Decision Making for Patients with Asymptomatic Severe Aortic Stenosis

The Case for Preemptive Aortic Valve Replacement Surgery

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Abstract: Aortic stenosis disease typically progresses from mild to severe as patients age beyond 50, during which time patients are generally asymptomatic and their quality of life will remain similar to that of the general population. Most patients with Asymptomatic Severe Aortic Stenosis (ASAS) will develop one or more symptoms of angina, dyspnea, or syncope within five years. As there is no medicinal cure for the disease, these newly symptomatic patients will require Aortic Valve Replacement (AVR) surgery soon after onset of symptoms because without it 75% of them will die within three years from the first symptoms onset. The proper treatment of ASAS patients before they become symptomatic is subject to debate. The American College of Cardiology and American Heart Association (ACC/AHA) recommend "watchful waiting" for the onset of symptoms after which they recommend AVR surgery. Review of results of studies based on recently improved surgical outcomes indicate that preemptive AVR surgery before onset of symptoms produces vastly improved survivability compared to the watchful-waiting protocol. ACC/AHA guidelines for treatment of severe aortic stenosis accordingly should be modified to reflect this new reality by recommending early AVR surgery in place of watchful waiting for most all ASAS patients.

1 INTRODUCTION

The proper treatment of Asymptomatic Severe Aortic Stenosis (ASAS) patients during the asymptomatic period is controversial. Though the cardiologist knows from testing that AVR surgery will soon be needed, the patient is reluctant to have surgery because he does not experience symptoms. The cardiologist is also reluctant to recommend surgery because of the operative mortality risk which until recently was substantial. Consequently the American College of Cardiology and American Heart Association (ACC/AHA) recommend (in Bonow, R., Carabello, B., et al. 2006) "watchful waiting" for the onset of symptoms before considering Aortic Valve Replacement (AVR). But if onset of symptoms is not quickly recognized and acted upon the patient is subject to sudden death, as is explained in the Section 2 discussion that follows. Cardiology researchers have been seeking an indicator or combination of indicators that can reliably signal when onset of symptoms is imminent so that early AVR surgery in such patients may be warranted, especially when very low surgical mortality risk is expected. Operative mortality risk in a high volume AVR surgical theater with highly experienced surgeons is now typically 1% to 2% for isolated AVR surgery and 3% to 5% for more complex AVR surgery as reported in Egrie et al., (2010) and Stanford SHC (2013). Complex AVR as used herein involves one or more of: repair and/or replacement of multiple heart valves, coronary bypass, or debridement of a heavily calcified aortic valve, in addition to AVR.

Review of event-free survival data from one large study presented and discussed in Section 3 indicates astoundingly large 43% mortality is experienced with those ASAS patients during the watchful-waiting period of five years. With such large attrition, the question that comes to mind is how many of those ASAS patients who died during watchful waiting would have survived had all them been given, and all accepted, the option of having early AVR surgery in today's expected low operative mortality risk for this surgical procedure?

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Accordingly, the watchful-waiting data from this and other studies is reanalyzed in Section 3 to yield predicted survival percentages for both 2% and 5% operative mortality risk for AVR surgery. Predicted survival from early AVR surgery is shown to be vastly superior to survival from watchful waiting. Moreover, the data from a recent study is very significant and unique because it directly compares actual AVR surgery survival to watchful waiting survival of ASAS patients. The AVR surgery subgroup of patients experienced significantly superior survival compared to the subgroup of patients in watchful waiting. Finally, in two separate studies of elderly patients, long term survival of ASAS patients is compared between those who had AVR surgery with those who were in watchful waiting and did not have AVR surgery. The long term survival of patients who underwent AVR surgery was again vastly superior in both studies. Moreover their long term survival was also significantly superior to the survival of the referent general population when matched for age and gender.

These results make a strong case for changing the recommended treatment protocol for ASAS patients. In other words, the time has come for the ACC/AHA to reconsider their position on the treatment of asymptomatic patients with severe or extremely severe aortic stenosis and recommend early AVR surgery for most all such patients. Exceptions might include patients with significant comorbidities like cancer.

It should be noted throughout this paper that advocacy for AVR surgery treatment of ASAS patients applies equally to asymptomatic patients who have very severe or extremely severe aortic stenosis. Asymptomatic severe aortic stenosis (ASAS) and asymptomatic extremely severe aortic stenosis are defined in Table 1, Section 2. Asymptomatic very severe aortic stenosis designation and criteria for its designation may vary by author. This topic is expanded when treating such data and is further discussed in Section 3.

2 DISCUSSION

The American College of Cardiology and American Heart Association (ACC/AHA) have jointly issued severity-grading criteria of aortic stenosis as well as provided guidelines for aortic valve replacement (Bonow, 2006). A succinct restatement of ACC/AHA's severity grading of aortic stenosis is shown in Table 1, and summary restatement of its guidelines for asymptomatic patients are excerpted and restated below Table 1. Note also that Table 1 and AVR guidelines are the result of combining separate data in Bonow et al., (2006 pp. 97, 101, 107 and 120).

Table 1: ACC/AHA grading of aortic stenosis.

	EXTREMELY SEVERE	SEVERE	MODERATE	MILD
Jet velocity (m/s)	>5.0	>4.0	3.0-4.0	<3.0
Mean aortic gradient (mm Hg)	>60	>40	25-40	<25
Aortic valve area (cm^2)	<0.6	<1.0	1.0-1.5	>1.5
Indexed* aortic valve area (cm^2/m^2)	-	<0.6	-	-

*indexed to patient's body surface area

The corresponding ACC/AHA guidelines from Bonow et al., (2006) regarding advisability of AVR in asymptomatic aortic stenosis patients are as follows:

1. AVR may be considered for asymptomatic patients with severe aortic stenosis and any of the following:
   - An abnormal response to exercise.
   - A high likelihood of rapid progression of aortic stenosis disease.
   - When surgery might be delayed at the time of symptom onset.
2. AVR may also be considered for asymptomatic patients with extremely severe aortic stenosis and when the patient's expected operative mortality is 1.0% or less.

The protocol expressed in these guidelines for treatment of ASAS patients is commonly referred to in the literature as watchful waiting, in which the patient is medicinally treated and periodically monitored or tested for the onset of symptoms. It is important to note that these ACA/AHA guidelines from Bonow et al., (2006) are based on older pre 2000 valve-prosthesis technology and AVR surgical outcomes that have since greatly improved. For example ACA/AHA guidelines in Bonow et al (2006 p. 108) quotes the average perioperative mortality values thusly: *"3% to 4% for isolated AVR, 8.8% mortality for AVR in patients over age 65 which can also reach 13% mortality in low-volume AVR centers"*. These mortality percentages have been at least halved in recent practice as can be seen, for example, in Egrie et al., (2010) and Stanford (2013)

and in the two studies of AVR in the elderly patients reported in Section 3.3. Moreover ACA/AHA properly anticipated this progress where they state in Bonow et al (2006 p. 109) *"... as improved valve substitutes are developed and methods of valve replacement become safer, the risk-benefit balance may change to favor earlier intervention in aortic stenosis".* It appears that the time for favoring and recommending earlier AVR intervention has arrived.

2.1 The Problem with Watchful-waiting Protocol

The big problem with watchful-waiting protocol as deduced from data presented and discussed below is that a significant percentage of ASAS patients routinely die from the underlying aortic stenosis disease during watchful waiting that would have survived if they had they had undergone early AVR surgery before the onset of symptoms. The same logic applies to asymptomatic patients with extreme aortic stenosis, as they should be recommended for immediate AVR surgery, asymptomatic or not.

Supporting this position are the results from four studies described in Section 3 that compare survival rates from watchful waiting to predicted and actual results of early AVR. But before delving into the results of the studies it is important to note that survivability is reduced from three causes: aortic stenosis disease, normal aging effects, and mortality risk associated with AVR surgery. An overview of survivability versus age and the impact of onset of aortic stenosis symptoms on survivability are each illustrated in Figure 1.

Gender-specific survivor curves of the general population based on 2007 U.S life expectancy data obtained from the Life Expectancy Calculator (2013) are depicted in Figure 1. For example, 91.2% females aged 60 are survived to the present from the100% of that group when born. The corresponding percentage survivors for males aged 60 is 85.2%. The studies of Carabello (2012), Shah (2012), and others agree that ASAS patients have approximately equal life expectancy as the general population during the time they remain asymptomatic. After onset of symptoms the life expectancy of symptomatic patients with aortic stenosis nosedives as is illustrated by the two dotted "no-surgery" lines, with the result that three quarters of those patients die within three years if they do not undergo AVR surgery, according to Carabello (2012) and Shah (2012).

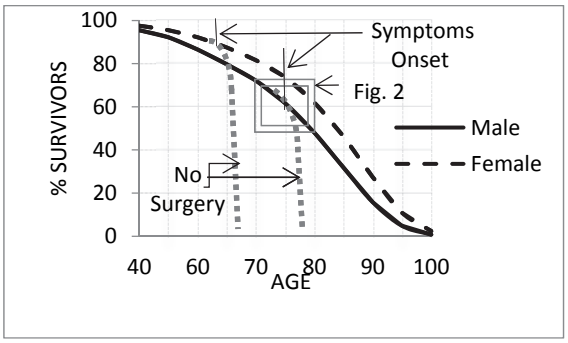

Figure 1: General Population Average Survival versus Age and Illustrated Effect of Symptoms Onset on Survival without AVR Surgery. (The "No Surgery" data was adapted from Shah (2012, Fig.1A, p. 2).

2.2 "Watchful Waiting" Makes the ASAS Patient a Ticking Time Bomb

The onset of symptoms has to be detected early and reported quickly to the monitoring cardiologist. The penalty for not promptly undergoing AVR surgery after first onset of symptoms is the loss of 2% survivability for every month of delay according to Carabello (2012). Realize that the latter penalty for a one-month delay equates or exceeds to the 30-day mortality risk of 1% to 2% for isolated AVR surgery, the latter is based on operative mortality risk data of Egrie et al., (2010) and others. Early detection and prompt reporting of the onset of symptoms is not only vitally important, it is also difficult to achieve outside the clinically controlled environment of hospital or health clinic for various reasons, including those reasons described in 2.2.1 - 2.2.4.

2.2.1 Onset of Symptoms is often Masked

Recalling that ASAS patients enjoy the same quality of life as the general population while they are asymptomatic, there is a natural tendency for them to deny the existence and seriousness of symptoms once they do occur. Bonow (2006, p. 103) adds *"It is important to emphasize that symptoms may be subtle and often are not elicited by the physician in taking a routine clinical history".*

2.2.2 Sedentary and Low-aerobic Demand Sports and Routine Yard Work do not Produce Symptoms

A physically inactive ASAS patient will frequently not recognize the onset of symptoms because of lack

of the type of exercise that would unequivocally bring on the symptom; example activities that don't produce symptoms are card playing, watching TV, and watering the roses. Also, golfing from a golf cart is generally not sufficiently aerobic to bring about symptoms of progressing aortic stenosis disease.

2.2.3 Advancing Age and Medications often Produce Similar Symptoms

Dyspnea symptoms of extreme shortness of breath, tiredness and feelings of exhaustion following exercise are often and incorrectly attributed to advancing age. Angina can sometimes be confused with expected muscular soreness from repetitive types of yard work. Syncope can be confused with expected side effects of medications being taken for hypertension and other health problems.

2.2.4 Physical Intensity and Performance Level in Sports and Work are often Lowered in the Face of Symptom-related Declining Capabilities

A tennis player, for example, will often opt to make the games and points shorter when he becomes extremely tired and may play less often to mask a loss of vigor from what the player thinks are simply the vagaries of advancing age. This same adaptive behavior can also mask the real onset of symptoms of aortic stenosis disease.

Clearly there is a need for educating all aortic stenosis patients on what to watch for and to immediately report suspected onset of symptoms. "Valve Clinics" should be established at hospitals where aortic stenosis patients can be educated and more closely monitored during watchful waiting. Exercise stress tests should be periodically employed for all ASAS patients in clinical settings to see if they produce symptoms. The stress test is often intentionally avoided by cardiologists for fear, mostly unsupported, that it can bring on heart failure, and is of itself yet another reason that symptoms are sometimes not recognized early enough to keep mortality rates low. Suffice it to say that watchful waiting for onset of symptoms is a dangerous protocol for ASAS patients. It will be shown herein that a much safer alternative to watchful waiting is early AVR surgery. But it is to be expected that watchful-waiting protocol will not be abandoned anytime soon, so care must be exercised to make it work as well as possible.

2.3 The AVR Surgery Option

There are two categories of AVR cardiac surgery considered herein: Isolated AVR surgery and more involved or what is referred in this paper as complex AVR surgery. Isolated AVR surgery involves the removal and replacement of the aortic valve only and is usually performed using minimally invasive surgery techniques. The 30-day expected mortality risk from Isolated AVR is 1% to 2% as demonstrated in Egrie (2010), Stanford (2013), Kang (2010) and Varadajaran (2006), and depends on the experience of the surgical team and AVR surgery volume of the hospital; the more conservative 2% is used herein in survivability calculations for Isolated AVR surgery. Complex AVR surgery can involve surgical repair and/or replacement of multiple heart valves, coronary bypass, debridement of a heavily calcified aortic valve, and a host of other cardiovascular surgical procedures in addition to AVR. The 30-day expected mortality from complex AVR is 3% to 5% also as demonstrated in Egrie et al., (2010) and Stanford (2013) depending on the experience of surgical team and AVR volume of the hospital; the more conservative 5% is used in survivability calculations herein. As a point of interest, Isolated AVRs constituted about one-half of the 2532 total AVRs performed by one surgical group during the 11 year period 1998-2008 as reported in Egrie (2010, p. 16).

Survivability from the Isolated AVR surgery option with 30-day 2% mortality risk is illustrated in Figure 2. Note that all calculations that follow are based on male life expectancy only, which is the more conservative choice since male life expectancy is shorter.

A portion of the General Population Survivors (solid black line) is replicated from the small rectangular area in Figure 1 spanning the ages 74.5 years to 76.5 years. That line shows the expected decline of the male general population survivors from aging factors alone based on Life Expectancy Calculator (2013). At age 75, for example, 61.6% of all males are survived, and at age 76 the male survivors reduces to 59.2% in nearly linear fashion.

Assume, for the following discussion, that a group of 100 ASAS male patients all aged 75 opt to have Isolated AVR surgery for which the expected 30-day operative mortality risk is 2%. Those patients' 2% mortality risk is comprised of 1.67% mortality risk from surgery (line pointed down) and 0.33% mortality risk from normal aging effects on the general population during the 30-day postoperative period (shown by very short line

segment parallel to the general population aging line). Of the initial 100 ASAS patients, two of them do not survive AVR surgery (dotted arrow facing down towards 0%). The remaining 98 are all survivors (arrow pointed up), and they rejoin the general population group in life expectancy (parallel lines shown for clarity only). Importantly, the AVR surgery survivors can expect at least the same, and possibly greater life expectancy compared to that of the general population as is reported in the two AVR survival studies in Section 3.3.

The more complex AVR surgery with 30-day mortality risk of 5% is similarly represented by Figure 2, except the mortality dip would be 3% larger. But the 95% surgery survivors are also expected to attain equal or better life expectancy compared to the general population as is discussed in Section 3.

2.4 The ASAS Patient Asks: Which is Less Risky, Watchful Waiting or Early AVR Surgery?

At a minimum, the informed views of the patient should be considered along with those of the cardiologist and cardiothoracic surgeon. Accordingly, the ASAS patient should be informed that he has two options: (1) watchful waiting for symptoms, after which his/her survival percentage decreases by 2% per month according to Carabello (2012), or (2) Isolated AVR surgery for which there is a 30-day mortality risk of 2%. Also the patient should be informed it is not unreasonable to expect that it could take up to three months or so from actual symptoms onset (as opposed to delayed recognition of symptoms onset) to the time of being wheeled into the operating room for AVR surgery, so that option (1) could incur up to three times more mortality risk compared to option (2).

It should also be noted that the Isolated AVR operative mortality risk 2% could equate to only a fraction of the yearly mortality risk from aging. For example the general-population male on his 75th birthday has a 4% probability of dying before age 76. Isolated AVR surgery adds only 1.67% mortality risk which is equivalent to 6 months' (or 4.7%) loss in life expectancy. However, to a 40 year male the 2% operative mortality risk equates to about 6.72 years (or 18%) loss of life expectancy, and is therefore a decision that should not be taken lightly. Isolated AVR operative mortality risk of < 1% remains a highly desirable goal especially for younger, < 55-year patients.

3 STUDIES COMPARING WATCHFUL WAITING TO AVR SURGERY

The principal source of survival data from watchful-waiting protocol treatment of asymptomatic patients with aortic stenosis disease comes from eight studies that are aggregated in Bonow et al., (2006, p.104). Of those only the Pellikka et al., (2005) study is examined herein because of its being the largest, comprising over ½ of the total patients, all of whom were asymptomatic with severe aortic stenosis disease, and it alone provides results in sufficient detail relating to the issue of relative efficacy of watchful waiting protocol compared to early AVR surgery.

3.1 Pellikka et al., (2005) Watchful Waiting Study

622 ASAS patients, average age 72 years, Vmax ≥ 4.0 m/s, were followed up for a period of five years. The patients were reevaluated at intervals of six months or one year and they were told to report promptly for reevaluation at onset of symptoms. Those with verified symptoms were recommended for AVR surgery. A summary of results pertinent to the present study is shown in Figure 3. Of particular interest is that by the end of the five-year study period 265 (43%) patients died and 357 (57%) patients survived; also of the 352 patients who did undergo AVR surgery 86 (24%) died.

If at the beginning of the study all 622 patients had available to them and all opted for AVR, with either the 2% operative risk for Isolated AVR surgery or the 5% operative mortality risk associated with complex AVR (defined in Section 2.3), their predicted 5-year survival rates would have been 81% and 78% respectively. These are both markedly superior to the 57% survival rate actually experienced. Far fewer patients would have died: 118 for Isolated AVR and 134 for complex AVR, fatality numbers that are about one-half the 265 total deaths experienced. Yet, these results are not too surprising when considering that the results of the Pellikka (2005) retrospective study represent 24 year-old (1984-1995) AVR surgical and valve prosthesis technologies. Also as noted above, the mortality rate for those who elected to undergo AVR surgery was an abysmally large 24%. It is not surprising then that, as shown in Figure 3, 90 patients (30%) opted not to have AVR surgery even after their having developed deadly symptoms.

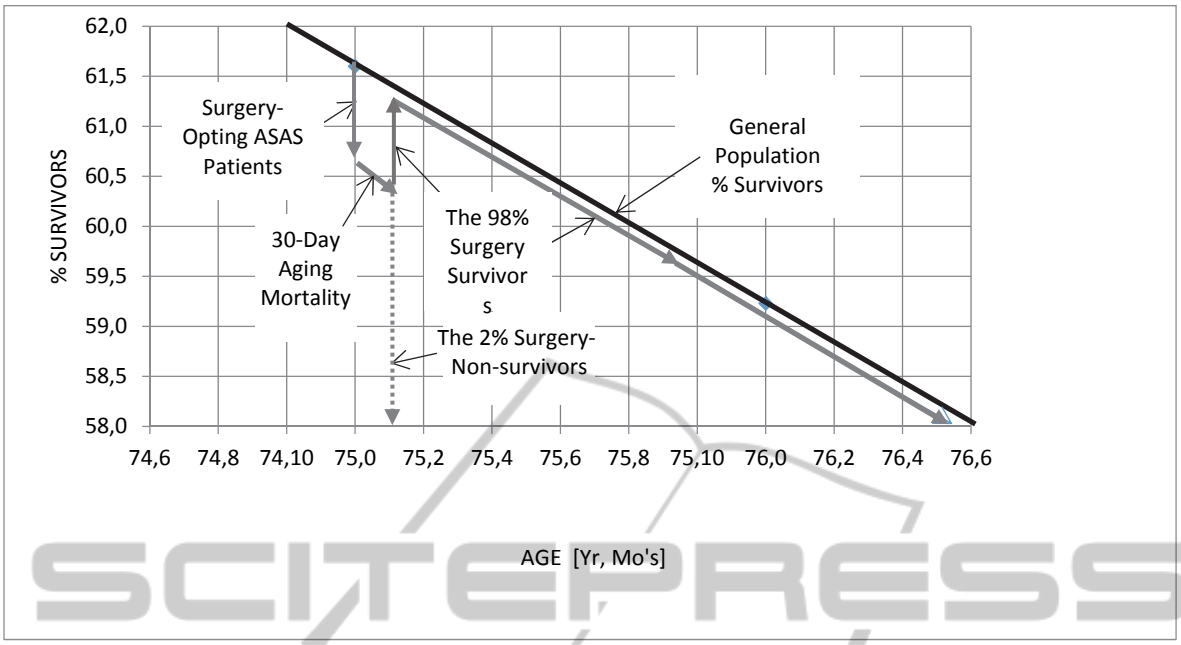

Figure 2: Illustration of Isolated AVR Surgical Option with 30-Day 2% Operative Mortality for a Group of 100 Male Patients All Aged 75 years.

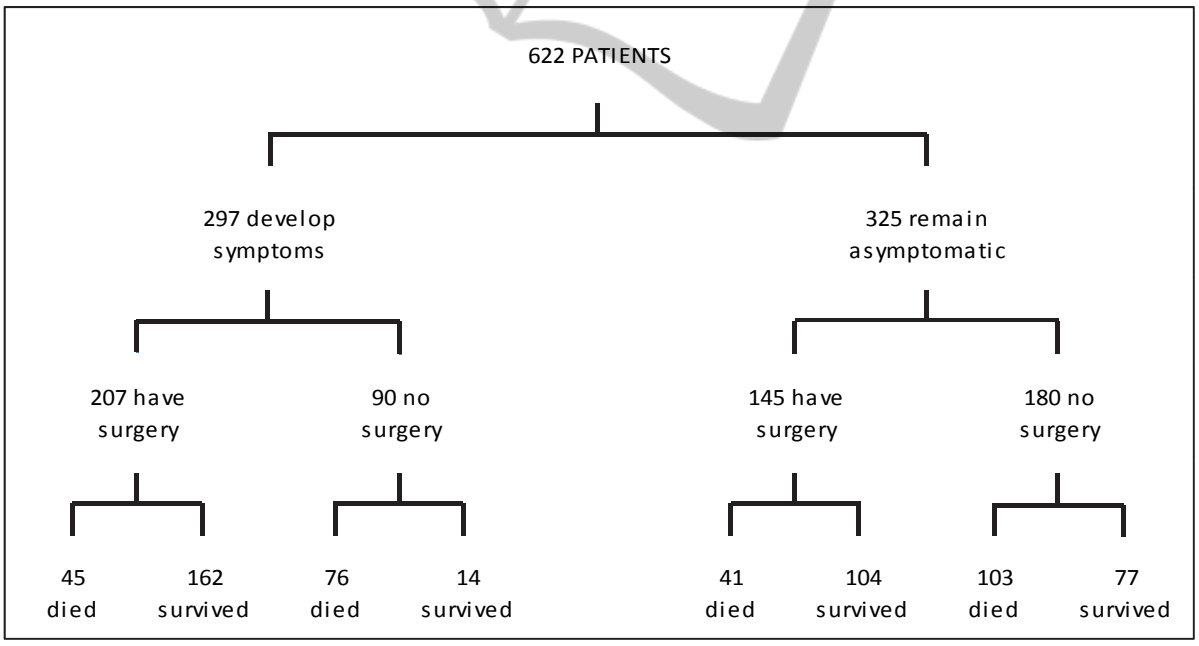

Figure 3: Distribution of Patients Who Developed Symptoms, Did Not Develop Symptoms, Underwent AVR Surgery, Survived or Died over the Five Year Study Period; from Pellikka et al., (2005, p. 4, Figure 2 with modified wording).

Pellikka et al., (2005, p. 6) similarly sensed this reality by stating *"Early referral to aortic valve surgery, even in the asymptomatic patient, probably would have improved survival"*.

3.2 Kang et al., (2010) Study Comparing Early AVR Actual Surgery Survival to Watchful Waiting Survival

A noteworthy recent study by Kang et al., (2010) uniquely compares early AVR actual surgery results

against conventional treatment (watchful waiting) results in a group of 197 asymptomatic very severe aortic stenosis patients. That group was split into two subgroups, one slated for early AVR surgery and the other subgroup for traditional watchful waiting. Very severe aortic stenosis is defined by the authors as "*a critical stenosis in the aortic valve, area ≤ 0.75 cm^2, accompanied by either a peak aortic jet velocity ≥ 4.5 m/s or a mean transaortic pressure gradient ≥ 50 mm Hg. There were no significant differences between the two subgroups in terms of age, gender, or LV ejection fraction"*. AVR surgery was performed on 102 patients and conventional treatment *[ed. watchful waiting]* was employed for the other group of 95 patients whose mean age was 63.

The authors (Kang et al., 2010, p. 1, Abstract) state *"During a median follow-up of 1501 days the operated group had no operative mortalities, no cardiac deaths, and 3 non-cardiac deaths; the conventional treatment* [ed. watchful waiting] *group had 18 cardiac deaths and 10 non-cardiac deaths"*.

Admittedly this is a small study, but the results nevertheless are very compelling. Early, or preemptive, AVR surgery won hands down compared to watchful waiting. Additional comparative experimental studies to validate these results are recommended.

3.3 Two Studies of Elderly Patients with Severe Aortic Stenosis Comparing their Long-term Survival from AVR Surgery to No-AVR (Watchful Waiting) and to a Control Group

These are two important studies for two reasons:

(1) They directly compare the long term survival of (A) Severe Aortic Stenosis (SAS) patients who underwent AVR surgery to (B) SAS patients in watchful waiting who did not have AVR surgery, and to (C) control group of U.S. general population that is matched for age and gender.

(2) Elderly patients with severe aortic stenosis are often denied AVR surgery because of their advanced age. Both studies' results, shown below, strongly refute the advanced-age argument.

The respective results of the two studies, by Varadajaran and Kapoor, (2006) and Egrie and Gaudiani, (2010) are shown in Table 2.

Table 2: Elderly SAS patients' long-term survival comparison with AVR, No-AVR, and control group.

Varadajaran, et al., (2006)	**1 year**	**2 year**	**5 year**
US GP 85 year Male	89%	79%	50%
AVR Group (n = 55)	87%	78%	68%
No-AVR (n= 222)	52%	40%	22%
Egrie et al., (2010)	**1 year**	**2 year**	**5 year**
US Age and Gender Matched, ≥ 75 years	89%	79%	51%
Isolated-AVR (n = 371)	91%	87%	67%
No-AVR Group (n = ?)	65%	41%	8%

3.3.1 Varadajaran et al., (2006) Elderly ASAS Patients, Aged 85 ± 4 Years, AVR Long-term Survival Study

277 ASAS patients, 85 ± 4 years had aortic valve area < 0.84 cm^2 in this retrospective study. The 1, 2, and 5 year survival percentages of the AVR group are vastly superior to the No-AVR group, and the 5-year survival of the AVR group is also significantly superior to the reference US general population 85-year male expected survival per the U.S. Life Expectancy Calculator (2013).

3.3.2 Egrie et al., (2010) Elderly, Age > 75 Years, Isolated-AVR Surgery Long-term Survival Study

371 aortic stenosis patients aged 75 and over underwent Isolated AVR surgery from 2004 to 2008 and were followed through 5 years after surgery. Importantly, it should be noted that all 371 patients were screened to be free of coronary disease or cancer, otherwise they would not have been selected for Isolated AVR surgery. The 1, 2, and 5 year survival percentages of the Isolated-AVR surgery group are greatly superior to corresponding percentage survivors in the No-AVR group. Moreover, the 2 and 5 year Isolated-AVR survival percentages also are significantly superior to the age and gender matched U.S. general population.

4 CONCLUSIONS

1. Predicted and actual survival from preemptive early AVR surgery with either 2% or 5% operative mortality risk are shown to be overwhelmingly superior compared to watchful-waiting protocol in studies of 717 asymptomatic severe aortic Stenosis (ASAS) patients.

2. Actual long-term survival of 426 elderly, 75-90 year old patients with severe aortic stenosis who underwent AVR surgery is vastly superior to survival of those similarly afflicted patients without AVR surgery; and their survival rates are also significantly superior to expected survival of age and gender-adjusted general population control group.

3. ACC/AHA 2006 Guidelines in Bonow (2006) for management of aortic stenosis disease should be revised to recommend preemptive early AVR surgery when aortic stenosis disease has progressed to their defined "severe" level regardless of whether the patient is symptomatic or asymptomatic.

4. Mortality risk from just a single month of watchful waiting after onset of aortic stenosis symptoms equates or exceeds the 30-day 1% to 2% operative mortality risk from Isolated AVR surgery.

5. Onset of symptoms from aortic stenosis disease is often masked causing delayed detection. Also, symptoms are sometimes mistaken for benign effects of ageing, and are sometimes not promptly communicated to the monitoring cardiologist. Such delays increase mortality risk by 2% per month, one month of which equates or exceeds the 1% to 2% operative mortality risk of Isolated AVR surgery.

6. ASAS patients should be thoroughly apprised of the vastly superior probable survival from early AVR surgery compared to the more risky watchful-waiting protocol. Moreover, advanced age should, by itself, never be reason to preclude AVR surgery.

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