Halt Aortic Stenosis Progression in the Elderly (HAPIE): The Effect of Atorvastatin on the Progression of Mild and Moderate Aortic Stenosis

Renato Apolito

A. Study Purpose

Aortic stenosis (AS) is a common and serious condition that involves the narrowing of the aortic valve area (AVA). It is estimated that between 2-9% of people over age 65 are afflicted.[2, 5] With time, the narrowing of the aortic valve area progresses and hemodynamic compromise becomes more pronounced, leading to the classic and ominous triad of symptoms of syncope, angina, and dyspnea, prompting the urgent need for aortic valve replacement (AVR). If the valve is not surgically replaced in the symptomatic patient, the risk of sudden death may approach 50% at 2 years and 100% at 5 years.[1] Although, certain modifiable risk factors, such as increased low-density lipoprotein cholesterol (LDL-C), have been shown to be associated with a more rapid progression of AS[7], the progression from asymptomatic to symptomatic varies significantly among individuals, making the optimal timing of AVR largely unpredictable. However, the echocardiographic parameters of progression (measured by annual decrease in AVA and increase in mean and peak transvalvular pressure gradients) has been shown in numerous studies to be much more consistent.[5, 6]

It is now accepted that aortic stenosis is one extreme of the spectrum of calcific valvular degeneration. Histopathological studies have revealed that this process is similar, but not identical, to arteriosclerosis. It is therefore no wonder why up to 50% of people with AS have coronary artery disease.[1] Lipid infiltration, associated with a subsequent inflammatory response characterized by oxidized LDL-C, lipid-laden macrophages (foam cells), and T-cells infiltration,[1] appear to be the major driving force behind aortic stenosis and its progression.

Currently, there is no known medical therapy for early, asymptomatic AS, and the only treatment for symptomatic AS is aortic valve replacement (AVR). Surgery, however, carries a morbidity and mortality rate anywhere from 4-24% depending on the patient's comorbidities, need for simultaneous coronary artery bypass (CABG), and experience of the surgeon.[1] There is also the small, but additional risk and burden of lifetime anticoagulation in patients chosen to receive a prosthetic valve. Therefore, medical therapy aimed at treating early, asymptomatic AS with the hope of delaying or preventing the need for AVR would spare thousands of patients from the associated operative and post-operative risks annually.

Evidence now exists that statins have anti-inflammatory properties in addition to lowering cholesterol. Given that LDL-C has been implicated in hastening the progression of AS, and that this is an active inflammatory process, it would stand to reason that hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) may have a role in slowing the progression of AS. However, there has only been one trial to date to evaluate the role of statins for this purpose. A study by Novaro et al. looked at 174 patients retrospectively, using echocardiography to evaluate the change in peak and mean transvalvular pressure gradient as well as the AVA, in subjects on statins versus no therapy.[4] Their results showed a significant decrease in the progression of AVA narrowing and peak pressure gradient over a mean interval of 21 months. The study's results are encouraging and provide enough evidence to warrant further investigation. We plan to conduct a double-blind, randomized placebo-controlled trial to investigate whether 40 milligrams of atorvastatin daily will halt the echocardiographic progression of AS.

B. Study Design And Statistical Analysis

Using an unpaired t-test and based on the results from a previous retrospective study[4], we calculated that we would require a total of 400 subjects (200 in each arm) to achieve a power of 80% testing at p=0.05. Stratified randomization of subjects to placebo or atorvastatin will be implemented in order to achieve two well-matched study groups. Subjects will be stratified according to the number of AS risk factors they have (1-5). Risk factors used to stratify are: hypertension, tobacco use, age >75, male gender, and high-normal total and LDL-C as defined by the third report of the National Cholesterol Education Program (NCEP).

The follow-up period will last approximately 2 years and is based on evidence from previous studies on the anatomic rate of progression of AS.[4, 6] The main endpoints will be the change in AVA, mean and peak transvalvular pressures as measured by experienced echocardiographers, blinded to the study, using standard transthoracic echocardiography (TTE). The results will be analyzed using the unpaired t-test as well as by multiple regression analysis to assess the effects of statin therapy adjusted for AS risk factors.

C. Study Procedures

Once recruited and randomized, subjects will undergo routine TTE to assess progression of AS initially, at 1 year, and at 2 years. They will also undergo phlebotomy to assess liver function and creatine phosphokinase enzyme levels at 0,1,2, 6, 12, and 24 months, as well as lipid profiles at 0, 6, 12, and 24 months. Lipid profiles will not be made known to the investigator until the completion of the study in order to preserve the double-blind design. This periodic monitoring does not breach any known standard of care for asymptomatic AS, is essential to collect data vital to the study, and will be used to assess any untoward effects of statin therapy.

D. Study Drug

Atorvastatin (Lipitor™ ; manufactured by Pfizer Pharmaceuticals) is an FDA-approved, commonly used statin that reduces total cholesterol (TC) and LDL very effectively. It is indicated for use in people with hyperlipidemia, as defined by the NCEP. The drug was chosen over other brands of statins due to evidence that it lowers LDL-C and TC because it is more effective and is as safe as other statins currently on the market.[11] The drug will be initiated at 10 mg orally per day and doubled every two weeks until a dose of 40 mg daily is reached. The drug will be given to subjects when it would not otherwise be recommended as routine standard of care.

Atorvastatin has been in use for many years and has a proven safety record. Similar to other drugs in its class, the most serious side effects of the drug include:

1. Transaminitis has an incidence of 0.07% and is defined as > or = 3 fold increase of the upper limit of normal of AST or ALT. It is universally reversible even when the drug is not discontinued (even though this is recommended).[10]
2. Rhabdomyolysis has only been reported in one person taking atorvastatin in conjunction with a fibrate. The patient made a full recovery with cessation of both drugs.[10]

E. Study Subjects And Recruitment

Subjects will be recruited from the echocardiography laboratory of Columbia Presbyterian Medical Center. All patients identified by TTE to have mild or moderate AS will be screened for inclusion criteria and exclusion criteria until a total of 400 subjects are recruited.

Inclusion criteria are as follows: age over 60, mild to moderate AS by TTE (defined as an AVA of 1.0-1.8 cm^2 and a mean transvalvular pressure gradient < or = 50 mm Hg), left ventricular ejection fraction (EF)> or = 0.5

Exclusion criteria are as follows: symptomatic AS (regardless of the valve area or mean pressure gradient); evidence of rheumatic heart disease; recent or current use of statins for > than 6 weeks; current or recent use of any other lipid-lowering agent; known adverse reaction (rhabdomyolysis, transaminitis, etc.) or hypersensitivity to a statin; endstage renal disease requiring hemodialysis; diabetes mellitus; clear indication for lipid-lowering drug therapy as defined by NCEP guidelines.

F. Confidentiality

Study data and patient identification will be coded and kept in locked cabinets in the Echocardiography Laboratory office located in PH 944.

G. Study Location

All studies will be conducted in the Echocardiography Laboratory procedure room in PH 963.

H. Risks And Benefits

The risk of phlebotomy, which will be performed to the extent of 30 milliliters of blood from each patient at 0, 1, 2, 6, 12, and 24 months is very small and includes excess bleeding as well as infection. Both risks will be minimized by using experienced technicians, thorough cleansing of the venipuncture site, and by the use of a small (23-25 gauge) butterfly needle.

There is also a small risk of transaminitis and rhabdomyolysis, as described above, associated with atorvastatin use. More common and less severe side effects of atorvastatin are myalgias (1-5%) flatulence (2%), and dyspepsia (2%).

The benefits of the study are potentially substantial but purely speculative. It is possible that those placed on statin therapy will halt or slow their progression to symptomatic AS, thereby delaying or avoiding eventual AVR and its associated morbidity and mortality.

I. Costs And Compensation

No costs will be incurred to participants of this study. Because of the time, participants will be reimbursed in the amount of $20 for each phlebotomy and TTE session. A check will be issued within a week of the day of completion of the study.

J. References

1. Hinchman DA, Otto, CM: Valvular Disease in the Elderly. Cardiology Clinics; 17(1): 137-58, 1999

2. Lindroos M, Kupari M, Heikkila J, et al: Prevalence of aortic valve abnormalities in the elderly: An echocardiographic study of a random population sample. J Am Coll Cardiol 21:1220, 1993

3. Executive summary of the Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

4. Novaro, et al. The Effect of Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors on the Prgression of Calcific Aortic Stenosis. Circulation. 2001; 104:2205-2209.

5. O'Brien KD, Reichenbach DD, Marcovina SM, et al: Apolipoproteins B, (a) and E accumulate in the morphologically early lesion of "degenerative" valvular aortic stenosis. Arterio and Thrombosis 16:523, 1996

6. Otto CM, Pearlman AS, Gardner CL: Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. J Am Coll Cardiol 13:545, 1989

7. Otto CM, Burwash IG, Legget ME, et al: A prospective study of asymptomatic valvular aortic stenosis: Clinical, echocardiographic, and exercise predictors of outcome. Circulation 95: 2262, 1997

8. Pohle, K, et al. Progression of Aortic Valve Calcification: Association with Coronary Atherosclerosis and Cardiovascular Risk Factors. Circulation 2001; 104:1927-1932

9. Stewart BF, Siscovick D, Lind BK, et al: Clinical factors associated with calcific aortic valve disease. J Am Coll Cardiol 29:630, 1997

10. Micromedex Healthcare Series Website

11. Wierzbicki, AS. Expert Opinion Pharmacotherapy 2001 May; 2(5):819-30

Lay Summary

Halt Aortic Stenosis Progression in the Elderly (HAPIE): The Effect of Atorvastatin on the Progression of Mild and Moderate Aortic Stenosis

A. Study Purpose:

The aortic valve is a tri-leaflet valve that lies at the opening between the left ventricle (the main pumping portion of the heart) and the aorta (the main artery of the body). Aortic stenosis is the narrowing of this valve and it is a common and serious disorder among the elderly. Once the aortic valve narrows, it becomes very difficult for the heart to pump blood to the rest of the body. As a result, the left ventricle hypertrophies, or grows in size, in order to squeeze blood past the narrowed aortic outlet. The narrowing usually progresses to the point that the heart can longer adapt. Once the valve becomes too narrow, heart failure, angina (chest pain), or sudden death can occur. Once these symptoms appear, the only way to treat the person is to replace the valve. The operation is complicated, invasive and it can be risky in some people. In addition, some people will have to take a "blood-thinner" called coumadin for the rest of their lives if a man-made metallic valve is chosen.

Recently, one study showed that it may be possible to slow the progression of valve narrowing in people with an early stage of aortic stenosis by taking cholesterol lowering drugs called statins. This study, however, was very limited and so another, larger and more thorough study needs to be performed in order to see if statins really can slow the progression of aortic stenosis. Statins are among the most commonly used drugs in the United States today. They are very safe, even when used in people with relatively low cholesterol. Although statins are normally used in people with elevated cholesterol, its use in patients with normal or high normal cholesterol with aortic stenosis is experimental.

We would like to perform a study which involves giving people with mild aortic stenosis atorvastatin (commonly known as Lipitor™) or a placebo to see if this statin can truly slow the progression of aortic stenosis and delay, or even avoid the eventual need for surgery.

B. Study subjects and Recruitment Method

A total of 400 subjects will be selected from the echocardiography laboratory at Columbia Presbyterian Medical Center once they meet certain predetermined criteria. Consent will be obtained after the patient's primary physician and the patient have agreed to participate in the research trial. Subjects must be greater than 60 years of age, have evidence of aortic stenosis without any of the cardinal symptoms of sever disease, and have normal heart function. They must also not have any of the exclusion criteria that have been established by the research team.

C. Study procedures

Once subjects are selected and consent has been obtained, each person will be randomly assigned to receive either the treatment drug (atorvastatin) or a placebo ("sugar pill"). In addition to the initial echo (an ultrasound of the heart), blood tests will also be sent to assess liver function, muscle function, and cholesterol.

The subjects will have their blood tested and be evaluated by a physician at 0, 1, 2, 6, 12, and 24 months. They will undergo repeat echo at 1 and 2 years after the initiation of the trial.

D. Issues

There is very little risk to the participant in this particular study. Blood will be drawn from a vein in the arm to the extent of 10-30 milliliters. There is a very small risk of excess bleeding and infection, which will be minimized by the use of experienced phlebotomists, by thoroughly cleansing the area where blood will be drawn, and by using very small needles to draw the blood.

Those subjects receiving atorvastatin will be exposed to a very small risk of rhabdomyolysis or muscle breakdown (there has only been one reported case out of the millions who have used this drug) and liver dysfunction (which is rare and always reversible once the drug is stopped). The subjects will be monitored closely for these side effects by periodic follow-up and blood tests.