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**Emerging Concepts in CHF Management and Hypertension Control**

A report from The American Society of Hypertension (ASH)’s 17th Annual Scientific Meeting, 2002, New York, NY

In May of 2002, the city of New York played host to the world’s leading physicians and researchers in the world of cardiovascular medicine.

The 17th Annual Scientific Meeting of the American Society of Hypertension was the venue for the presentation of a broad range of original research in hypertension and related fields.

In this issue of Cardiology Bulletin, we present some of the more intriguing study results presented during this four-day series of meetings.

For a comprehensive compilation of abstracts from the 17th ASH, consult the American Journal of Hypertension abstract issue (Am J Hypertens 2002; 15[4 Suppl.]).
Two studies presented at the 17th Annual Scientific Meeting of the American Society of Hypertension (ASH) statistically demonstrated the link between caffeine consumption and hypertension.

Although caffeine consumption has been recognized as a cardiovascular risk factor, these studies are among the first to investigate the biologic processes involved.

One study, a collaboration between Greek and Australian researchers, looked at the effects of caffeine on 10 patients with hypertension. Specifically, the investigators sought to determine the effects on aortic stiffening, which is an independent predictor of the risk of cardiovascular disease morbidity and mortality. Stiffening was measured by pulse-wave velocity.

The study was a crossover design, in which patients were randomized to receive either 250 mg of caffeine (approximately equivalent to two or three cups of coffee) or placebo on one day, followed by the alternate treatment on the next study day.

The investigators found that, on the days patients consumed the caffeine pill, pulse-wave velocity increased and arteries stiffened. On the placebo days, however, there was no such increase in wave velocity.

Systolic and diastolic pressures were also measured as secondary endpoints in this study. The researchers found that systolic pressure increased by 11.4 mmHg and diastolic pressure by 7.7 mmHg (Figure 1). These effects lasted for at least three hours.

A separate study, performed at the State University of New York, in Buffalo, examined the effects of caffeine on small- and large-artery compliance. Decreased artery compliance is known to be strongly associated with cardiovascular disease. The effects of caffeine on artery compliance, however, has not been well defined. The investigators of this study examined changes in large-artery elastic index (LAEI) and small-artery elastic index (SAEI) in response to caffeine.

The study was designed as a single-blind, crossover format in healthy volunteers. The study group consisted of 16 subjects (nine men and seven women) aged 21 to 62 (mean 35) years.

Measurements were made at baseline, 20, 40, and 60 minutes after administration of 200 mg of caffeine or placebo.

As shown in Table 1, the investigators found that caffeine decreased small-artery compliance, which in turn increased blood pressure and systemic vascular resistance (SVR).

Caffeine did not, however, have a significant effect on the compliance of large arteries.

The investigators concluded that the increased arterial stiffness in response to caffeine may contribute to hypertension and increased cardiovascular disease. This sentiment was echoed by researchers involved in the Greek/Australian study.

“This study proves that people with hypertension face the risk of higher blood pressure and increased arterial stiffness when they consume caffeine,” said Dr. Charalambos Vlachopoulos, one of the Greek/Australia study’s lead investigators.

References:

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<th></th>
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<tr>
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<td>66 ± 9</td>
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SBP: systolic blood pressure; DBP: diastolic blood pressure; LAEI: large-artery elastic index; SAEI: small-artery elastic index; SVR: systemic vascular resistance
Patients who take acetylsalicylic acid (ASA) before going to bed can expect significantly greater blood pressure reductions than those who take ASA at other times.

That was the message conveyed by Spanish researchers at the 17th Annual Scientific Meeting of the American Society of Hypertension (ASH).1

While organizers of some studies have examined the anti-hypertensive effects of ASA, results have been inconsistent. The investigators of this study speculated that circadian-rhythm-related changes in several physiologic pathways can affect the efficacy of the drug. The body’s tendency to absorb ASA more quickly in the morning than in the evening illustrates this phenomenon.

The investigators followed 109 mild hypertensives divided into three groups: those who took ASA upon awakening, those who took ASA at bedtime and those who took the agent according to nonpharmacological hygienic-dietary recommendations.

Blood pressure and heart rate were measured with an ambulatory device every 20-30 minutes over a 48-hour period both before and after three months of intervention.

The investigators found that subjects who took ASA at bedtime exhibited a highly significant reduction (systolic change: -7.6 mmHg; diastolic change: -6.1 mmHg) in blood pressure (Figure 1). There was no effect on blood pressure in either of the other two groups.

The researchers concluded that timing of administration might account for discrepancies in previous studies on the hypertensive effects of ASA.

"Timed administration of low-dose aspirin could be a valuable approach, not only for the prevention of major cardiovascular events, but also for the control of blood pressure in patients with mild to moderate essential hypertension," said Ramon C. Hermida, PhD, director of Bioengineering & Chronobiology Labs at the University of Vigo in Spain and the study’s lead investigator.

Moreover, the investigators also stressed the importance of identifying patients taking ASA and controlling for the drug’s effects in future antihypertension medical trials.

The same investigators also examined the effects of ASA dose timing in women at risk for pre-eclampsia. In two separate reports, the investigators presented the effects on blood pressure2 and the incidence of complications.3

A placebo-controlled trial was conducted with 241 pregnant women, randomly assigned to one of six different groups (treatment or placebo, each with three different administration times). The three administration times investigated were 1) upon awakening; 2) eight hours after awakening; and 3) at bedtime.

There was no effect of ASA on BP at time 1 (compared with placebo).

A BP reduction was, however, highly statistically significant when ASA was given at time 2 and, to a greater extent, at time 3 (bedtime). The mean reductions at bedtime were 12.6 mmHg systolic and 8.5mmHg diastolic, as compared to placebo.

The incidence of complications was also significantly affected by the timing of ASA administration. For women who received their dose upon awakening, the incidence of preeclampsia, gestational hypertension, IU GR, and preterm delivery were 15.5%, 25.9%, 15.5%, and 12.1%, respectively. For those who received their ASA at bedtime, the incidence of these complications was 1.7%, 6.8%, 3.4% and 0%, respectively (Figure 2).

References:
Physicians have been told repeatedly that the vast majority of patients with hypertension are not at target blood pressure (BP). The reasons are complex but include failure to use higher-dose medications when appropriate and combination drug therapy. This is starting to change, but for the vast majority of hypertension, most family physicians prefer to use single-drug therapy and are only adding a second agent from time to time.

Clinical trials suggest that only one-third of hypertensive patients can be controlled with a single agent; many patients will require three to four drugs to achieve target BP. Currently, all antihypertensive agents lower BP to a similar magnitude in the order of 5-15 mmHg. Omapatrilat is member of a new class of agents called vasopeptidase inhibitors, and is being studied in the management of hypertension and other cardiovascular diseases. For the first time, a monotherapy has been shown to provide an extra 5 mmHg of BP lowering compared to other agents.

The OCTAVE trial, which is reviewed below, evaluated more than 25,000 patients in the management of hypertension. The trial was designed as a short-term trial looking at the effectiveness or tolerability of omapatrilat in three groups of patients with hypertension versus best medical therapy. The BP-lowering effects of omapatrilat compared to conventional therapy will be accurately interpreted in the pages that follow. Evaluation of the antihypertensive effect of this new drug compared to previous agents will follow the review of its pharmacologic characteristics.

**Pharmacology of Omapatrilat**

At a symposium of the 17th Annual Scientific Meeting of the American Society of Hypertension (ASH), Dr. John B. Kostis, a lead investigator of the OCTAVE study (and the chairman of this symposium), described the pharmacologic attributes of omapatrilat. As he pointed out, omapatrilat is the most widely studied of the vasopeptidase inhibitors, with approximately 35,000 patients having been exposed to the drug in clinical study.

Simply put, the vasopeptidase inhibitors exert their therapeutic effects through a two-pronged mechanism of action. Generally speaking, they inhibit the activity of both the angiotensin-convert- ing enzyme (ACE), as well as neutral endopeptidase (NEP). Independent inhibition of each of these metalloproteases has been associated with improved outcomes in hypertension.

More precisely, the inhibition of NEP prevents the degradation of natriuretic peptides, thereby enhancing vasodilatation, while ACE inhibition reduces vasoconstriction, together resulting in significant decreases in systolic BP, diastolic BP and vascular tone without activation of the reflex renin angiotensin aldosterone system or sympathetic nervous system (Figure 1).

**Efficacy of Omapatrilat: Previous Clinical Trials**

At the same ASH symposium, Dr. Michael Weber presented the results of clinical trials conducted and presented before the development of the OCTAVE protocol.

Omapatrilat has been compared to established antihypertensive agents amlodipine and lisinopril. In the amlodipine trial, both agents were titrated to the maximum recommended doses (10 mg for amlodipine and 80 mg for omapatrilat) in 430 patients.

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**Do We Need a New Class of Antihypertensive Agents?**

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**Figure 1** Dual Mechanisms of Action of Omapatrilat

![Diagram](image_url)
Dr. Weber presented the graph shown in figure 2, which compares the mean systolic blood pressure changes over the 24-hour dosing period through the use of ambulatory BP monitoring. The changes were consistently more dramatic in the omapatrilat group compared to the amlodipine group. The average difference between the two treatment groups was 5.9 mmHg for systolic and 4.4 mmHg for diastolic pressures.

Dr. Weber also described the results of a trial comparing omapatrilat's BP-lowering efficacy to lisinopril's by ambulatory BP monitoring in 317 patients at maximum doses.2

The results, shown in Figure 3, demonstrated that patients in the omapatrilat group had significantly greater reductions in both systolic and diastolic BPs compared to those in the lisinopril group.

As Dr. Weber stated, the results of clinical trials have consistently shown that omapatrilat has a more robust antihypertensive effect than other agents currently available.

**TOLERABILITY AND SAFETY**

As with any new drug, side effects and toxicities need to be properly identified and dealt with. In the initial studies of omapatrilat, there were no statistically significant differences in terms of overall incidence of adverse effects or serious adverse events with omapatrilat in comparison with amlodipine or lisinopril.

It was discovered, however, that angioedema occurs in approximately 2% of patients treated with omapatrilat. One-third of this angioedema occurs during the first day and two-thirds by week four.

What is unclear to most physicians, however, is that the incidence of angioedema with ACE inhibitors is 0.6%. Patients more likely to develop angioedema include African blacks (5.5% with omapatrilat and 1.6% with enalapril). In addition, smokers are more prone to angioedema.

In the more than 6,000 patients enrolled in omapatrilat studies prior to OCTAVE, it was found that 44 (0.7%) experienced some form of angioedema.

As Dr. Weber explained, this higher incidence of angioedema in the initial clinical trials prompted the designers of the OCTAVE study to include rigorous standards for the detection of angioedema in that study.

The following pages provide a review of the efficacy and safety data from the OCTAVE study.

References:
At the 17th Annual Scientific Meeting of the American Society of Hypertension (ASH), Dr. Henry Black presented the results of the OCTAVE study to attendees of a special symposium.

OCTAVE (Omapatrilat Cardiovascular Treatment Assessment vs. Enalapril) was a multinational trial involving almost 3,500 investigators and more than 25,000 patients with hypertension.

Before Dr. Black took to the podium to present the data from OCTAVE, however, the study protocol was described by Dr. John Kostis.

OCTAVE STUDY PROTOCOL

Patient population. The OCTAVE investigators enrolled more than 25,000 patients, who were divided into three separate groups: Group 1 consisted of those who had hypertension but were untreated at baseline (n=9,292); Group 2 included those with treated but uncontrolled stage I hypertension (n=11,224); and Group 3 was made up of those with treated but uncontrolled stage II hypertension (n=4751).

All three groups were randomized on a 1:1 ratio to receive one of two active treatments: omapatrilat or the ACE inhibitor enalapril.

In Group 2, the study drugs replaced whatever medications the patients were on previously. In Group 3, the study drugs were added to the existing regimens.

Entry criteria. The OCTAVE study was designed to mimic, as closely as possible, a real-life clinical setting. With that in mind, the patients had a wide range of comorbidities (including 13% with diabetes and 32% with hypercholesterolemia) (Table 1). In groups 2 and 3, the patients were being treated with a wide range of antihypertensive medications, including diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers and others. This too is reflective of clinical practice.

All patients were over the age of 18 with documented hypertension (defined as either systolic BP > 140 mmHg or diastolic BP > 90 mmHg).

Titration. The OCTAVE study was designed in an attempt to produce similar reductions in BP with both omapatrilat and enalapril (goal < 140/< 90 mmHg). The trial protocol called for an initial forced titration, from the starting dose (10 mg for omapatrilat, 5 mg for enalapril) to 20 mg and 10 mg, respectively, at two weeks. At four weeks after study initiation, the investigators could then titrate the dose further to reach the BP target (to 40 mg for omapatrilat and to 20 for enalapril). At six weeks, the dose could be titrated again, if necessary, to the maximum dose (80 mg and 40 mg, respectively).

Following the first eight weeks, if necessary to reach the target BP, the physicians could add adjunctive therapy(ies) to the existing regimens.

Endpoints. The primary efficacy endpoints of the study were to compare the change in systolic BP from baseline to week 8 (end of study drug titration period) and differences in the need for adjunctive therapies over the total 24-week treatment period.

In terms of safety, the investigators sought to evaluate the incidence of all adverse events, with a

<table>
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particular focus on angioedema. The protocol specifically called for the investigators to report all events that they thought might be attributable to angioedema.

All cases were then blindly reviewed by an expert panel to determine if, indeed, they were cases of angioedema.

**OCTAVE: EFFICACY RESULTS**

Dr. Black broke down his presentation into a discussion of the data collected at week 8 and at the study’s conclusion at week 24.

**Week 8 results.** At week 8, which was before investigating physicians were allowed to add adjunctive therapies, there were striking differences between the two therapies. As shown in Figure 4a, omapatrilat produced significantly greater reductions in systolic BP compared to enalapril, while fewer omapatrilat patients required the maximum titrated dose (Figure 4b). This was true for all three groups of patients (Groups 1, 2 and 3). Furthermore, these results were obtained despite the fact that the investigators were comparing significantly higher doses of enalapril to lower doses of omapatrilat.

The percentage of patients in each group reaching the treatment goals at week 8 was also significantly higher in those patients in the omapatrilat groups than in the enalapril groups (Figure 4c).

The superiority seen with omapatrilat in Groups 2 and 3 were also irrespective of the type(s) of antihypertensive the patients were receiving at baseline. Figure 5 shows the changes in systolic BP for Group 2, based on the types of antihypertensive the patients were on at baseline.

Similarly, patients with significant cardiovascular risk factors (diabetes, renal disease, severe hypertension, isolated systolic hypertension, MI, angina, stroke) also experienced a more significant reduction in BP with omapatrilat compared to enalapril (Figure 6).

**Week 24 results.** Dr. Black explained that physicians were allowed to add adjunctive agents to the treatment regimens during the final 16 weeks of the study. The protocol was designed this way to try to ensure that the BP achieved would be similar in both the enalapril and omapatrilat groups.

As the week 24 results showed, however, the study did not play out that way. BP efficacy continued to be superior in the omapatrilat groups compared to enalapril.
Dr. Black showed graphs of the major efficacy variables as documented at week 24. The results were strikingly similar to those seen at week 8. As shown in Figure 7a, omapatrilat therapy was again associated with significantly greater reductions in systolic BPs at the study endpoint in all three groups compared to enalapril. Despite the fact that significantly fewer patients required adjunctive therapies with omapatrilat (Figure 7b), significantly more patients in that group reached the target BP level of < 140/< 90 mmHg (Figure 7c).

As was the case with the eight-week data, Dr. Black demonstrated that omapatrilat was associated with greater BP reductions in high-risk groups, such as those with diabetes, renal disease and previous MI.

**Efficacy Summary.** The efficacy results from OCTAVE more than confirmed the earlier research that treatment with omapatrilat achieves superior BP-lowering efficacy compared to conventional agents. As Dr. Black explained, even in a trial that was designed to bring about similar levels of BP control, patients in the omapatrilat group experienced, on average, a more significant drop in their BP compared to those in the enalapril group, despite lower doses and less adjunctive therapies.

**OCTAVE: SAFETY RESULTS**

The OCTAVE investigators were quite rigorous in detecting and reporting adverse effects in this trial. Beyond the stated goal of vigilantly looking for angioedema, Dr. Black explained that any other adverse effects were also diligently recorded.

The overall incidence of adverse effects other than angioedema was similar for both treatment groups (51.0% for omapatrilat and 50.4% for enalapril). Serious adverse events were also experienced at approximately the same rate (3.5% for omapatrilat, 3.7% for enalapril).

**Angioedema.** Angioedema is an infrequent but well known adverse effect of ACE inhibition. In the SOLVD trial, for example, 0.4% of patients in the enalapril group experienced angioedema, compared to 0.1% in the placebo group. As Dr. Kostis explained, however, the problem with earlier ACE inhibitor studies was the highly variable way in which angioedema was looked for and reported.
In the SOLVD study, for example, investigators were only instructed to look for angioedema halfway into the trial. Prior to that instruction, angioedema was lumped into the "other" category. An analysis of the reporting data showed that when the investigators were told to look for angioedema, they found it.

In the OCTAVE study, quantification and qualification of angioedema was one of the primary endpoints; the study was prospectively designed to rigorously report any event that could possibly be angioedema, including swelling of the neck and face. Occurrences of angioedema in the OCTAVE study were grouped into three classifications: Level 1) those who did not require treatment or were treated with antihistamines only; Level 2) those who were treated with epinephrine, but had no airway compromise; and Level 3) those with airway compromise, treated with epinephrine or mechanical airway protection.

The incidence of all three levels of angioedema was higher in the omapatrilat group than the enalapril group. Level 1 angioedema was seen in 1.28% of omapatrilat patients, compared to 0.52% of enalapril patients, an absolute difference of 0.76%. Level 2 angioedema was reported in 0.87% and 0.17%, respectively, an absolute difference of 0.70%. Level 3 cases were very rare, only occurring in 2 patients (0.01%) in the omapatrilat group.

In attempting to determine the potential risk factors for the development of angioedema with omapatrilat, Dr. Black showed that, although the highest incidence was during the first day of dosing (0.70%), the effects could be seen further along in the course of therapy as well. The period from day 2 to week 4 saw 0.66% of angioedema cases, while 0.1% occurred after week 21.

In terms of at-risk patient groups, the study investigators determined that black race was a risk factor for angioedema for both enalapril and omapatrilat, while those who were current smokers had a significantly increased risk for angioedema with omapatrilat, but not with enalapril. This is the first observation of a possible link of smoking to angioedema.

**OCTAVE Summary**

The investigators of the OCTAVE study concluded that omapatrilat was a more efficacious BP-lowering drug than enalapril, despite study protocol efforts to achieve similar BP reductions in both treatment groups. This greater efficacy was observed across all treatment groups and at all time points measured in the study.

Angioedema was more prevalent in the omapatrilat group than in the enalapril group, but airway compromise was rare (approximately 0.01%). Although cases were reported throughout the trial period, the likelihood of angioedema decreased greatly after the first day of therapy.

Apart from angioedema, the incidence of adverse effects was comparable between the two agents.

**Other Omapatrilat Reports**

Although the OCTAVE study was the one that dominated discussions concerning omapatrilat, there were other reports presented at the ASH conference as well.

**Overture.** During the same session, Dr. Milton Packer presented data from the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) study in heart failure patients.

This trial, which included almost 6,000 patients, compared the effects of enalapril and omapatrilat in patients with heart failure. The primary endpoints of the study were all-cause mortality and hospitalization for heart failure requiring intravenous treatment. Dr. Packer showed graphed data for the primary endpoints; at one year, there is a trend towards superiority for omapatrilat in both endpoints. In the all-cause mortality endpoint, for example, the relative risk reduction in favor of omapatrilat was 6% (p=0.339). In the combination of death and hospitalization for heart failure, the risk reduction was also 6% (p=0.187). In terms of CV death or CV hospitalization, a secondary endpoint, omapatrilat was associated with a statistically significant 9% relative risk reduction compared to enalapril (p=0.024).
The prespecified reference standard for non-inferiority was the SOLVD treatment trial using enalapril. However, the definition of hospitalization in SOLVD was different than the one used in OVERTURE. SOLVD included all hospitalizations by investigators, regardless of treatment or treatment duration, whereas the OVERTURE protocol only included hospitalizations in which intravenous CHF treatment was required. As a result, the US Food & Drug Administration requested that the OVERTURE results be evaluated using the same criteria.

Using these criteria, omapatrilat demonstrated statistically significant superiority over enalapril in the OVERTURE population. There were 1,041 patients who died or were hospitalized for heart failure in the enalapril group and 941 in the omapatrilat group (hazard ratio 0.89 [95% CI, 0.82 to 0.98], p=0.012).

In this population, there were no significant differences in the incidence of angioedema. Dr. Packer explained that patients with heart failure are less likely to have vasodilator adverse events than patients with earlier-stage cardiovascular diseases (e.g., hypertension).

CHOIR. The results of the Conduit Hemodynamics of Omapatrilat International Research (CHOIR) study were also presented at the 17th Annual ASH scientific meeting. The investigators of this study found that, compared to enalapril, omapatrilat produced significantly greater reductions in peripheral and central pulse pressure in association with a pressure-independent reduction in proximal aortic stiffness. These findings were attributed to the favorable effect of natriuretic peptides on central conduit vessel function.

**Conclusions and Physician Perspectives**

Getting to BP targets is often a difficult task. It is clear that the management of hypertension involves two components when using BP medications:

#1 Lowering BP to <140/<90 mmHg for most hypertensive patients, and to <130/<80 mmHg for high-risk patients (such as diabetics).

#2 Blocking neurohormonal activity. HOPE and LIFE are examples of numerous clinical trials showing vascular protection beyond BP reduction.

Having a new antihypertensive such as omapatrilat, which provides additional BP lowering potency, is a welcome addition. This is especially true in that the drug appears to work in high-risk groups (i.e., diabetes) and those requiring combination drug therapy, providing additional BP reductions. This must, however, be tempered with the knowledge that a serious side effect called angioedema occurs more often with omapatrilat than with ACE inhibitors.

AT₁ receptor blockers (ARBs) may cause less angioedema than ACE inhibition. In the recent OPTIMAAL study, which showed that patients fared better on an ACE inhibitor (captopril) than with an ARB (losartan), angioedema was reported in 0.4% of patients treated with relatively low doses of losartan and 0.8% of the captopril-treated patients, despite less rigorous reporting of angioedema than in the OCTAVE study.

It is clear that angioedema occurs with ARBs, ACE inhibitors and vasopeptidase inhibitors. It is an adverse event that physicians and patients need to be aware of. With the results of OCTAVE, we now know that with omapatrilat, angioedema occurs more frequently than with ACE inhibitors, but the vast majority of the incidence of angioedema occurs early and is mild and transient.

With education, omapatrilat appears to be a reasonable option for difficult-to-control patients with hypertension, patients with multiple risk factors and patients with CHF.

Reference:

Marriage can influence high blood pressure, Canadian researchers reported at the 17th Annual Scientific Meeting of the American Society of Hypertension (ASH).

The study, a multidisciplinary effort at the University of Toronto, examined whether differences in jobs or amount of marital support were associated with changes in cardiovascular risk factors.1

In the study, researchers examined 103 unmedicated men and women with mild hypertension. They were followed for three years.

The investigators found that men whose jobs caused mental strain were more likely to have higher blood pressure than men whose jobs did not cause stress. Women, however, remained unaffected by on-the-job stress.

The study subjects were monitored by 24-hour ambulatory blood pressure monitoring. Of that group, 72 underwent echocardiography to measure left-ventricular mass (LVM).

One of the most striking findings was the difference in LVM between those whose marriages were classified as having a strong marriage (as measured by a psychiatric assessment tool) and those who did not have a strong marriage.

"We showed that, at baseline, marriage, but not work, was related to left-ventricular mass at three years," said Dr. Brian Baker, a member of the University of Toronto’s Department of Psychiatry and the lead study investigator. "If marital adjustment was worse, left-ventricular mass was greater."

As shown in Figure 1, LVM decreased by 8.0% in the “strong marriage” group, while it increased by 6.3% in the “weak marriage” group.

The strong marital support group also had lower diastolic blood pressure, mean arterial pressure and albuminuria than the weak marital support group.

Reference:

Canadian Researchers Link Job, Marital Stress to Cardiovascular Risk Factors