone	10 (32)
Sotalol	2 (6)
Verapamil	2 (6)

LVEF: Left ventricular ejection fraction; LA: Left atrial; AF: Atrial fibrillation.



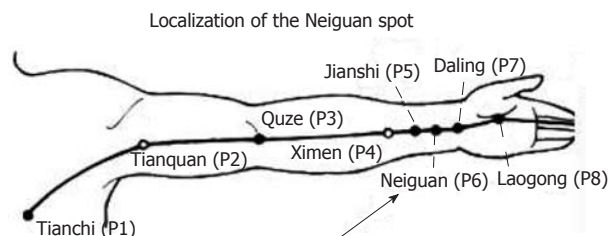
**Figure 1 Schematic representation of the temporal changes of the factors that favor or oppose to atrial fibrillation.** Initial (left side) triggers play a major proarrhythmic role and need to be targeted by therapeutic interventions. With time and the change from paroxysmal to persistent atrial fibrillation (AF), both triggers and structural alterations become critical and both have to be targeted by therapy. Finally, when structural alterations become extensive and not reversible, AF becomes permanent. The timing of this journey varies from patient to patient and is likely to be related to cardiac and non-cardiac factors. RF: Radio frequency; AA: Antiarrhythmic; ACE-I: Angiotensin converting enzyme inhibitor.

nese language), which is reported to have a calming and sedative effect on cardiac excitability<sup>[19]</sup>; BL-15 (Xinshu in modern Chinese language), which is reported to have a modulating effect on the autonomic nervous system<sup>[20]</sup>.

The effects of acupuncture were evaluated in a 12 mo follow-up period in both sets of patients.

## ANTIARRHYTHMIC EFFECTS OF ACUPUNCTURE

In all patients with persistent AF<sup>[15]</sup>, electrical cardioversion restored sinus rhythm without complications. During the following 12-mo observation period, 35 of 80 patients enrolled in the study experienced a recurrence of AF with a cumulative incidence of 43.8%. In comparison with controls, Neiguan spot puncturing



**Figure 2** Insertion point for acupuncture. The PC-6 (Neiguan in modern Chinese language) spot situated in the heart meridian is indicated by an arrow.

was associated with a significant reduction in the AF recurrence rate. The cumulative proportion of patients with AF recurrences was 35% in the active acupuncture group, 27% in the reference group of patients treated with amiodarone, and was significantly smaller than in patients with no antiarrhythmic drugs (54%) or treated with sham acupuncture (69%).

As indicated in Figure 3, there was a significant difference between the 2 active treatment groups (amiodarone or acupuncture) and the 2 control groups (sham acupuncture and no antiarrhythmic drugs). Among clinical or echocardiographic parameters, only left atrial diameter, history of hypertension and left ventricular ejection fraction were significantly associated with AF recurrence.

When considering patients with paroxysmal AF, we measured the number and duration of symptomatic episodes in order to determine the arrhythmic burden (average number and duration in minutes of AF episodes for each patient) and compared the control period with the first 2 mo after acupuncture and an additional 10 mo follow-up period. As illustrated in Figure 4, acupuncture was associated with a significant reduction in the number of AF episodes from a median of 15 [interquartile range (IQR), 6-50] to 2 (IQR, 1-10;  $P = 0.0018$ ) and in AF burden from 100 (IQR, 30-180) to 6 (IQR, 1-20;  $P = 0.0002$ ). The antiarrhythmic effect of acupuncture persisted during the 10-mo follow-up period.

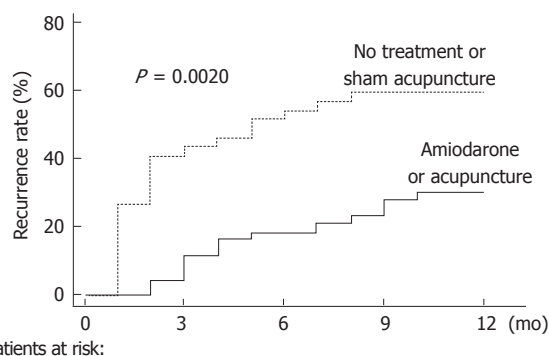
Acupuncture treatment did not cause bleeding, hematoma or infection. No pain or vaso-vagal reactions were reported with needle insertion.

## HOW TO EXPLAIN THE OBSERVED RESULTS

### Possible effects of Neiguan puncturing

These findings indicate that acupuncture of the Neiguan spot exerts an antiarrhythmic effect similar to that of amiodarone in patients with persistent AF and is additive to common antiarrhythmic drugs in patients with symptomatic paroxysmal AF. Although these results deserve confirmation in a larger patient population, they are, in our opinion, of relevant physiopathological and clinical interest and open new perspectives in the management of AF patients in relation to traditional and Western medicine.

In the Traditional Chinese Medical Doctrine<sup>[11,21]</sup>,



No treatment or sham acupuncture	37	22	18	16	15
Amiodarone or acupuncture	43	41	36	33	30

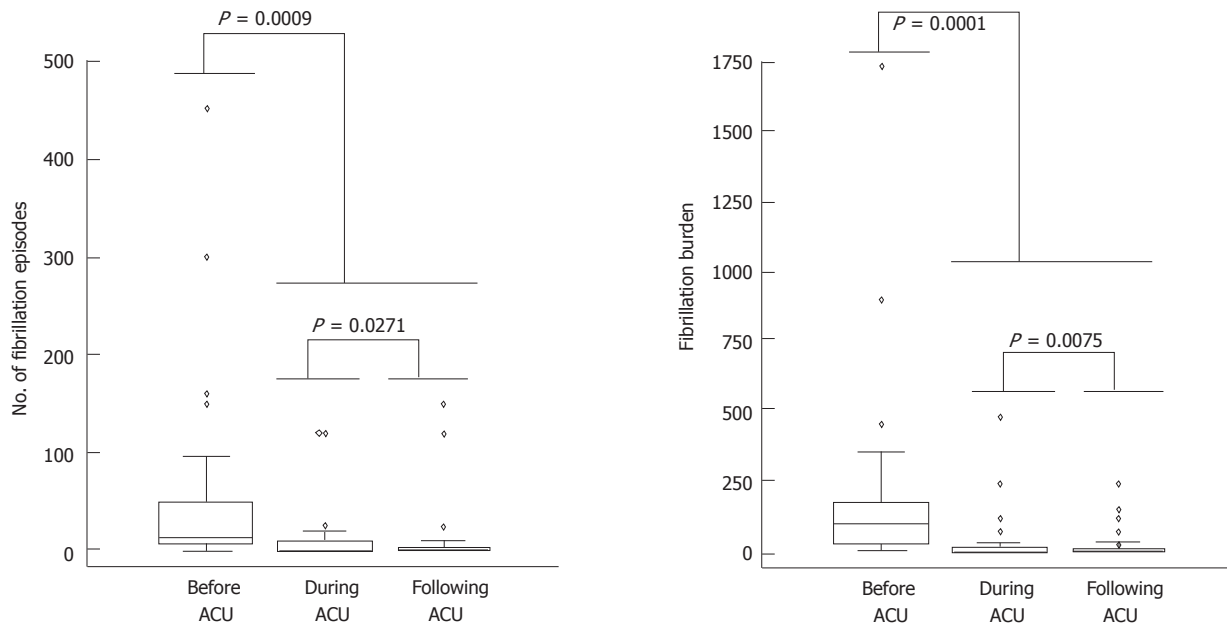
**Figure 3** Cumulative recurrence rate. Kaplan and Meier plots of recurrence of atrial fibrillation after electrical cardioversion in patients receiving amiodarone or acupuncture (solid line) compared with no treatment or sham acupuncture (dotted line).

AF, like most supraventricular arrhythmias, is related to Heart Yin deficiency in the absence of structural disorders or to Heart Yang deficiency in the presence of a cardiac disease. The Neiguan spot is located in the portion of the heart meridian situated in the forearm and is responsible for blood flow and pulse rate control. Its malfunction has been associated with anxiety and restlessness and cardiac pain.

In the Western world, puncturing of the Neiguan spot has been used to treat chest pain, sickness and vomiting during chemo-embolization procedures<sup>[22]</sup> and to limit the symptoms related to fullness-tension in the chest and palpitations<sup>[23]</sup>. Reductions in the electrocardiographic signs of myocardial ischemia and plasma levels of endothelin have also been reported<sup>[23,24]</sup>.

Electroacupuncture of the Neiguan spot has also been associated with an effect on the autonomic nervous system and, in particular on the sympatho-vagal interaction<sup>[25,26]</sup>. In one of the first studies, Kong *et al.*<sup>[27]</sup> was able to restore a more physiological sympatho-vagal balance after acupuncture by measuring heart rate variability. More recently, however, in a systematic review<sup>[28]</sup> in which the effects of acupuncture on heart rate variability were studied in different patient populations and experimental conditions, contrasting results were observed. For example in healthy subjects, acupuncture determined a significant attenuation of signs of sympathetic activation and reduced vagal modulation induced by a stress state in comparison to sham acupuncture<sup>[29]</sup>. Other studies, however, failed to detect similar changes in heart rate variability parameters when subjects were exposed to mental stress testing or other stressors<sup>[28]</sup>. On the other hand, Flachskampf *et al.*<sup>[12]</sup>, reported that 6 wk of acupuncture significantly lowered median 24-h ambulatory blood pressure and that the effect was no longer present after cessation of acupuncture treatment.

The possibility that acupuncture may exert its anti-



**Figure 4** Number of atrial fibrillation episodes and atrial fibrillation burden in the period before, immediately after and during follow-up of acupuncture treatment in patients with paroxysmal atrial fibrillation. Comparison of the different experimental conditions was made using Friedman's non-parametric analysis of variance for repeated measurements. ACU: Acupuncture.

arrhythmic effect through an action on the autonomic nervous system is therefore a plausible hypothesis although not tested in our studies. Indeed, several clinical and experimental reports have indicated that an imbalance of autonomic control mechanisms due to either an increase in vagal or sympathetic neural activity directed to the heart may favor the initiation and maintenance of AF episodes<sup>[1,2]</sup>. In patients who developed AF during Holter recordings<sup>[30,31]</sup>, signs of either an increased vagal or sympathetic modulation of the sinus node were commonly detected in the minutes preceding AF initiation: a finding that in our opinion, suggests that an imbalance between the two branches of the autonomic nervous system rather than a specific predominance of one component is the most important pro-arrhythmic factor.

The possibility that the antiarrhythmic effect of acupuncture might be related to a stabilization of sympathetic and vagal control mechanisms rather than to a direct antiadrenergic or vagomimetic effect is therefore appealing and is substantiated by recent experimental findings. In fact, whereas direct high threshold cardiac vagal ganglia stimulation has been associated with a pro-fibrillatory effect<sup>[32,33]</sup>, bilateral low-level vago-sympathetic nerve stimulation has been found to suppress effectively high-frequency stimulation-induced focal AF at atrial and pulmonary vein sites<sup>[34-36]</sup>. Whether acupuncture of Neiguan spot might exert similar effects on cardiac autonomic ganglia remains to be determined and at the moment it is an interesting hypothesis.

#### Antiarrhythmic effects of acupuncture

We observed that the antiarrhythmic efficacy of acupuncture was similar to that of amiodarone in patients with persistent AF and additive to traditional antiar-

rhythmic drugs in patients with symptomatic paroxysmal AF. Of interest were the findings that, in the former group, acupuncture matched the efficacy of the most active available antiarrhythmic drug<sup>[37]</sup> and that sham-acupuncture patients had an AF recurrence rate similar to that of patients with no antiarrhythmic therapy. We interpreted this result as indirect evidence of the fact that only specific spot puncturing rather than simple needling was the mechanism responsible for acupuncture efficacy, thus making it unlikely a placebo effect as frequently suspected in Western medicine.

When we consider patients treated with acupuncture, few additional considerations appear of interest. In patients with persistent AF, the antiarrhythmic effect of acupuncture was particularly evident in the first weeks after cardioversion, i.e., the period with the highest recurrence rate<sup>[38]</sup> where autonomic mechanisms may play a major pro-arrhythmic role<sup>[39]</sup>. Unfortunately, our study does not allow us to infer the possibility that, in patients with early AF recurrence but already on antiarrhythmic drugs, acupuncture might exert an additive antiarrhythmic action. This possibility, however, is suggested by the results obtained in patients with paroxysmal AF. Most of these patients were on propafenone, flecainide or amiodarone. Puncturing of the Neiguan spot resulted in a significant reduction of the arrhythmic burden that persisted during the whole follow-period. Even taking into account the small number of patients treated with acupuncture and the fact that only symptomatic episodes were measured, one could hypothesize that acupuncture could enhance the antiarrhythmic efficacy of these drugs by a combination effect on atrial electrical properties and autonomic mechanisms.

Finally, it has to be mentioned that acupuncture was



safe, without any pro-arrhythmic effect and with limited cost. All these factors should be considered when evaluating the efficacy of therapeutic intervention for an epidemic disease as AF.

These data were obtained in 2 small study populations and the recurrence rate was documented during control visits or by the patients' perception of symptoms. In particular, when considering data obtained in patients with paroxysmal AF, it must be pointed out that the numbers were small and that patients were treated with different antiarrhythmic drugs, and no sham acupuncture was used to rule out a placebo effect. Nevertheless, the persistency of the antiarrhythmic effect of acupuncture on symptomatic AF during the 10-mo follow-up period make this possibility unlikely. It must be also stated that for economic reasons we were unable to use a trans-telephonic monitoring system or internal or external loop recorders to detect asymptomatic or brief self-terminating AF episodes. Finally, this was a single center study with an active acupuncture team led by a cardiologist with a recognized training in traditional Chinese Medicine.

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## Short-term outcomes in heart failure patients with chronic obstructive pulmonary disease in the community

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### Abstract

**AIM:** To establish the short term outcomes of heart failure (HF) patients in the community who have concurrent chronic obstructive pulmonary disease (COPD).

**METHODS:** We evaluated 783 patients (27.2%) with left ventricular systolic dysfunction under the care of a regional nurse-led community HF team between June 2007 and June 2010 through a database analysis.

**RESULTS:** One hundred and one patients (12.9%) also had a diagnosis of COPD; 94% of patients were treated with loop diuretics, 83% with angiotensin converting enzyme inhibitors, 74% with  $\beta$ -blockers; 10.6% with bronchodilators; and 42% with aldosterone antagonists. The mean age of the patients was  $77.9 \pm 5.7$  years; 43% were female and mean New York Heart Association class was  $2.3 \pm 0.6$ . The mean follow-up was  $28.2 \pm 2.9$  mo.  $\beta$ -blocker utilization was markedly

lower in patients receiving bronchodilators compared with those not taking bronchodilators (overall 21.7% vs 81%,  $P < 0.001$ ). The 24-mo survival was 93% in patients with HF alone and 89% in those with both comorbidities ( $P =$  not significant). The presence of COPD was associated with increased risk of HF hospitalization [hazard ratio (HR): 1.56; 95% CI: 1.4-2.1;  $P < 0.001$ ] and major adverse cardiovascular events (HR: 1.23; 95% CI: 1.03-1.75;  $P < 0.001$ ).

**CONCLUSION:** COPD is a common comorbidity in ambulatory HF patients in the community and is a powerful predictor of worsening HF. It does not however appear to affect short-term mortality in ambulatory HF patients.

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**Key words:** Heart failure; Chronic obstructive pulmonary disease; Short-term mortality

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### INTRODUCTION

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are major causes of presentation to both primary and secondary care in the United King-

dom National Health Service (NHS)<sup>[1,2]</sup>. Both diseases independently carry high morbidity and high mortality, alongside high health-care costs, and negative impacts on quality of life and functional status<sup>[3]</sup>. Despite most research examining each disease in isolation several studies have suggested considerable comorbidity<sup>[3-5]</sup>, possibly due to shared risk factors including tobacco smoking. Recently, investigators have suggested that up to 32% of all HF patients have co-existing COPD, including 10% of all acutely hospitalized HF cases<sup>[3]</sup>. In addition, COPD patients have been found to be 4.5 times more likely to develop HF than disease-free control individuals<sup>[4]</sup>, with these values suggested to be an underestimation due to the misdiagnosis of COPD<sup>[5,6]</sup>.

The majority of reports examining the interaction between the two diseases have taken place in secondary care. In hospitalized patients with both HF and COPD, diagnostic challenges differentiating the cause of the acute exacerbations has been emphasized<sup>[7]</sup>. Patients with co-existence of the diseases have greater mortality and longer hospital stay than patients with chronic HF or COPD alone<sup>[8]</sup>. This has led to the suggestion that COPD is a short-term prognostic indicator of cardiovascular morbidity and mortality in secondary care<sup>[7]</sup>.

However, little evidence exists on the prognosis of patients with both HF and COPD in the community and primary care setting. This study aims to establish the short-term outcomes of HF patients in the community who have concurrent COPD. The authors hypothesize that the comorbidity of HF and COPD in the community will lead to a worse prognosis than when HF alone is present due to diagnostic challenges, and challenges in effectively treating both conditions.

## MATERIALS AND METHODS

The Leicestershire County and Rutland Primary Care Trust (LCRPCT) covers a fairly rural setting with a population of 750 000 according to the 2001 census. Approximately 0.8% of the population have been identified with left ventricular systolic dysfunction (LVSD). The specialist HF team comprises a group of five full-time-equivalent advanced nurse practitioners with clinical supervision by a community physician. The specialist respiratory team comprises a similar group of advanced nurse practitioners clinically supervised by a Respiratory Nurse Consultant and a General Practitioner (GP) with a special interest in Respiratory Medicine. The teams work closely with local GPs, and indeed local GPs refer patients directly to the team. The strategy of the Community Health Services of LCRPCT for delivering specialist care for long-term conditions (LTC) is to develop models of care within other chronic diseases and to centrally locate the running and administration of the service through a single point of access, known as the LTC Hub. Although clinicians will work along care pathways of the disease, they will coordinate care for all patients with comorbid conditions, ensuring that the correct clinician with the

**Table 1 Baseline clinical characteristics of patients with heart failure, comparing those with and without chronic obstructive pulmonary disease for June 2007 to June 2010 (SD)**

Baseline features	HF patients with COPD (n = 101)	HF patients without COPD (n = 682)
Age, yr	75.8 (6.9) <sup>b</sup>	71.3 (4.4)
Gender (M/F, %)	58/42	56/44
LVEF, %	33.6 (10.7) <sup>b</sup>	38.9 (4.8)
Ischemic cause, %	64.5 (4.8)	68.9 (10.2)
Duration of HF, yr	7.2 (2.3)	5.9 (4.2)
Duration of COPD, yr	6.9 (1.6)	----
NYHA status	2.6 (1.2)	2.4 (1.4)
FEV1/FVC ratio, %	53.6 (7.4)	----
Heart rate	71.4 (12.8)	73.4 (11.8)
Blood pressure, mmHg	125 (17.2)/76 (10.1)	129 (11.4)/81 (9.3)
eGFR	57.4 (12.9)	60.2 (13.5)
BMI	23.8 (5.3)	24.6 (3.9)

HF: Heart failure; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated glomerular filtration rate; LVEF: Left ventricular ejection fraction; BMI: Body mass index; FEV: Forced expiratory volume; FVC: Forced vital capacity. <sup>b</sup>*P* < 0.01 *vs* patients without COPD.

appropriate skills responds to the changing needs of the patients. A central tenet of the service is to work in an integrated manner with all clinicians who could possibly manage the patient. HF patients are referred into the service by GPs following diagnosis for case management, by secondary care physicians post-hospitalization and by other internal stakeholders within the Primary Care Trust.

## Patients

In the current study, we analyzed 783 patients with HF under the care of both HF and COPD teams between June 2007 and June 2010. Patient data was reviewed in an anonymized fashion through the NHS Shared Care records database operated by the primary care trust. Consequently specific patient consent forms were not required to evaluate the data. Ethical approval was not required as this was an observational study involving health services practice. The current population represented 27.2% of the total HF patients in the area under supervision. The diagnosis of HF was initially made by a secondary care physician based on the patient's history, symptoms, and physical signs, and was validated by transthoracic echocardiography. Patients were considered to have COPD if they had positive diagnostic spirometry results or if they filled > 2 prescriptions for ipratropium bromide before the index study date. In addition, oral prednisolone use in the 12 mo before the start of the study was used as a marker of the severity of pulmonary disease. The baseline characteristics of the study patients and their comorbidities are recorded in Tables 1 and 2, respectively. In brief, the mean age of the study group was 77.9 ± 5.7 years. There were slightly more males in the study group (57%). Patients were followed up during the entire study period. Cause of death and hospitalization date were ascertained using hospital



**Table 2** Comorbidity in patients with heart failure, comparing those with and without chronic obstructive pulmonary disease for June 2007 to June 2010 *n* (%)

Condition	HF patients with COPD ( <i>n</i> = 101)	HF patients without COPD ( <i>n</i> = 682)
Cardiovascular risk factors		
Diabetes	17 (17)	136 (20)
Hypertension	43 (43) <sup>b</sup>	382 (56)
Dyslipidemia	24 (24)	177 (26)
Smoker	57 (57) <sup>b</sup>	164 (25)
Ex-smoker	31 (31) <sup>b</sup>	136 (20)
Cardiovascular disease		
Previous MI	27 (27)	198 (29)
Angina	49 (49)	355 (53)
Previous stroke	20 (20)	130 (19)
Atrial fibrillation	21 (21) <sup>b</sup>	184 (27)
Non-cardiovascular factors		
Cancer	24 (24)	177 (26)
Depression	31 (31) <sup>b</sup>	143 (21)

MI: Myocardial infarction; HF: Heart failure; COPD: Chronic obstructive pulmonary disease. <sup>b</sup>*P* < 0.01 *vs* patients without COPD.

records, death certificates and hospital autopsy records.

### Statistical analysis

Statistical analysis was performed using SAS software. Statistical methods included the Chi-square test, the  $\chi^2$  test and Fisher's exact test where appropriate for categorical data, proportions and means. Logistic regression was used to determine factors associated with COPD diagnosis. Variables were entered into the model based on clinical relevance and published predictors of COPD diagnosis. The final adjusted model included the following covariates: age, sex, year and presence of COPD, angina, previous myocardial infarction, atrial fibrillation and hypertension. Age was treated as a continuous variable. All statistical tests were two-tailed and *P* < 0.001 was considered statistically significant. To obtain the distribution curve for the survival time, an estimated value of Kaplan-Meier was calculated, and differences in survival time were analyzed using the log-rank test.

## RESULTS

The data from 783 patients were analyzed. Mean follow-up was  $28.2 \pm 2.9$  mo. The baseline characteristics of the two study groups are presented in Table 1. The crude prevalence of COPD in patients with HF in this region was 12.9%. The prevalence was slightly higher in men (*n* = 58, overall 7.4%). Table 2 displays the comorbidities associated with the HF patients in this study. The majority of patients with HF and COPD were recorded as current or previous smokers, as opposed to 45% of those without COPD (*P* < 0.001). Despite this, the prevalence of smoking-related cardiovascular and non-cardiovascular comorbidity was similar in the two groups (Table 2). This included a prior history of myocardial infarction, angina, stroke and cancer. The prevalence of hypertension in HF patients with COPD was signifi-

**Table 3** Pharmacological treatments of patients with heart failure, comparing those with and without chronic obstructive pulmonary disease for June 2007 to June 2010 *n* (%)

Treatment	HF patients with COPD ( <i>n</i> = 101)	HF patients without COPD ( <i>n</i> = 682)
Cardiovascular treatment		
Beta-blocker	21 (22) <sup>b</sup>	555 (81)
ACE-inhibitor	49 (49)	382 (56)
Angiotensin receptor blocker	11 (11)	82 (12)
Spirolactone	54 (54) <sup>b</sup>	189 (28)
Loop diuretic	61 (61) <sup>b</sup>	525 (77)
Calcium channel blocker	31 (31)	184 (27)
Amiodarone	5 (5)	41 (6)
Aspirin	60 (60)	436 (64)
Warfarin	15 (15) <sup>b</sup>	130 (20)
COPD treatment		
Beta agonist	61 (61) <sup>b</sup>	20 (3)
Inhaled anti-muscarinic	27 (27) <sup>b</sup>	6 (1)
Inhaled steroid	53 (53) <sup>b</sup>	19 (3)
Oral steroids	24 (24) <sup>b</sup>	2 (0.003)

HF: Heart failure; COPD: Chronic obstructive pulmonary disease. <sup>b</sup>*P* < 0.01 *vs* patients without COPD.

cantly lower than in those without COPD (43% *vs* 56%, *P* < 0.001). The prevalence of atrial fibrillation was also significantly lower in the HF and COPD patients than in those without COPD (21% *vs* 27%, *P* < 0.001). A possible explanation for this was that on examination of the echocardiographic data, the left atrial diameter of the COPD and HF group was a mean of  $5.1 (\pm 0.6)$  cm *vs*  $5.6 (\pm 0.3)$  cm in the HF patients (*P* < 0.001).

Pharmacological treatment in both study groups is listed in Table 3. Only 22% of patients with HF and COPD were prescribed beta-blockers, as opposed to 81% of those without COPD (*P* < 0.001). This contrasted strikingly with the prescription of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, amiodarone and antiplatelet drugs where no significant difference was noted between groups. More patients with COPD were prescribed aldosterone antagonists (54% *vs* 28%, *P* < 0.001), but on comparison they had less loop diuretics prescribed (61% *vs* 77%, *P* < 0.001). Beta agonists were the most frequent therapy for COPD (61%), followed by inhaled corticosteroids (53%) and anti-muscarinic drugs (27%).

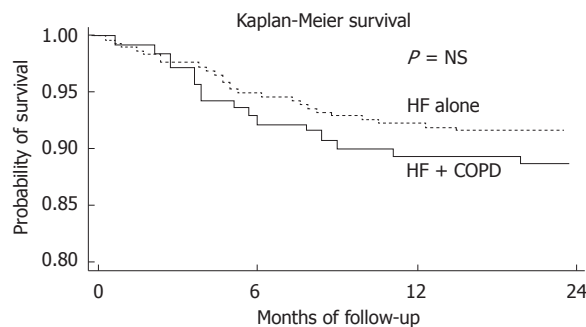
There were 94 deaths recorded during the study period (12%). The 24-mo survival was 93% in patients with HF alone and 89% in those with both comorbidities (*P* = not significant; Figure 1). On univariate analysis, a baseline diagnosis of COPD did not predict the likelihood of survival, with a relative risk of death from any cause of 1.07 (95% CI: 0.89-1.54; *P* = 0.428, Table 4). After adjustment for demographic data, clinical characteristics, and medical treatment, the relation proved to be still insignificant (Table 4). To estimate the trend in risk of 2-year mortality, we employed spline functions for baseline COPD comorbidity.

However, the presence of COPD was associated with an increased relative risk for re-hospitalization on

**Table 4 Association between chronic obstructive pulmonary disease diagnosis and clinical outcomes in the patient cohort for June 2007 to June 2010**

Outcome	COPD and HF	HF alone	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
HF hospitalization	36 (36)	143 (21)	1.78 (1.49-2.11)	< 0.001	1.56 (1.4-2.1)	< 0.001
All-cause mortality	29 (29)	177 (26)	1.07 (0.89-1.54)	0.428	1.02 (0.77-1.5)	0.225
Major CV events (non-fatal MI, stroke)	19 (19)	61 (9)	1.34 (1.1-1.53)	< 0.001	1.23 (1.03-1.75)	< 0.001
CV death	22 (22)	155 (23)	0.92 (0.68-1.06)	0.357	0.96 (0.77-1.13)	0.149

HF: Heart failure; COPD: Chronic obstructive pulmonary disease; HR: Hazard ratio; CV: Cardiovascular; MI: Myocardial infarction.



**Figure 1 Kaplan-Meier survival curve in patients with heart failure, comparing those with and without chronic obstructive pulmonary disease for June 2007 to June 2010.** HF: Heart failure; COPD: Chronic obstructive pulmonary disease; NS: Not significant.

univariate analysis [hazard ratio (HR): 1.78; 95% CI: 1.49-2.11;  $P < 0.001$ ]. This association remained strongly significant after adjustment for covariates (Table 4). This association was also strongly reported in the development of major cardiovascular events such as non-fatal myocardial infarction and stroke, where the presence of COPD increased relative risk by 23% (HR: 1.23; 95% CI: 1.03-1.75;  $P < 0.001$ ).

## DISCUSSION

Chronic diseases, including cancer, cardiovascular disease, chronic respiratory diseases and metabolic syndromes (hypertension, diabetes and dyslipidemias)<sup>[9]</sup>, are increasing in the developed world and result in a substantial economic and social burden<sup>[10]</sup>. This cost increases exponentially when chronic diseases co-exist in patients<sup>[8-11]</sup>. Patients with two or more long-term conditions account for only one-quarter of the population of all elderly people (> 65 years old) but for > 50% of the overall costs<sup>[10-12]</sup>.

This is the first study we know of which examined the epidemiology and outcomes of patients with HF (LVSD) and co-existent COPD in the community. Prior reports have involved epidemiology and management of these patients hospitalized with worsening HF<sup>[13]</sup>, attending specialized HF clinics<sup>[14]</sup> or enrolled in clinical trials<sup>[15,16]</sup>, and there is one report of Scottish community patients<sup>[17]</sup>. We describe several key findings. The presence of COPD was associated with increased risk of HF hospitalization and major adverse cardiovascular events. However, it did not affect short-term mortality

outcomes in these patients.

Remarkably, very few reports describe the prevalence of COPD in HF patients. The prevalence in our study was 12.9% and was similar to that observed in a community HF clinic in Hull, United Kingdom (12.1%)<sup>[18]</sup>. CHARM-Overall reported a rate of 8.9%<sup>[19]</sup>, but they included both preserved and lowered ejection fraction HF patients. The co-existence of both these diseases should not be a surprise, as both diseases share smoking as the most common risk factor. In our sample, nearly 50% had a history of smoking in the development of HF and this rose to nearly 80% in patients who suffered both HF and COPD. Cigarette smoking is associated with a 45% higher risk of HF in men and an 88% higher risk of development of HF in women after adjustment for other known risk factors for HF, including coronary heart disease<sup>[20,21]</sup>.

The prognosis of these patients may well be linked to both conditions sharing the same pathogenetic features. Chronic inflammation is present in both HF and COPD. It has been hypothesized that, as a consequence of mutual mechanisms of systemic cellular and humoral inflammation, HF and COPD occur more commonly in the presence of each other<sup>[22]</sup>. It is this common inflammatory pathway that has been the target of research and drug development in recent years. However, there has been conflicting reports in the COPD literature to suggest that this common pathway may not be the only mechanism involved. Interestingly, Simon-Tuval *et al.*<sup>[23]</sup> recently reported that the severity of airflow restriction in COPD patients, and hence a marker for increasing inflammation, does not necessarily predict outcomes of COPD patients in terms of exacerbations or hospitalizations. Other common mechanisms are the renin-angiotensin-aldosterone system and sympathetic nervous system. In HF, there is no doubt that neurohormonal blockers have a beneficial effect<sup>[24]</sup>, whilst in COPD, adequately designed trials are distinctly lacking<sup>[25]</sup>.

An interesting historical aspect is also the so-called “prejudice” against  $\beta$ -blocker use in HF patients with co-existent COPD. This is clearly borne out in our sample of patients where only one-fifth of the patients with both conditions were prescribed such medication. Differentiating asthma from COPD and assessing airflow obstruction is well within the remit of a GP. Indeed the ability to do this has become a part of the remuneration package provided to GPs within the United Kingdom under their current funding structure (The Quality and

Outcomes Framework of the GP contract)<sup>[26]</sup>. Withholding life-saving therapy with  $\beta$ -blockers to patients with concomitant HF and COPD should thus become a practice of the past. Sadly, as our study demonstrates, there is work to be done to promote this key intervention within community settings.

More recently, a large retrospective study of COPD prescribing in primary care in Italy showed that the breakdown of medications were as follows: inhaled  $\beta$ -agonist 37.4%, inhaled antimuscarinics 61.6%; inhaled corticosteroids 15.3%; and combination inhalers ( $\beta$ -agonist and corticosteroids) 32%<sup>[27]</sup>. Although clearly there may be differences in the medication trends between European countries both the European Respiratory Society and Global Initiative of Obstructive Lung Disease guidelines<sup>[28,29]</sup> provide consensus internationally for the prescribing of medications for COPD. The blend of medications for the COPD and HF group in our study showed comparable percentages for inhaled  $\beta$ -agonists (61%) but much lower percentages for inhaled antimuscarinics (21%). Our figures for inhaled corticosteroids included both those given singly or in combination with an inhaled long-acting  $\beta$ -agonist, and thus were also comparable with the Italian study. This suggests that the treatment could have been optimized with antimuscarinics for these patients. Whether this would have aided in improving cardiovascular outcomes in these patients is unknown and possibly a question for further research.

Boudestein *et al.*<sup>[30]</sup> also recently suggested that the presence of a diagnosis of HF is a strong independent predictor of all-cause mortality in patients with a diagnosis of COPD. Unfortunately, our study did not concur with those results for the short term, possibly due to the time limit constraint, with the Dutch study lasting twice as long.

This study has implications for the management of patients with the comorbidities of HF and COPD. Based on our study and previous research, it would appear that each of these conditions may have potentially independent adverse effects on the disease progression of each condition individually. Although beyond the scope of this study, the need for a combined and integrated approach to managing these comorbidities within the community would seem an appropriate strategy.

## COMMENTS

### Background

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are common co-morbidities. The combination presents diagnostic challenges and has been linked with worse prognosis in patients admitted to hospital. There is hardly any prognostic data in patients with both co-morbidities in the community.

### Innovations and breakthroughs

HF and COPD independently carry high morbidity and high mortality, alongside high health-care costs, and negative impacts on quality of life and functional status. However, these co-morbidities are increasingly common in patients and their impact on these parameters have not been well documented in the primary care setting. This study aims to establish the short term outcomes of HF patients in the community who have concurrent COPD. The authors hy-

pothesise that the comorbidity of HF and COPD in the community will lead to a worse prognosis than when HF alone is present due to diagnostic challenges and challenges in effectively treating both conditions.

### Applications

This study has implications for the management of patients with the co-morbidities of heart failure and COPD. Based on the study and previous research, it would appear that each of these conditions may have potentially independent adverse effects on the disease progression of each condition individually.

### Terminology

HF: A chronic disease state of the heart that results in specific cardiac symptoms (breathlessness and fluid overload/lethargy) and signs. The disease is incurable and has a poor long term prognosis; COPD: A chronic condition of bronchial inflammation caused primarily by smoking. Characterized by breathlessness and lethargy as well.

### Peer review

The authors evaluated the prevalence and prognostic impact of chronic obstructive pulmonary disease in 783 patients with systolic heart failure managed in the community between June 2007 - June 2010. The prevalence of COPD was 12.9% and it was associated with increased heart failure hospitalization, major cardiovascular events but not mortality.

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## Management of chronic heart failure: Role of home echocardiography in monitoring care programs

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### Abstract

**AIM:** To identify a possible role of home echocardiography for monitoring chronic heart failure (CHF) patients.

**METHODS:** We prospectively investigated 118 patients hospitalized during the last year for CHF who could not easily reach the pertaining District Healthcare Center. The patients were followed up with 2 home management programs: one including clinical and electrocardiographic evaluations and also periodic home echocardiographic examinations (group A), the other including clinical and electrocardiographic evaluations only (group B).

**RESULTS:** At the end of the 18-mo follow-up no significant differences were observed between the 2 groups as regards the primary endpoint: rehospitalization oc-

curred in 4 patients of the group A and in 6 patients of the group B; major cardiovascular events occurred in 2 and in 3 patients, respectively. No significant differences were observed with respect to the secondary endpoints: one vascular event appeared in both the groups, 3 cardiovascular deaths occurred in group A and 2 in group B. No significant differences were observed between the 2 groups as regards the composite endpoint of death plus hospitalization.

**CONCLUSION:** Home echocardiography for monitoring of CHF patients does not improve the cardiovascular endpoints. In our CHF patients, a low incidence of vascular events was observed.

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**Key words:** Echocardiography; Chronic heart failure; Home monitoring; Care programs; Cardiovascular events

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### INTRODUCTION

Heart failure is one of the most important public health problems in developed countries<sup>[1]</sup>. Due to the large

and increasingly ageing population, the direct costs of chronic heart failure (CHF) are continuously growing and can be estimated between 1% and 2% of the total health care budget<sup>[2]</sup>. However, as compared with other common cardiovascular diseases, the epidemiological knowledge of heart failure is incomplete, due to the lack of practical definitions and the small number of simple diagnostic techniques adopted<sup>[3]</sup>.

Echocardiography is a simple and cheap technique used worldwide for the diagnosis of heart failure<sup>[4]</sup> especially in asymptomatic patients, who represent most young male and female subjects affected<sup>[5]</sup>. Heart failure, however, can be determined by different clinical syndromes with different echocardiography patterns: from the classic picture of clinical symptoms associated with ventricular systolic dysfunction to the more difficult diagnosis of some features of heart failure without echocardiographic signs<sup>[6]</sup>.

All the epidemiological studies confirm that the high cost of heart failure treatment programs are due to the frequent and repeated hospitalizations<sup>[7]</sup>. In order to decrease the incidence of rehospitalization and improve the quality of life of heart failure patients, the recent heart failure management programs<sup>[8]</sup> have been based on close monitoring through telephone follow-up and periodic home assessment of the functional status, with appropriate medical therapy.

Home monitoring care is usually conducted with periodic visits and electrocardiograms performed by the referring physicians. Today, to our knowledge, no heart failure home monitoring program has been implemented using more expensive and heavyweight diagnostic instruments.

In the present study, we prospectively investigated a cohort of 118 patients hospitalized during the last year for CHF and monitored with 2 home management programs, one based on clinical and electrocardiographic evaluations, the other also using periodic handheld echocardiographic monitoring.

## MATERIALS AND METHODS

### Patient enrollment

The present study prospectively evaluated patients with CHF referred to the territorial District Healthcare Center between 30 January and 30 July 2009. All the recruited CHF patients, aged 70 years or older, gave their informed consent to the study. To be included in the trial, the patients should have been admitted to the hospital for worsening of clinical symptoms or for the appearance of acute cardiovascular events at least once during the last year, and discharged from hospital with a diagnosis of New York Heart Association (NYHA) class III heart failure. In addition, enrolled patients could not easily reach the pertaining District Healthcare Center for various reasons (e.g., physical barriers, the absence of a lift, and too great distance between home and hospital without help). Patients who were waiting for cardiac surgery or patients who had undergone a cardiac operation

**Table 1 Clinical and laboratory parameters of the chronic heart failure patients**

	Group A	Group B
Sex (M/F)	31/29	29/29
Age (yr)	77 ± 7	78 ± 6
Weight (kg)	73 ± 16	75 ± 20
Height (cm)	164 ± 4	162 ± 8
Body mass index	28 ± 4	26 ± 6
Systolic blood pressure (mmHg)	140 ± 12	136 ± 10
Diastolic blood pressure (mmHg)	81 ± 8	83 ± 10
Creatinine (mg/dL)	1.8 ± 0.4	1.7 ± 0.6
Azotemia (mg/dL)	62 ± 12	59 ± 10
Uricemia (mg/dL)	6.5 ± 3.0	6.6 ± 2.6
Na (mmol/L)	143 ± 5	141 ± 8
K (mmol/L)	5.0 ± 0.2	4.9 ± 0.8
C-reactive protein (mg/dL)	0.9 ± 0.4	0.9 ± 0.6
B-type natriuretic peptide (pg/dL)	586 ± 260	600 ± 244

Data are expressed as mean ± SD. Differences between groups are not significant.

within 3 mo were excluded from the trial.

At the end of the 6-mo recruitment period, 118 CHF patients (60 male, 58 female; mean age, 78 ± 8 years) were enrolled in the trial. Anthropometric characteristics and laboratory data are summarized in Table 1. An ischemic etiology was diagnosed in 49 subjects (42%), a hypertensive etiology in 25 (21%), cardiac valve failure in 21 (18%), and idiopathic dilated cardiomyopathy in 23 (19%). Diabetes was present in 24 patients (20%), hypertension in 58 (49%) and permanent atrial fibrillation in 28 (24%). In 20 patients (17%) the glomerular filtration rate was decreased as in stage III-IV kidney disease, and 2 patients were on dialysis 2 or 3 times per week. Seventeen patients (14%) were affected by chronic obstructive pulmonary disease and 32 patients (27%) showed signs of previous ischemic cerebral events. The results of echocardiography examinations at the beginning of the trial are shown in Table 2.

### Follow-up

The patients enrolled were randomized into 2 groups of 60 and 58 subjects, and treated according to evidence-based guidelines: (1) group A with 60 patients was home monitored with clinical evaluations and electrocardiogram (ECG) every 3 mo, and also echocardiography examinations on the 6th, 12th and 18th months (Vivid E General Electric Medical System, Milwaukee, United States); and (2) group B with 58 patients was home monitored with clinical evaluations and ECG every 3 mo.

All the patients completed the Minnesota Living Heart Failure Questionnaire at the beginning and at the end of the trial, and received the telephone number of the physicians.

Events occurring during the 18-mo follow-up and the results of the final echocardiography performed in all patients were transmitted to an independent observer, unaware of the features of the follow-up.

At the end of the trial, the randomization code was

**Table 2** Echocardiographic parameters in the 2 chronic heart failure groups at the beginning of the study and at the end of the study

	At the beginning of the study		At the end of the study	
	Group A	Group B	Group A	Group B
End diastolic volume (mL)	170.8 ± 72.8	166.8 ± 78.4	168.8 ± 71.4	170.1 ± 74.2
End systolic volume (mL)	106.3 ± 64.2	105.3 ± 70.2	108.1 ± 60.1	109.3 ± 60.8
Stroke volume (mL)	60.2 ± 15.8	57.6 ± 18.2	56.2 ± 15.4	57.3 ± 18.3
Ejection fraction (%)	35.8 ± 11.8	35.0 ± 14.0	35.7 ± 10.8	35.8 ± 12.6
Isovolumetric relaxation time (ms)	97.2 ± 25.6	93.9 ± 29.7	97.6 ± 26.2	94.1 ± 30.6
Peak E wave velocity (m/s)	0.86 ± 0.98	0.85 ± 0.68	0.83 ± 0.52	0.88 ± 0.44
Peak A wave velocity (m/s)	0.67 ± 0.69	0.66 ± 0.19	0.66 ± 0.49	0.69 ± 0.32
Peak E deceleration time (ms)	187.6 ± 67.2	190.4 ± 64.4	187.9 ± 63.2	191.7 ± 69.2
TDI peak E' wave velocity (m/s)	0.09 ± 0.06	0.08 ± 0.09	0.08 ± 0.04	0.08 ± 0.05
TDI peak A' wave velocity (m/s)	0.08 ± 0.05	0.08 ± 0.07	0.06 ± 0.09	0.07 ± 0.04
E/E' ratio	10.75 ± 6.31	10.62 ± 5.14	10.5 ± 5.3	11.08 ± 6.2
Pulmonary systolic pressure (mmHg)	24 ± 8	28 ± 6	26 ± 12	30 ± 10

Data are expressed as mean ± SD. Differences between groups are not significant. TDI: Tissue Doppler imaging.

**Table 3** Endpoints in the 2 chronic heart failure groups (%)

Endpoint	Group A	Group B
Primary endpoint		
Hospitalization	6 (10)	9 (15.5)
Worsening symptoms of HF	4	6
Major vascular events	2	3
Secondary endpoint		
Home treated vascular events	1 (1.7)	1 (1.7)
Cardiovascular death	3 (5)	2 (3.4)
Combined endpoint		
Cardiovascular deaths + hospitalizations	9 (15)	11 (18.9)

Differences between groups are not significant. HF: Heart failure.

opened and the events occurring and the echocardiography examinations were ascribed to the 2 groups for comparison.

### Endpoints

The primary endpoint was rehospitalization for worsening of heart failure symptoms and/or for the appearance of major vascular events during the 18-mo follow-up. Secondary endpoints included home treated vascular events, cardiovascular death and the composite endpoint of death plus rehospitalization.

### Statistical analysis

The CHF hospitalization rate was assumed to be 50% per year<sup>[9-11]</sup>. Assuming a significance level of 5%, a power of 90%, a duration of the trial of 18 mo and an expected hospitalization rate of 20% per year in the echocardiographic group, we could observe significant differences if each group had at least 55 CHF patients.

Data are expressed as mean ± SD. Differences between continuous variables were evaluated using the unpaired two-tailed Student *t* test. Discrete variables were summarized by frequency (percent). Differences between discrete variables were assessed using the Chi-square test, the Fisher exact test being used when necessary. A *P* value < 0.05 was considered statistically significant.

## RESULTS

During the 18-mo follow-up, 15 patients were hospitalized, 6 in group A (4 for worsening of the symptoms, one for myocardial infarction, one for ischemic stroke) and 9 in group B (6 for worsening of the symptoms, 3 for myocardial infarction). In addition, one home-treated myocardial infarction occurred in group A, and one home-treated stroke occurred in group B. Finally, during the 18-mo follow up, 3 patients of Group A (one male, 2 female), and 2 patients in Group B (one male, one female) had cardiovascular death (Table 3).

The routine laboratory analysis did not show any difference between the 2 groups, either at baseline or at the end of the study. From the CHF common baseline value of 580 ± 269 pg/dL, B-type natriuretic peptide changed to 360 ± 205 pg/dL in Group A and to 420 ± 260 pg/dL in Group B (not significant). The echocardiography parameters obtained in both groups at the end of the trial are shown in Table 2.

The answers to the Minnesota Living Heart Failure Questionnaire at the end of the trial were substantially similar in both groups.

## DISCUSSION

Heart failure represents one of the most important public health problems in Western countries, with a higher incidence in ageing subjects, and a related increase in the health care costs<sup>[1,2]</sup>. CHF home care should reduce the frequent, repeated and expensive hospitalizations and improve the management of patient disability in the last stages of the illness. An upgrading of CHF home care could be achieved with the use of some recent technological innovations such as home telemonitoring of patients. In this regard, recent clinical studies have provided different results. In the Home-HF study, 182 patients with a recent hospitalization for heart failure were randomly assigned to daily telemonitoring of symptoms, body weight, blood pressure, heart rate and blood oxygen saturation or to a package of intensive,

conventional, expert care (control group). There were no differences in rate and duration of hospitalization for any cause, though the home monitoring group showed a significantly lower rate of hospitalization for worsening heart failure<sup>[12]</sup>. The results on the hospitalization rate disagree with the findings of the Home or Hospital in Heart failure (HHH) study, in which 461 CHF patients with a recent hospitalization and left ventricular ejection fraction lower than 40% were randomly assigned either to conventional care ( $n = 160$ ) or to telemonitoring ( $n = 301$ ). There was no significant effect of home telemonitoring in reducing cardiac death plus heart failure hospitalization, or in reducing the number of re-hospitalizations or the bed-days occupancy for heart failure<sup>[13]</sup>. It is interesting to note that telemonitoring of CHF patients did not demonstrate any effect on mortality rate either in the Home-HF and in the HHH study.

In our study, a home care program which included periodic echocardiography has been adopted. Periodic home echocardiography, in fact, could be useful for the early detection of a sudden decrease in systolic function so that one could consider a different therapeutic approach, e.g., resynchronization therapy. In addition, home echocardiography could clarify the cause of new onset clinical signs, for example the diagnosis of new onset aortic stenosis could be made and the related treatment (transcatheter aortic valve implantation or surgical valve replacement) could be chosen. This study was designed to detect differences in the medical history of 2 different home monitored groups of patients. No significant differences were observed between the 2 groups as regards the primary endpoint, (rehospitalization and/or the appearance of major vascular events). Rehospitalization for worsening of heart failure symptoms occurred in 4 patients of the echocardiography monitored group and in 6 patients of the usual care group; hospitalization for the appearance of major cardiovascular events occurred in 2 and in 3 patients, respectively. No significant differences were observed between the 2 groups with respect to the secondary endpoints: one major vascular event was treated at home in group A and one vascular event was treated at home in group B, cardiovascular deaths occurred in 3 (5%) patients of the echocardiographic group and in 2 (3.4%) patients of the usual-care group. No significant differences were observed between the 2 groups with respect to the composite endpoint of death plus hospitalization: 9 patients (15%) in the echocardiography group, 11 patients (19.9%) in the usual care group, respectively.

These data agree with those recently reported by Chaudhry *et al.*<sup>[14]</sup>, who, in a population of 1653 CHF patients randomly assigned to undergo either telemonitoring (826 patients) or usual care (827 patients), concluded that telemonitoring did not improve either the primary endpoints (readmission for any reason or death for any cause) or the secondary one (hospitalization for heart failure, number of days in hospital and number of hospitalizations). As mentioned earlier, in the Home-HF trial<sup>[12]</sup>,

in which expensive electronic instruments monitoring daily signs and symptoms were used, no differences in rate and duration of hospitalization for any cause were reported. Home echocardiography also could be expensive. However, it is intriguing that different and more costly interventions are not clearly associated with lower hospitalizations or cardiovascular events<sup>[15]</sup>. In addition, an absolute low rate of mortality and a low incidence of major vascular events (primary endpoint) were observed in our CHF patients burdened by a high cardiovascular risk (NYHA class III or at least one hospitalization during the last year). Again, we observed a low rate of the combined endpoint of death plus hospitalization. The data obtained in our study substantially differ from the data of the EuroHeart Failure Survey<sup>[16]</sup>, in which 24% of the 11 327 CHF patients included were readmitted to the hospital within 12 weeks of discharge, and a significantly higher mortality rate (13.5%) was observed.

There are several possibilities for these unexpected results. First, all patients were followed at home by their cardiologist, with specific expertise in the ambulatory management of CHF. Therefore, all the patients had physical examinations with evaluation of vital parameters and routine laboratory analysis at the programmed and evidence-based times. Second, upgrading of clinical and laboratory evaluation was performed in particular in patients who live in places with physical barriers making it difficult to reach the pertinent District Healthcare Center, and in fact the home monitored patients living in these remote places answered the Minnesota questionnaire in the same way. Third, all patients were treated according to current guidelines with all the necessary adjustments of the drugs dosages at each visit.

In our study, however, home echocardiography did not improve the cardiovascular outcomes of CHF patients.

Further studies with a large number of patients and a longer follow-up are needed to clarify which could be the better home monitoring program for improving the natural history and the prognosis of patients with chronic heart failure.

## COMMENTS

### Background

To decrease the incidence of re-hospitalization and improve quality of life of chronic heart failure (CHF) patients, home monitoring programs may be beneficial.

### Research frontiers

Comparison of 2 home monitoring programs: (1) clinical evaluations and electrocardiographic (ECG) every 3 mo, and echocardiography examinations on the 6th, 12th and 18th months; and (2) clinical evaluations and ECG every 3 mo only.

### Innovations and breakthroughs

Home echocardiography did not improve the cardiovascular outcomes of CHF patients.

### Applications

Home monitoring programs are aimed at improving the natural history and the prognosis of patients with CHF.

### Peer review

The paper is well written and methodology sound. The findings highlights the importance of regular monitoring and proper treatment of heart failure based on guidelines on outcome and not necessarily investigations that were not prompted by the clinical symptoms and signs of patients.



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## A nutraceutical combination improves insulin sensitivity in patients with metabolic syndrome

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### Abstract

**AIM:** To test the efficacy of a proprietary nutraceutical combination in reducing insulin resistance associated with the metabolic syndrome (MetS).

**METHODS:** Sixty-four patients with MetS followed at a tertiary outpatient clinic were randomly assigned to receive either placebo or a proprietary nutraceutical combination (AP) consisting of berberine, policosanol and red yeast rice, in a prospective, double-blind, placebo-controlled study. Evaluations were performed at baseline and after 18 wk of treatment. The homeostasis model assessment of insulin resistance (HOMA-IR) index was the primary outcome measure. Secondary endpoints included lipid panel, blood glucose and

insulin fasting, after a standard mixed meal and after an oral glucose tolerance test (OGTT), flow-mediated dilation (FMD), and waist circumference.

**RESULTS:** Fifty nine patients completed the study, 2 withdrew because of adverse effects. After 18 wk there was a significant reduction in the HOMA-IR index in the AP group compared with placebo ( $\Delta$ HOMA respectively  $-0.6 \pm 1.2$  vs  $0.4 \pm 1.9$ ;  $P < 0.05$ ). Total and low density lipoprotein cholesterol also significantly decreased in the treatment arm compared with placebo ( $\Delta$ low density lipoprotein cholesterol  $-0.82 \pm 0.68$  vs  $-0.13 \pm 0.55$  mmol/L;  $P < 0.001$ ), while triglycerides, high density lipoprotein cholesterol, and the OGTT were not affected. In addition, there were significant reductions in blood glucose and insulin after the standard mixed meal, as well as an increase in FMD ( $\Delta$ FMD  $1.9 \pm 4.2$  vs  $0 \pm 1.9$  %;  $P < 0.05$ ) and a significant reduction in arterial systolic blood pressure in the AP arm.

**CONCLUSION:** This short-term study shows that AP has relevant beneficial effects on insulin resistance and many other components of MetS.

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**Key words:** Metabolic syndrome; Insulin resistance; Homeostasis model assessment index; Nutraceuticals; Berberine

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## INTRODUCTION

Metabolic syndrome (MetS) is a clustering of components associated with type 2 diabetes mellitus (T2D) and increased risk of cardiovascular (CV) events<sup>[1]</sup>. Although there are different criteria for the identification of MetS, scientific societies agree that abdominal obesity, impaired glucose metabolism, dyslipidemia and arterial hypertension represent the key components<sup>[2]</sup>. Estimates of its prevalence may vary depending on the definition, but the resulting increase in morbidity and mortality is a matter of great concern<sup>[3]</sup>. Even though MetS is characterized by wide phenotypic and biologic heterogeneity, insulin resistance and visceral obesity are the key features of the syndrome<sup>[1,4]</sup>.

Since no single pathogenetic pathway has to date been identified as a valuable therapeutic target in the syndrome, current management still addresses the various components of MetS individually, by means of both lifestyle modifications and pharmacological therapy. This kind of approach is frequently burdened by therapeutic failure and patient frustration, and most often requires a multi-drug regime; therefore, the need of a process-oriented, disease-modifying treatment aimed at attenuating disease progression and reducing the risk of CV events is increasingly recognized.

A recent study by our group has investigated the effects of a proprietary nutraceutical combination (AP) on lipids and endothelial function, demonstrating how a treatment with a single tablet containing berberine (BRB), policosanols, and red yeast rice (RYR) significantly lowered total and low density lipoprotein cholesterol (LDL), simultaneously improving endothelial function, in a population with mild to moderate hypercholesterolemia. In addition, a subgroup of insulin-resistant patients showed significant improvements in the homeostasis model assessment of insulin resistance (HOMA-IR), QUICKI, and McAuley indices<sup>[5]</sup>. Since BRB has already shown effects on lipid metabolism, T2D, insulin resistance, and nitric oxide production<sup>[6-8]</sup>, we hypothesized that its synergistic action with policosanols and RYR might be useful in the management of the different components of the MetS. Therefore, the aim of this study was to investigate the effects of AP in patients with MetS.

## MATERIALS AND METHODS

### Study design

The study was a prospective, single-center, randomized, double-blind, placebo-controlled trial consisting of a screening visit and an 18 wk treatment period.

The study protocol was approved by the Ethics Committee of the University of Naples "Federico II", and written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki. The trial was registered at clinicaltrials.gov with ID NCT01087632.

### Patients and treatment

Study participants were recruited between September

2009 and February 2010 at the outpatient clinic of our department.

Eligibility criteria were: (1) age between 18 and 65 years; (2) diagnosis of metabolic syndrome, defined as the presence of a waist circumference > 102 cm (male), > 88 cm (female), associated with at least two of the following: triglycerides  $\geq$  1.7 mmol/L; high density lipoprotein (HDL) < 1.03 mmol/L (male), < 1.29 mmol/L (female); systolic blood pressure  $\geq$  130 mmHg or diastolic blood pressure  $\geq$  85 mmHg or need for antihypertensive therapy; fasting glucose  $\geq$  5.6 mmol/L; and (3) ability to understand and give informed consent to clinical experimentation.

Exclusion criteria were: (1) proven intolerance to any component of AP; (2) pregnancy or breastfeeding; (3) treatment with hypoglycemic agents; (4) moderate to severe liver dysfunction (Child B-C); (5) abnormal renal function (serum creatinine greater than 2 mg/dL); (6) serum triglycerides > 5.6 mmol/L; and (7) a history or current symptoms of heart failure.

The nutraceutical combination used in this study consisted of a single tablet containing BRB 500 mg, RYR (monacolin K 3 mg), and policosanols 10 mg (AP, Armolipid Plus<sup>®</sup>, Rottapharm Madaus, Italy).

Patients with concomitant diseases were included provided their clinical conditions and treatment had been stable during the previous 6 mo. Sixty four patients meeting the eligibility criteria were enrolled in the study. Patients were randomized to receive either one tablet of AP or placebo once daily after supper. The placebo tablet, identical in taste and appearance to the AP tablet, consisted of inactive compound and did not contain any carbohydrates. Randomization and blinding were provided by Rottapharm Madaus SpA (Monza, Italy), which also funded the study.

### Outcomes

The primary endpoint was the absolute change from baseline of the HOMA-IR index. Secondary endpoints were the reductions in fasting and post-prandial glucose and insulin levels, waist circumference, total cholesterol, LDL and triglycerides (TG), and the improvement in endothelial-dependent flow-mediated dilation (FMD) in relation to AP treatment.

### Clinical and biochemical measurements

Initial screening included medical history, physical examination, evaluation of anthropometric parameters, routine blood tests, serum renal and hepatic markers, measurements of serum insulin, glucose and lipids concentrations.

Study assessments were performed at baseline and after 18 wk of treatment. Patients were evaluated after an overnight fast of 14 h, with a physical examination and medical history; arterial blood pressure, anthropometric and impedentiometric parameters were measured. Endothelial-dependent dilation was assessed with the FMD of the brachial artery using Doppler ultrasonography, according to the Guidelines of the International Brachial Artery Reactivity Task Force<sup>[9]</sup>. The forearm was occluded by cuff inflation to at least 50 mmHg

**Table 1** Comparison of group characteristics at baseline

	AP	Placebo
Number (M/F)	29 (20/9)	30 (18/12)
Age	53 ± 7	50 ± 12
Weight (kg)	90 ± 13	96 ± 18
BMI	32.2 ± 4.6	34.7 ± 5.1
Waist circumference (cm)	110 ± 9	115 ± 13
Systolic blood pressure (mmHg)	125 ± 13	125 ± 14
Diastolic blood pressure (mmHg)	78 ± 8	81 ± 8
Fasting glucose (mmol/L)	5.72 ± 1.22	4.72 ± 0.67 <sup>a</sup>
Fasting insulin (pmol/L)	90 ± 42	90 ± 69
HOMA-IR	3.2 ± 1.5	2.7 ± 2.2
Triglycerides (mmol/L)	1.76 ± 0.86	1.92 ± 0.83
Total cholesterol (mmol/L)	5.40 ± 1.00	5.09 ± 1.03
HDL cholesterol (mmol/L)	1.08 ± 0.26	1.18 ± 0.35
LDL cholesterol (mmol/L)	3.49 ± 0.19	3.05 ± 1.00
Flow mediated dilation (%)	6.8 ± 3.1	6.8 ± 1.9
Concomitant medications ( <i>n</i> )		
ACE-I/ARB	26/29	24/30
Statins	8/29	8/30
Beta-blockers	10/29	10/30

AP: Nutraceutical consisting of berberine, policosanol and red yeast rice; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; HOMA-IR: Homeostasis model assessment of insulin resistance; BMI: Body mass index; HDL: High density lipoprotein; LDL: Low density lipoprotein. <sup>a</sup>*P* < 0.05.

above systolic pressure for 5 min, resulting in a reactive hyperemia after the release of the cuff, and the increased shear stress led to endothelial-mediated vasodilatation. FMD was measured with an ultrasound scanner with a 7.5 MHz linear transducer (Toshiba PLT-704AT); five consecutive discrete measurements were obtained and averaged into the final value at each time point. Later, a blood sample was taken for biochemical measurements of glucose, insulin (radioimmunoassay method), lipids (total, LDL, HDL cholesterol and TG), serum renal and hepatic markers (creatinine, aspartate aminotransferase; alanine aminotransferase). Then, all the patients received a standard mixed meal, and blood samples were collected at 30, 60 and 120 min after meal consumption for the evaluation of serum glucose and insulin levels. The next day a standard oral glucose tolerance test (OGTT) was performed. The HOMA-IR index was calculated as follows:  $\text{HOMA-IR} = [\text{fasting glucose (in mg/dL)} / 18] \times [\text{fasting insulin (in } \mu\text{UI/mL)} / 22.5]$ .

All patients received dietary counseling from a specialist. At baseline, patients were asked to maintain their usual diet. Then, after 6 wk of treatment, they received an individualized isocaloric diet based on estimated ideal weight. Concomitant medications and adverse events were monitored throughout the study.

### Statistical analysis

The study was powered in accordance with a predetermined statistical analysis plan. A sample size of 30 patients in each of the 2 study arms was calculated based on a predicted dropout rate of 6%, a power of 0.8, and an  $\alpha$ -error probability of 0.05, to detect an absolute between-group difference of 0.8 in the change of HOMA-IR index given an expected standard deviation (SD) of

variations of 1 between changes in the primary endpoint variable after treatment.

The paired-samples *t* test was used for within-group comparisons. The unpaired, two-tailed *t* test was used for between-group comparisons of baseline characteristics and changes after treatment. The data are presented as mean ± SD.

## RESULTS

Sixty four patients meeting the eligibility criteria were randomized to receive a tablet of AP or placebo once a day after supper. Fifty nine patients (29 in the AP arm and 30 in the placebo arm) completed the study, whereas 3 were lost to follow-up and 2 withdrew from the study (one in the AP group and one in the P group) because of non-serious adverse events (constipation).

Patients' clinical characteristics was shown in Table 1. At baseline, the 2 groups were comparable in age, sex, smoking status, concomitant medications, anthropometric parameters, lipid levels. In the placebo group, 8 patients were being treated with statins, and 25 patients with antihypertensive drugs (40% with  $\beta$ -blockers, 92% with angiotensin receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACE-I)). Similarly, in the AP group, 8 patients were being treated with statins, and 27 patients with antihypertensive drugs (41% with  $\beta$ -blockers, 96% with ARB or ACE-I). Baseline fasting glucose levels were significantly higher in the AP arm compared with the placebo group. However, the HOMA-IR index was comparable in the 2 groups.

After 18 wk of treatment, the comparison of absolute changes from baseline between the 2 groups showed a significant decrease in the HOMA-IR index in the AP arm (from  $3.2 \pm 1.5$  to  $2.6 \pm 1.3$  *vs* from  $2.7 \pm 2.2$  to  $3.2 \pm 2.6$ , *P* < 0.05) (Table 2, Figure 1A). Among secondary endpoints, although no significant difference was observed between the 2 arms in the reduction of fasting glucose (from  $5.72 \pm 1.22$  to  $5.28 \pm 1.11$  mmol/L *vs* from  $4.72 \pm 0.67$  to  $4.55 \pm 0.67$  mmol/L, *P* > 0.05), fasting insulin decreased significantly in the AP group as compared with placebo (from  $90 \pm 42$  to  $76 \pm 42$  pmol/L *vs* from  $90 \pm 69$  to  $111 \pm 90$  pmol/L, *P* < 0.05) (Figure 1B). In addition, there was a significant improvement in the post-prandial mean blood glucose and insulin levels in the AP arm compared with placebo (respectively from  $7.00 \pm 1.89$  to  $6.67 \pm 1.61$  mmol/L *vs* from  $5.89 \pm 1.33$  to  $6.05 \pm 0.89$  mmol/L, and from  $306 \pm 125$  to  $298 \pm 159$  pmol/L *vs* from  $409 \pm 194$  to  $507 \pm 347$  pmol/L, *P* < 0.05 for both) (Figure 1B). No significant variations were observed for OGTT parameters both within-group and between-group.

Total cholesterol and LDL significantly decreased compared with placebo (respectively from  $209 \pm 38$  to  $178 \pm 23$  mg/dL *vs* from  $198 \pm 40$  to  $193 \pm 31$  mg/dL, and from  $136 \pm 8$  to  $105 \pm 21$  mg/dL *vs* from  $119 \pm 38$  to  $114 \pm 38$  mg/dL, *P* < 0.001), while no significant change was observed in HDL and TG levels (Figure 1B). Subjects who received AP had a significant improvement in FMD, whereas no change was observed in the placebo



Table 2 Summary of patient characteristics, primary and secondary endpoints

	AP			Placebo			$\Delta$ from baseline AP	$\Delta$ from baseline placebo	Between-group comparison of $\Delta$ (P)
	Baseline	18-wk	Within-group difference vs baseline (P)	Baseline	18-wk	Within-group difference vs baseline (P)			
Number (M/F)	29 (20/9)			30 (18/12)					
Age	53 $\pm$ 7			50 $\pm$ 11.9					
Smoker	3/29			3/30					
Weight (kg)	90 $\pm$ 13	88 $\pm$ 12	0.008	96 $\pm$ 18	95 $\pm$ 18	0.011	-1.6 $\pm$ 3.1	-1.3 $\pm$ 2.6	0.657
BMI (kg/m <sup>2</sup> )	32.2 $\pm$ 4.6	31.7 $\pm$ 4.4	0.013	34.7 $\pm$ 5.1	34.2 $\pm$ 5.1	0.008	-0.5 $\pm$ 1.1	-0.5 $\pm$ 0.9	0.805
Waist circumference (cm)	110 $\pm$ 9	107 $\pm$ 9	0.018	115 $\pm$ 13	114 $\pm$ 13	0.087	-2.4 $\pm$ 5.1	-1.2 $\pm$ 3.6	0.301
Systolic blood pressure (mmHg)	125 $\pm$ 13	120 $\pm$ 9	0.037	125 $\pm$ 14	126 $\pm$ 12	0.585	-5 $\pm$ 14	1 $\pm$ 12	0.047
Diastolic blood pressure (mmHg)	78 $\pm$ 8	75 $\pm$ 8	0.087	81 $\pm$ 8	78 $\pm$ 7	0.084	-3 $\pm$ 8	-3 $\pm$ 10	0.753
Fasting glucose (mmol/L)	5.72 $\pm$ 1.22	5.28 $\pm$ 1.11	0.006	4.72 $\pm$ 0.67	4.55 $\pm$ 0.67	0.006	-0.44 $\pm$ 0.78	-0.22 $\pm$ 0.39	0.186
Fasting Insulin (pmol/L)	90 $\pm$ 42	76 $\pm$ 42	0.165	90 $\pm$ 69	111 $\pm$ 90	0.119	-14 $\pm$ 35	21 $\pm$ 57	0.042
HOMA-IR	3.2 $\pm$ 1.5	2.6 $\pm$ 1.3	0.019	2.8 $\pm$ 2.2	3.2 $\pm$ 2.6	0.259	-0.6 $\pm$ 1.2	0.4 $\pm$ 1.9	0.023
Mean postprandial glucose (mmol/L)	7.00 $\pm$ 1.89	6.67 $\pm$ 1.61	0.085	5.89 $\pm$ 1.33	6.05 $\pm$ 0.89	0.309	-0.33 $\pm$ 1.00	0.16 $\pm$ 0.78	0.046
Mean postprandial Insulin (pmol/L)	306 $\pm$ 125	298 $\pm$ 159	0.793	409 $\pm$ 194	507 $\pm$ 347	0.017	-7 $\pm$ 115	100 $\pm$ 215	0.023
OGTT Glucose at 2 h (mmol/L)	8.89 $\pm$ 3.44	8.33 $\pm$ 3.00	0.216	6.94 $\pm$ 1.94	7.17 $\pm$ 1.89	0.478	-10 $\pm$ 47	4 $\pm$ 25	0.153
Triglycerides (mmol/L)	1.76 $\pm$ 0.86	1.73 $\pm$ 0.85	0.933	1.92 $\pm$ 0.83	2.07 $\pm$ 1.28	0.375	-0.01 $\pm$ 0.89	0.17 $\pm$ 1.03	0.467
Total cholesterol (mmol/L)	5.40 $\pm$ 1.00	4.60 $\pm$ 0.59	< 0.001	5.09 $\pm$ 1.03	5.08 $\pm$ 0.82	0.253	-0.82 $\pm$ 0.76	-0.13 $\pm$ 0.60	< 0.001
HDL cholesterol (mmol/L)	1.08 $\pm$ 0.26	1.08 $\pm$ 0.23	0.757	1.18 $\pm$ 0.35	1.1 $\pm$ 0.28	0.054	0.00 $\pm$ 0.13	-0.08 $\pm$ 0.21	0.074
LDL cholesterol (mmol/L)	3.49 $\pm$ 0.19	2.69 $\pm$ 0.54	< 0.001	3.05 $\pm$ 1	2.93 $\pm$ 0.99	0.200	-0.82 $\pm$ 0.68	-0.13 $\pm$ 0.55	< 0.001
Flow mediated dilation (%)	6.8 $\pm$ 3.1	8.7 $\pm$ 3.3	0.021	6.8 $\pm$ 1.9	6.8 $\pm$ 2.1	0.982	1.9 $\pm$ 4.2	0 $\pm$ 1.9	0.032

AP: Nutraceutical consisting of berberine, policosanol and red yeast rice; OGTT: Oral glucose tolerance test; HOMA-IR: Homeostasis model assessment of insulin resistance; BMI: Body mass index; HDL: High density lipoprotein; LDL: Low density lipoprotein.

group (Table 2, Figure 1B); the mean values of the baseline brachial artery diameter were comparable between groups.

A slight reduction in body weight was observed in both groups. Waist circumference was significantly reduced in the AP group compared with baseline (from 110.3  $\pm$  9.5 cm to 107.9  $\pm$  8.6 cm,  $P$  < 0.001), but no significance was found compared with placebo.

After 18 wk of treatment, systolic blood pressure significantly decreased in the AP group, compared with placebo (from 125  $\pm$  13 to 120  $\pm$  9 mmHg *vs* from 125  $\pm$  14 to 126  $\pm$  12 mmHg,  $P$  < 0.05).

### Safety

No changes in renal and hepatic parameters were observed throughout the study period. AP was generally well tolerated and no serious adverse event occurred.

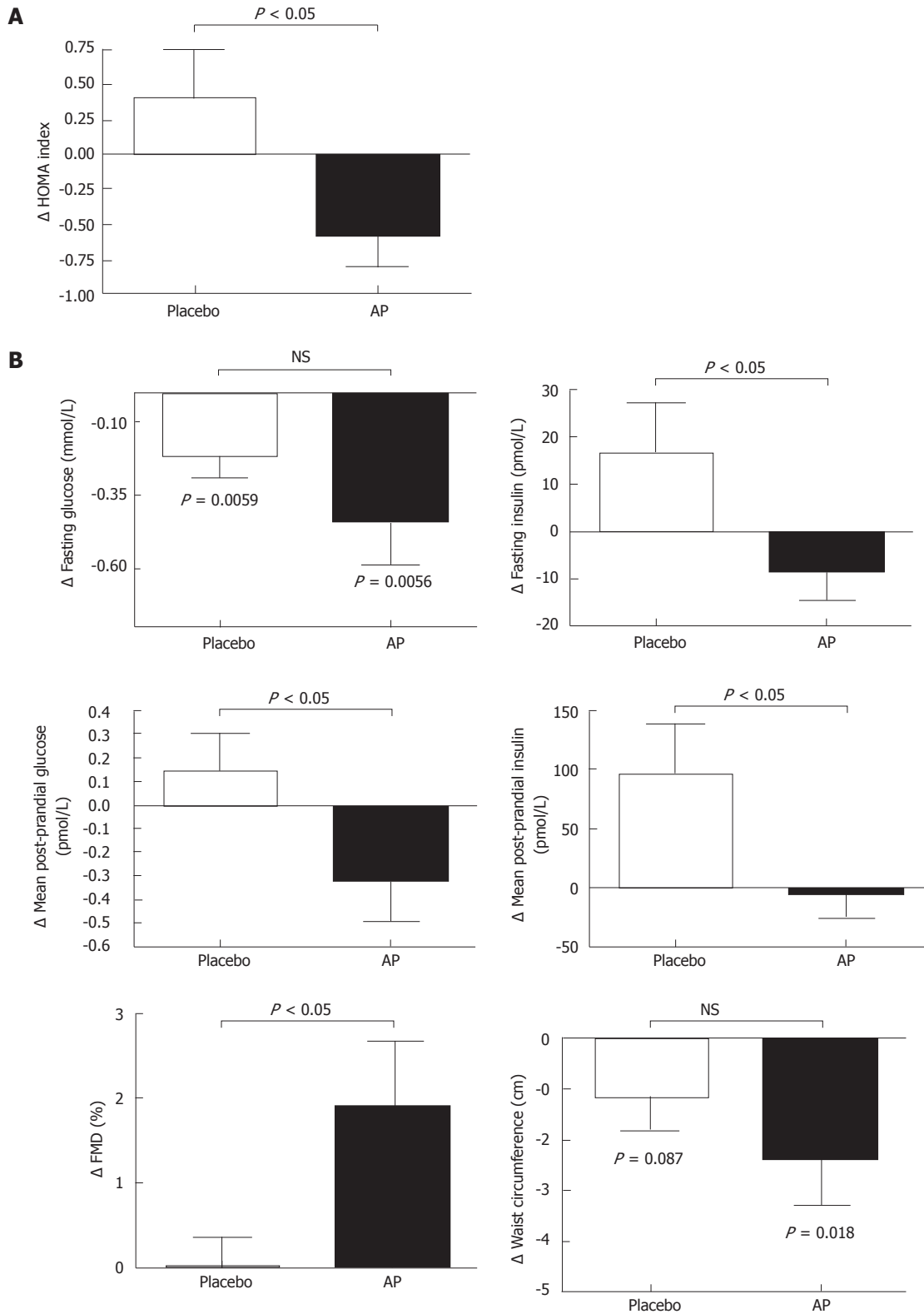
## DISCUSSION

This study shows that AP is effective and safe in reducing insulin resistance in a group of patients with MetS. We observed a significant reduction in the HOMA-IR index after 18 wk of treatment; this finding was accompanied by an improvement of postprandial glucose handling, as well as by beneficial effects on multiple clinical and biochemical parameters of MetS.

The HOMA index is a well validated surrogate measure of insulin resistance, and a strong predictor of CV risk in several classes of patients<sup>[10,11]</sup>. Mounting evidence from the last years supports the importance of the HOMA-IR index as a prognosticator even at values very close to the normal range, i.e., in patients not fit-

ting a diagnosis of T2D. Recent studies demonstrated its independent value in the prediction of CV events in the general adult non-diabetic population<sup>[12,13]</sup>. In light of these epidemiological findings, our results appear strengthened in their clinical significance, strongly advocating further research in the field. The effect of AP on insulin resistance may be chiefly explained by the action of BRB on glucose metabolism. BRB has been used for more than 2000 years in traditional Asian medicine for the treatment of many unrelated disorders including diabetes mellitus. Two randomized controlled trials have investigated, to date, the metabolic effects of BRB on glucose metabolism in T2D patients: in both studies BRB was effective in improving glucose control and indices of insulin resistance, to an extent similar to commonly employed hypoglycemic agents, which were used as control<sup>[6,14]</sup>. Our results concerning insulin resistance substantially confirm that found in these reports in a different, "less advanced" population of patients with MetS. Of note, the dose of BRB employed in the aforementioned clinical experiences is much higher than the one used in our study (approximately twice as high).

Several experimental studies recently provided insights into the pharmacodynamic basis of such therapeutic effects of BRB, in which it differs substantially from all the most prescribed molecules in the field. In fact, BRB activates AMP-activated protein kinase leading to metabolic gene regulation, with beneficial effects on adipose tissue and muscle<sup>[7]</sup>; moreover, the AMP-mediated activation reduces insulin secretion by pancreatic  $\beta$ -cells<sup>[15]</sup>. Another recognized mechanism is the upregulation of insulin-receptor expression through protein kinase C activation<sup>[16]</sup>. On the other hand, evidence from



**Figure 1** Variations in the primary endpoint (A) and in secondary endpoints (B). AP: Nutraceutical consisting of berberine, policosanol and red yeast rice; HOMA: Homeostasis model assessment; FMD: Flow-mediated dilation.

both *in vivo* and *in vitro* studies suggest that part of the antihyperglycemic activity of BRB is due to a decrease in the availability of glucose after a meal. In particular, BRB suppresses intestinal disaccharidases, reducing the intestinal absorption of glucose<sup>[17]</sup>. This latter effect is

very interesting and may explain the slight but significant reduction in postprandial glycemia observed in the treated group.

AP treatment led to a significant reduction in total and LDL cholesterol, confirming previous reports<sup>[5,18]</sup>.

Interestingly, the therapeutic effect seemed evident also in those patients who were already under treatment with statins. These results are extremely meaningful in light of the recommendation to reduce LDL-cholesterol below 100 mg/dL to reduce the risk of CV events in patients with MetS. Both BRB and RYR monotherapy have been proven to reduce blood lipid levels at higher doses, even being advocated by many as a first-line therapy for statin-intolerant subjects; once again, the doses used in the present trial were much lower than the ones commonly used in the past monotherapy studies<sup>[19,20]</sup>.

The positive effects on both glucose and lipid metabolism were accompanied by a marked improvement in endothelial function. In fact, this study shows a significant increase in FMD values in the AP group compared with the placebo group. Such a finding may arise not only from the improvement of metabolic alterations, but also from the demonstrated antiproliferative and vasodilatory effects of BRB<sup>[21,22]</sup>. Moreover, BRB has shown beneficial effects on endothelial function also by inducing upregulation of the endothelial progenitor cells related to nitric oxide production. The importance of this improvement of vascular reactivity seems also reinforced by the unexpected reduction of blood pressure values in the treated arm.

In both groups, a slight reduction in body weight was observed and the magnitude of this reduction was comparable. This effect may be related to the diet. Nevertheless this slight weight loss in the placebo arm was not associated with an improvement in metabolic parameters, suggesting a beneficial effect of AP independent of weight loss. In addition, patients in the active arm also showed a trend to reduced waist circumference, which was not observed in the placebo arm. We can postulate that this reflects a better disposal of fat, with a relative reduction of visceral fat in the AP arm. The effect on waist circumference confirms previous results in animal models, in which treatment with BRB led to a significant reduction in abdominal fat<sup>[23]</sup>. However, we also acknowledge that study design and duration did not aim at demonstrating effects on anthropometric parameters.

In conclusion, we demonstrated that a combination of BRB, RYR and policosanol exerts beneficial effects on all components of MetS, despite the short duration of the study and the low doses of the individual components; the clinical benefit seems pleiotropic, involving both markers of insulin-resistance, dyslipidemia, and endothelial function. The treatment was well tolerated with negligible side effects.

Management of MetS is nowadays based on lifestyle intervention and treatment of its individual components. Effective prevention is based on strategizing health policies and mass intervention programs; anyway, given its high prevalence and significance, an effective therapy to contrast the cluster of components of MetS and reduce risk at the patient level is increasingly felt as an urgent need; if our results are confirmed by larger studies with harder outcome measures, we believe that nutraceuticals may play an important role in such a scenario, given their

strong rationale, pleiotropic action, efficacy, and tolerability. Upcoming research shall also focus on dose ranging, patient selection and association studies with other “pharmaceutical” molecules, i.e., statins, polyunsaturated fatty acids, and metformin, possibly in the context of large multicenter trials.

The results of this study should be interpreted in light of some limitations. This was a short-term study, while metabolic interventions may require longer periods to assess stable beneficial effects. On one hand, this could have led to an underestimation of the actual effects of chronic treatment; on the other hand, some long-term safety and tolerability questions, as well as efficacy on hard clinical endpoints, remain unanswered and need further investigation.

The improvement in the HOMA-IR index could have been influenced, at least in part, by the dietary intervention; however, patients in the placebo arm, who followed the same diet, experienced a slight worsening of the index. Another point is that, although this was a randomized study, fasting glucose levels were not well balanced between the 2 groups; since the groups appeared comparable regarding all other measures of insulin resistance, including the predefined primary endpoint, this inequality seems to be acceptable and justified by the wide phenotypic variability of MetS.

The present study shows that the administration of AP in a group of MetS patients is safe and effective in reducing more than one feature of MetS. Further studies are needed to investigate whether long-term treatment with this kind of nutraceutical combination may prevent CV and T2D complications.

## ACKNOWLEDGMENTS

Part of the results of the present study were first presented at the American College of Cardiology 2011 Scientific Sessions (New Orleans, LA).

## COMMENTS

### Background

Metabolic syndrome is responsible for a large part of the increase in the incidence of cardiovascular events developed countries have been witnessing in the last decades. Patients are mostly treated by means of lifestyle modification, counseling and multiple drug therapies, with frequent nonadherence and treatment failure. In this paper, the authors assessed the clinical benefits of a nutraceutical containing berberine, policosanol, and red yeast rice, on insulin resistance and several other parameters of metabolic syndrome, on top of current guideline-oriented therapy.

### Research frontiers

Research has long been focusing on integrated pleiotropic medications and drug combinations in metabolic syndrome. However, most pharmacological approaches to date have been addressing the consequences of the disease (i.e., lipid levels and platelet hyperaggregability) more than its underlying mechanisms (i.e., insulin resistance, visceral obesity). On the other hand, nutritional or nutraceutical supplements have to date proven of little or no benefit in this patient population.

### Innovations and breakthroughs

The findings can be of great interest to the readers, since authors demonstrate that a low dose of a nutraceutical combination effectively and safely reduces insulin resistance in patients with metabolic syndrome, with a general effect on

clinical and biochemical parameters; these changes were accompanied by a significant improvement in vascular reactivity and systolic blood pressure. The addition of nutraceuticals to lifestyle modification and pharmacological therapy might offer an innovation in this field, given the strong rationale, pleiotropic action, efficacy and good tolerability of these compounds.

### Applications

The applicability of the results could be surprisingly wide, because of the availability of this specific nutraceutical combination in several countries, and its good safety and tolerability profiles. Single, isolated experiences on selected patients seem to be warranted, especially in the setting of primary prevention and in individuals refusing "traditional" drug therapy. Nonetheless, authors must acknowledge that much larger and long-term studies will be needed to expand indications to the whole metabolic syndrome-population in a more systematic fashion. The current scenario of clinical research in primary prevention would probably require years and thousands of patients to test such treatments on hard event-based endpoints; however, large trials based on well-validated surrogate endpoints will certainly follow in the near future.

### Terminology

The term "nutraceutical" derives from the words "nutrition" and "pharmaceutical", and it can be defined as a product isolated or purified from foods, generally sold in medicinal forms, and demonstrated to have a medical benefit or to provide protection against chronic diseases. Many studies have investigated the beneficial properties of some of these substances on metabolic alterations, and the assessment of the most recent scientific evidence in the field led us to explore the potential efficacy on insulin resistance of a nutraceutical combination of berberine, red yeast rice, and policosanols.

### Peer review

This paper is well-written and interesting.

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## Brugada electrocardiographic pattern induced by fever

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### Abstract

Brugada syndrome is a major cause of sudden death in young adults. Fever has been described to induce a Brugada-type electrocardiogram in asymptomatic patients with a negative family history, to disclose Brugada syndrome and to increase the risk of death and induce T wave alternans in patients with diagnosed Brugada syndrome. Risk stratification is challenging and demands a careful evaluation. Here we present 2 case reports and review the literature.

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**Key words:** Brugada syndrome; Phenotype; Fever; Electrocardiogram

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### INTRODUCTION

Brugada syndrome (BS) is a channelopathy that may be familial or sporadic and is a major cause of sudden death in young men with no evidence of structural heart disease<sup>[1,2]</sup>. The electrocardiogram (ECG) is characterized by persistent ST segment elevation in the right precordial leads unrelated to ischemia, right bundle branch block and rapid polymorphic ventricular tachycardia capable of degenerating into ventricular fibrillation<sup>[3]</sup>. The ECG pattern may be dynamic and is often concealed. Sodium channel blockers, tricyclic antidepressants, anesthetics, cocaine, methadone, antihistamines, electrolyte imbalances and fever are recognized inducers<sup>[4]</sup>. Here we present 2 patients with Brugada-type ECG induced by fever, and review the current literature.

### CASE REPORT

#### Case 1

A 48-year-old male, renal transplant recipient was admitted to our hospital because of pneumonia. He denied a history of syncope or palpitations and his family history was negative for sudden death. On physical examination, his temperature was 39 °C and his heart rate was 120 beats/min. A cardiac examination was unremarkable. Because of atypical chest pain on admission, an ECG was performed that revealed sinus tachycardia and saddleback ST segment elevation in V1 and V2 (Figure 1, Panel A). Initial laboratory data showed an increased creatinine level (1.9 mg/dL; normal range, 0.5-1.5 mg/dL) and normal

Table 1 Brugada-type electrocardiogram induced by fever

Author	Age	Sex	Cause of fever	Test performed and results	Follow up	Events during follow up
Kum <i>et al</i> <sup>[5]</sup>	39	M	Pneumonia	Drug challenge (Flecainide); positive	NM	N/A
Patrino <i>et al</i> <sup>[6]</sup>	53	M	Influenza-like febrile illness	Drug challenge (Flecainide); positive	2 yr	No events
Saura <i>et al</i> <sup>[15]</sup>	69	M	Pneumonia	Drug challenge (Flecainide); negative	NM	N/A
Shinohara <i>et al</i> <sup>[16]</sup>	64	M	Common cold	Drug challenge (Pilsicainide); Positive; EPS PES positive ICD	1 yr	No VF was observed
Ott <i>et al</i> <sup>[17]</sup>	27	F	Viral pharyngitis	Echocardiogram; normal	NM	N/A
Sanchez <i>et al</i> <sup>[18]</sup>	54	F	Klebsiella oitoca catheter associated bacteremia	Echocardiogram; normal radionuclide stress test	NM	N/A
Wakita <i>et al</i> <sup>[19]</sup>	35	M	Measles	Drug challenge (Pilsicainide); positive; patient denied EPS	NM	N/A
Aramaki <i>et al</i> <sup>[20]</sup>	61	M	NM	Drug challenge (Pilsicainide); positive; coronary angiography; EPS PES	NM	N/A
Susuki <i>et al</i> <sup>[21]</sup>	59	M	NM		NM	N/A
	51	M	Pneumonia	Echocardiogram; AS HQ; serial cardiac enzymes negative	NM	N/A
Kalra <i>et al</i> <sup>[22]</sup>	35	M	Pneumonia	Drug challenge (Flecainide); positive; EPS negative	NM	N/A
Gavrielatos <i>et al</i> <sup>[23]</sup>	45	M	Cholecystitis	Holter: Low heart rate variability; SAECC: Positive late potentials; drug challenge test (Procainamide) positive; patient denied EPS and coronary angiography	NM	N/A
Mok <i>et al</i> <sup>[24]</sup>	53	M	Cholangitis	Drug challenge (Flecainide) borderline positive; cardiac MRI no structural heart disease; EPS PES negative	2 yr	No clinical events

M: Male; NM: Not mentioned; N/A: Not applicable; EPS: Electrophysiological study; SAECC: Signal average electrocardiogram; MRI: Magnetic resonance imaging; PES: Programmed electrical stimulation; VF: Ventricular fibrillation; ICD: Internal cardioverter defibrillator; AS HQ: Anteroseptal hypokinesia.

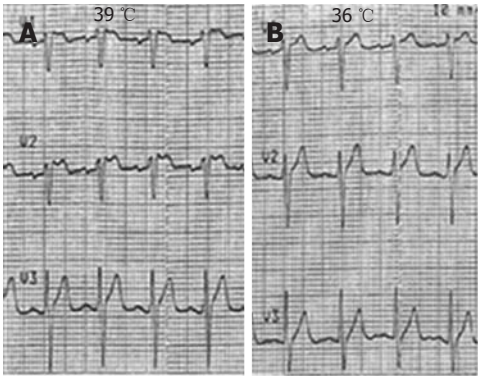


Figure 1 Electrocardiogram case 1. A: Saddleback ST segment elevation in V1 and V2 during the febrile episode; B: Normal electrocardiogram when the fever resolved.

potassium level (4.2 mEq/L). Troponin, creatine kinase (CK) and CK-MB were negative. An echocardiogram showed normal systolic function and absence of segmental abnormalities. ECG findings resolved when the patient became afebrile even though sinus tachycardia persisted (Figure 1, Panel B). One year after discharge, the patient remained alive with no episodes of syncope.

Case 2

A 69-year-old male was admitted to our hospital with a complicated urinary tract infection. His past medical history was significant for diabetes mellitus type 2 and benign prostatic hypertrophy. On physical examination his blood pressure was 120/80 mmHg, his heart rate was 80 beats/min and his temperature was 38 °C. Cardiac

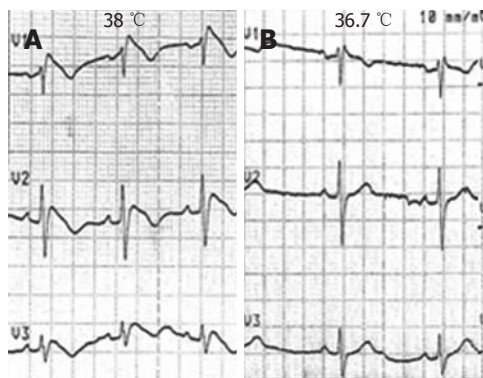
examination was unremarkable. His blood chemistry was within the normal range, including potassium (4.6 mEq/L). A routine ECG on admission revealed coved-shaped ST elevation in leads V1 through V3 (Figure 2, Panel A). An ECG performed when the patient was without fever showed incomplete right bundle branch block (Figure 2, Panel B). A transthoracic echocardiogram disclosed normal systolic function and absence of segmental wall motion abnormalities.

The family history was negative for syncope or sudden cardiac death. The patient was evaluated by cardiac electrophysiology, and conservative management was indicated. Two years after being discharged the patient remains well and free of cardiac events.

DISCUSSION

Predominance of outward ionic current (Ito) at the end of phase 1 of the action potential either because of an increase of its magnitude or because of a decrease in inward currents (INa, ICaL) causes loss of the action potential dome and marked shortening of the action potential. The greater density of the Ito current in the epicardium causes a transmural dispersion of repolarization that manifest as a J wave or ST-segment elevation<sup>[5]</sup>. Accelerated inactivation of the sodium channel can be temperature-sensitive<sup>[6,7]</sup>. Fever might also impair conductance of the sodium channel<sup>[8]</sup>.

Fever has been described to induce a Brugada-type ECG pattern in asymptomatic patients with a negative family history (Table 1)<sup>[9]</sup>, disclosing Brugada syndrome<sup>[10-12]</sup>, and to increase the risk of death, to induce



**Figure 2** Electrocardiogram case 2. A: Coved shaped ST elevation in leads V1 through V3 during the febrile episode; B: Incomplete right bundle branch block when the fever subsided.

T wave alternans and premature ventricular beats in patients with diagnosed Brugada syndrome<sup>[13,14]</sup>.

Risk stratification of asymptomatic patients with a Brugada-type ECG induced by fever and a negative family history remains a matter of debate. According to current guidelines, careful follow-up would be an appropriate option<sup>[1]</sup>. The diagnostic value of a drug challenge test as well as electrophysiological studies in this population is uncertain.

Type I and II Brugada ECG patterns should be included in the differential diagnosis of ST elevation in a patient with fever. Reversibility of ECG alterations when the patient is normothermic is crucial. Rapid treatment and consultation in an emergency department in case of fever should be considered. Asymptomatic patients with a Brugada-type ECG induced by fever with a negative family history of syncope or sudden death seem to have good prognosis, but careful follow-up is needed until we better define the clinical implications of this entity.

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## Severe mitral annular calcification in rheumatic heart disease: A rare presentation

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### Abstract

Severe mitral annular calcification (MAC) is frequently seen in patients with advanced age and chronic kidney disease, but it is rare in rheumatic heart disease (RHD). We hereby report a case of 45-year-old female with chronic RHD, who had severe MAC and mitral regurgitation. Fluoroscopy revealed a "crown"-like severe calcification of the mitral annulus. Autopsy of the heart revealed a calcified posterior mitral annulus, fused commissures, and calcified nodules at the atrial aspect of the mitral valve.

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**Key words:** Mitral annular calcification; Rheumatic heart disease; Mitral regurgitation; Autopsy; Aschoff nodule

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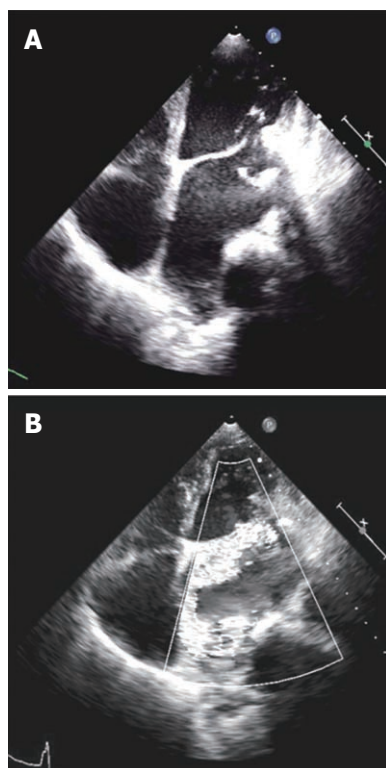
### INTRODUCTION

Mitral annular calcification (MAC) is a common feature in patients with chronic rheumatic heart disease (RHD), chronic kidney disease, and advanced age<sup>[1]</sup>. A severely calcified mitral annulus is frequently seen in patients with chronic kidney disease and degenerative valve disease, but it is rare in RHD. We hereby report a case of severe MAC in a chronic RHD patient and discuss the management issues related to it.

### CASE REPORT

A 45-year-old female with chronic RHD who was under medical treatment for 2 years, presented with atrial fibrillation and gross congestive heart failure. Her routine serum biochemistry tests, including urea and creatinine, were normal. Two-dimensional echocardiography showed a thickened, calcified, retracted posterior mitral leaflet with severe mitral regurgitation. The posterior mitral leaflet and adjacent mitral annulus were calcified (Figure 1). She improved with diuretics and other supportive treatment. Fluoroscopy in right anterior oblique 30° revealed a "crown"-like severe calcification of the mitral annulus (Figure 2). Her angiography showed normal epicardial coronaries. A left ventriculogram revealed an ejection fraction of 0.50, and grade III mitral regurgitation. The pulmonary artery systolic pressure was 58 mmHg. During the hospital stay awaiting cardiac surgery,



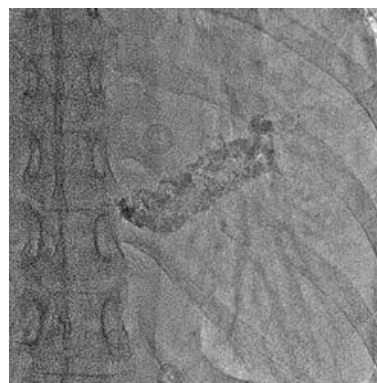


**Figure 1** Echocardiography in apical 4 chamber view. A: Calcified, thickened and retracted posterior mitral leaflet with adjacent mitral annular ring calcification; B: Color Doppler showing severe mitral regurgitation.

she had a sudden cardiac arrest and died. The autopsy revealed severe calcification of the posterior mitral valve ring, irregular calcified nodules on the posterior mitral leaflet, and commissural fusion of the posterior leaflet (Figure 3). Histopathology of the left atrial inner wall revealed Aschoff Nodule with fibrosis suggesting a rheumatic etiology<sup>[2]</sup>.

## DISCUSSION

MAC in patients with RHD usually involves commissures and leaflet tissue, with only late extension to the annulus. Severe MAC, as present in the index case, is rare in RHD, though it is often reported in patients with degenerative valve disease<sup>[3]</sup> and chronic kidney disease<sup>[4]</sup>. There is a risk of systemic non-thrombotic embolism of calcified material in such cases during the natural course of the disease and also at the time of percutaneous or surgical intervention<sup>[5]</sup>. MAC is usually associated with mitral stenosis because of restricted posterior mitral leaflet and annulus movement<sup>[6]</sup>. However, the index case had a thickened, retracted, poorly aligned posterior leaflet resulting into severe mitral regurgitation. Sudden cardiac death in the index case can be explained by a low ejection fraction of 0.50, left ventricular hypertrophy secondary to mitral regurgitation, and diuretics induced electrolyte imbalance<sup>[7]</sup>. Surgical treatment in such a case is technically difficult. There is need for adequate debridement and annular reconstruction prior to mitral



**Figure 2** Fluoroscopy image in right anterior oblique 30° view showing severe mitral annular calcification.



**Figure 3** Gross photograph of the inflow tract of the left heart showing a grossly dilated left atrium and ventricle. Both mitral leaflets show thickened and fused chordae. There is massive calcification of the posterior mitral annulus. Some of the calcified foci are visible as irregular nodules along the atrial surface of posterior leaflet.

valve repair or replacement<sup>[8,9]</sup>. Mitral valve repair may not be technically feasible in such cases because of severe calcification and the difficulty of suturing at the calcified site, mandating a prosthetic valve replacement. Intra-atrial valve placement instead of usual positioning at the mitral annulus has also been tried in such cases when there is technical difficulty in reconstruction or suturing at the calcified annulus<sup>[10,11]</sup>. The reoperation rate and technical complications are also higher in such cases<sup>[8,10,12]</sup>. Unfortunately, the index case died prior to surgical intervention, and autopsy confirmed severe MAC and also RHD.

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## MEETINGS

### Events Calendar 2012

January 18-21, 2012  
Ninth Gulf Heart Association  
Conference  
Muscat, Oman

January 27, 2012  
ESC Global Scientific Activities at  
the 23rd Annual Conference of the  
Saudi Heart Association  
Riyadh, Saudi Arabia

January 29-31, 2012  
Integrated management of acute and  
chronic coronary artery disease  
Innsbruck, Austria

January 30, 2012  
Webinar on "Best of Euroecho 2011"  
Sophia Antipolis, France

February 1-3, 2012  
American Heart Association and  
American Stroke Association  
International Stroke Conference 2012  
New Orleans, Louisiana,  
United States

February 3-5, 2012  
6th Asian-Pacific Congress Of Heart  
Failure 2012  
Chiang Mai, Thailand

February 9, 2012  
4th British Society for Heart Failure  
Medical Training Meeting  
London, United Kingdom

February 23-25, 2012  
Advanced Invasive Cardiac  
Electrophysiology  
Sophia Antipolis, France

February 24-26, 2012  
International Congress of  
Cardiology  
Hong Kong, China

February 28, 2012  
Echocardiography evaluation of  
patient with multivalvular disease  
Sophia Antipolis, France

February 29-March 3, 2012  
Winter ISHNE 2012  
Zakopane, Poland

March 8-10, 2012  
Cardiac Pacing, ICD and Cardiac  
Resynchronisation  
Vienna, Austria

March 8-10, 2012  
24th Colombian Congress of  
Cardiology and Cardiovascular  
Surgery  
Cali, Colombia

March 10-11, 2012  
23rd International Meeting  
"Cardiology Today"  
Limassol, Cyprus

March 14-18, 2012  
Ninth Mediterranean Meeting on  
Hypertension and Atherosclerosis  
Antalya, Turkey

March 15-17, 2012  
e-Cardiology 2012  
Osijek, Croatia

March 15-18, 2012  
China Interventional Therapeutics  
2012-CIT  
Beijing, China

March 16-17, 2012  
12th Annual Spring Meeting on  
Cardiovascular Nursing  
Copenhagen, Denmark

March 16-17, 2012  
3rd European Meeting: Adult  
Congenital Heart Disease  
Munich, Germany

March 16-18, 2012  
JCS2012 - The 76th Annual Scientific  
Meeting  
Fukuoka, Japan

March 20-23, 2012  
32nd International Symposium  
on Intensive Care and Emergency  
Medicine  
Brussels, Belgium

March 25-29, 2012  
16th International Symposium On  
Atherosclerosis 2012  
Sydney, Australia

March 28-31, 2012  
Rome Cardiology Forum 2012  
Rome, Italy

March 28-31, 2012  
Annual Spring Meeting of the  
Finnish Cardiac Society 2012  
Helsinki, Finland

March 30-April 1, 2012  
Frontiers In CardioVascular Biology

2012  
London, United Kingdom

April 5-7, 2012  
EAE Teaching Course on New  
echocardiographic techniques for  
myocardial function imaging  
Sofia, Bulgaria

April 12-14, 2012  
Cardiovascular Risk Reduction:  
Leading The Way In Prevention 2012  
National Harbor, MD, USA

April 12-15, 2012  
NHAM Annual Scientific Meeting  
2012  
Kuala Lumpur, Malaysia

April 18-21, 2012  
World Congress of Cardiology  
Scientific Sessions 2012  
Dubai, United Arab Emirates

April 19-21, 2012  
Delivering Patient Care in Heart  
Failure  
Sophia Antipolis, France

April 20-22, 2012  
7th Clinical Update on Cardiac MRI  
and CT  
Cannes, France

April 25-27, 2012  
Angioplasty Summit 2012  
Seoul, South Korea

April 25-28, 2012  
The 61st International Congress  
of the European Society of  
Cardiovascular and Endovascular  
Surgery  
Dubrovnik, Croatia

April 28-29, 2012  
24th Annual Scientific Meeting of  
the SCS  
Singapore, Singapore

May 3-5, 2012  
EuroPREvent 2012  
Dublin, Ireland

May 15-18, 2012  
EuroPCR Congress 2012  
Paris, France

May 17-20, 2012  
2nd International Meeting On  
Cardiac Problems In Pregnancy 2012  
Berlin, Germany

May 19-22, 2012  
Heart Failure 2012  
Belgrade, Serbia

May 23-26, 2012  
46th Annual meeting of the  
Association for European Pediatric  
and Congenital Cardiology  
Istanbul, Turkey

May 26-27, 2012  
Cardiovascular Spring Meeting 2012  
Vienna, Austria

June 7-9, 2012  
6th Congress of Asian Society of  
Cardiovascular Imaging  
Bangkok, Thailand

June 7-9, 2012  
6th Congress of Asian Society of  
Cardiovascular Imaging 2012  
Bangkok, Thailand

June 15-17, 2012  
13th Annual Cardiology Update  
Bhurban, Pakistan

June 21-24, 2012  
10th International Pulmonary  
Hypertension Conference and  
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July 19-22, 2012  
13th Annual South African Heart  
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August 25-29, 2012  
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September 29-October 4, 2012  
International Society of  
Hypertension 24th Annual Scientific  
Meeting 2012  
Sydney, Australia

October 4-6, 2012  
Magnetic Resonance in Cardiology  
Riva Del Garda, Italy

October 20-23, 2012  
Acute Cardiac Care 2012  
Istanbul, Turkey





## INSTRUCTIONS TO AUTHORS

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**Acknowledgments**

Brief acknowledgments of persons who have made genuine con-



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### Format

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English journal article (list all authors and include the PMID where applicable)

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

- 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

Organization as author

- 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]

Both personal authors and an organization as author

- 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]

No author given

- 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]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

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

### Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 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

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 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/index.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

### Statistical data

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

### Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as  $\chi^2$  (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

### Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h,



blood glucose concentration, *c* (glucose)  $6.4 \pm 2.1$  mmol/L; blood CEA mass concentration, *p* (CEA) =  $8.6 \pm 2.5$   $\mu$ g/L; CO<sub>2</sub> volume fraction, 50 mL/L CO<sub>2</sub>, not 5% CO<sub>2</sub>; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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### Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, *etc.*

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kbo I*, *Kpn I*, *etc.*

Biology: *H. pylori*, *E. coli*, *etc.*

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