Echocardiography Screening of Siblings of Children With Bicuspid Aortic Valve

WHAT'S KNOWN ON THIS SUBJECT: Left heart defects, such as bicuspid aortic valve, are heritable. Echocardiography screening has been recommended for first-degree relatives of patients with left heart defects. Such screening may allow timely recognition of complications such as progressive aortic dilation.

WHAT THIS STUDY ADDS: This study examines the utility and cost of echocardiography screening of siblings of patients with bicuspid aortic valve in clinical practice. Screening has high yield, and the cost compares favorably with those of other screening methods used in pediatrics.

abstract

BACKGROUND AND OBJECTIVE: Left heart defects, such as bicuspid aortic valve (BAV), are heritable. Consensus guidelines have recommended echocardiographic screening of first-degree relatives. The utility of this approach in siblings of children with BAV is not known. The objective of this study is to evaluate the yield of routine screening of siblings of children with BAV and undertake an economic analysis of this practice.

METHODS: Siblings of children with BAV who underwent echocardiographic screening in a single pediatric cardiology practice were identified. The anatomic features and hemodynamics of siblings newly diagnosed with BAV were recorded. A Markov model was constructed to determine cost-effectiveness ratios, and sensitivity analyses were performed.

RESULTS: There were 207 screened siblings of 181 children with BAV. The median age at screening was 7 years. BAV was identified in 21 (10.1%) of siblings screened. The median peak Doppler gradient was 18 mm Hg. Aortic insufficiency was mild or less in all. The mean cost to diagnose BAV in a sibling was $2109 per new case found. The estimated mean cost to avert a single aortic dissection in the third or fourth decade of life was $363 911. The estimated cost per life-year saved was $74 884 and ranged from $17 461 to $1 136 536 in sensitivity analysis.

CONCLUSIONS: Echo screening among siblings of those with BAV is effective and inexpensive and may lower the risk of the complications of such as dissection, although it comes at a moderate cost relative to benefits gained. Screening of siblings should be incorporated into clinical care. *Pediatrics* 2014;133:e1212–e1217

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KEY WORDS
screening, congenital heart disease, congenital heart defects, echocardiography

ABBREVIATIONS
BAV—bicuspid aortic valve
LVOTO—left-ventricular outflow tract obstructive

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Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation. Prevalence of BAV in the general population is estimated to be 1% to 2%, with a male predominance of 3:1.[1,2] Left heart defects, including BAV, are known to be heritable. Studies of first-degree relatives of patients with left-ventricular outflow tract obstructive (LVOTO) malformations show that up to 18% of first-degree relatives are also affected by LVOTO malformations.[3,4] The consensus American College of Cardiology and American Heart Association Guidelines for Management of Patients With Valvar Heart Disease recommend routine screening of first-degree relatives.[5] This recommendation is based on the premise that early detection of BAV may allow timely recognition of complications such as progressive aortic dilation. This in turn may allow one to prevent catastrophic complications such as acute aortic dissection.

Although the rationale for this recommendation is sound, little is known about the application of this strategy in an outpatient cardiology setting. Moreover, there is some concern that this strategy may be expensive relative to the benefits gained. The objectives of this study are to assess the utility of screening first-degree relatives of children with BAV in clinical practice, to consider the costs related to screening siblings, and to provide guidelines of regarding screening of siblings of children with BAV.

METHODS

Patients with isolated BAV were identified in an outpatient cardiology practice database from the years 2000 to 2012. All children (age <18 years) known to have isolated BAV in our practice were identified. To identify siblings, a multitiered approach was undertaken. Potential siblings were identified using home address and parental demographics. Additional review of the records was undertaken to confirm the relationship. The number of siblings who had undergone screening with complete 2-dimensional echocardiography was determined. A positive screen was defined as a diagnosis of BAV as determined by the guidelines of the American Society of Echocardiography.[5] For siblings who screened positive for BAV, clinic records were explored to see whether left heart lesions had been identified in extended family members. Patients' physical examination findings were recorded, if available. Screening of additional family members such as parents and offspring was not examined in this study.

Decision Analysis

We constructed a decision-analytic Markov model to evaluate clinical outcomes for a hypothetical cohort of siblings of children with BAV who did or did not undergo echocardiographic screening for BAV.[6,7] The model is depicted in Fig 1. Each health state was associated with an annual cost and a set of probabilities of subsequent events. We adopted a societal perspective for our model and followed the recommendations of the Panel on Cost-Effectiveness in Health and Medicine.[8]

Medical costs were considered from the societal perspective. The primary outcome was incremental cost-effectiveness ratio to avert death due to dissection of the ascending aorta. Costs are reported in 2012 US dollars.

Data and Assumptions

The cost of echocardiogram screening to identify 1 new patient with BAV was determined by current Medicare reimbursement rates for complete 2-dimensional congenital echocardiogram, which was $213.08, based on 2012 Medicare rates.[9] The cost of echocardiogram screening to avert 1 aortic dissection was calculated by using a base case scenario derived from published literature. The rate of dissection in young adults with BAV is significantly greater than that of the general population.[10] The estimated base event rate for aortic dissection in patients with BAV is 0.9 per 1000 patient-years. For patients who experience dissection, the estimated mortality is 22%.[11] For the purposes of this analysis, it was assumed that echocardiography detects BAV 80% of the time and that detection of BAV leads to surveillance, exercise restriction, or surgery to avert aortic dissection. With appropriate management, all dissections could be prevented. The analysis is limited to a 20-year time frame. Because early detection will result in periodic outpatient cardiology follow-up, our model assumes that patients are seen every 2 years and that this assessment includes a limited echocardiogram with each visit. The cost of the follow-up visit (*Current Procedural Terminology* 99214) and limited echocardiogram (*Current Procedural Terminology* 93304) are $96.01 and $101.77, respectively. In the scenario where routine echocardiographic screening is not routinely used, we assumed that 50% of siblings would be identified by age 20 years.

Cost-Effectiveness Analysis

Life Expectancy

Our model assumed that with early detection of screening, death from dissection would be 80% preventable. The model extended from 20 to 40 years of age. A longer time frame was not considered because other acquired factors such as atherosclerosis play a predominant role in dissection.

Discount Rate

All future costs and benefits were discounted at a rate of 3%. Discounting was used to calculate life-years lost.

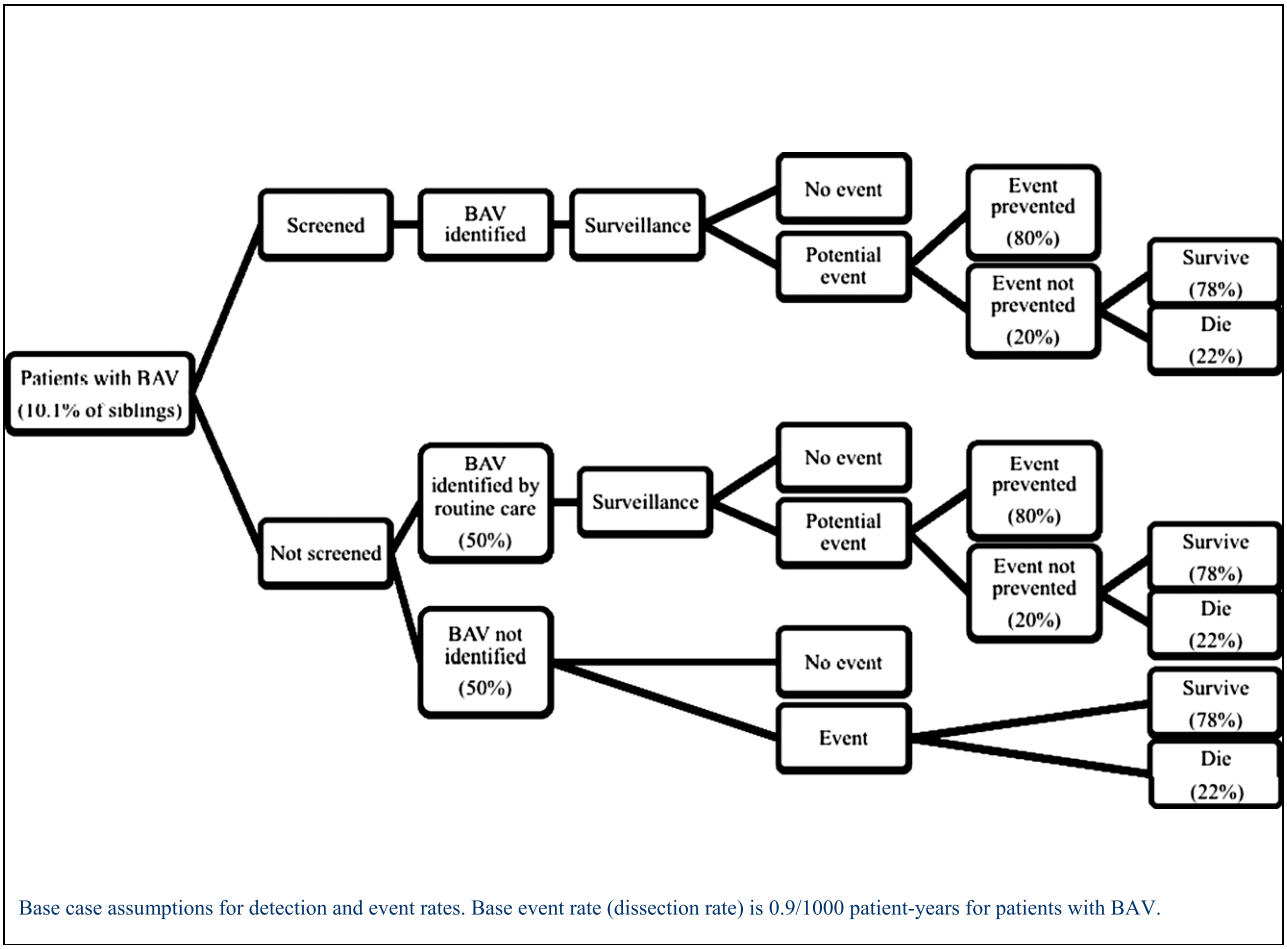

FIGURE 1
Markov model for clinical outcomes for children with BAV.

Sensitivity Analysis

For cost utility analysis we evaluated the sensitivity of the model to variations in key assumptions over various ranges. The event rate for aortic dissection in patients with BAV ranged from 0.4 to 1.4 per 1000 patient-years. BAV screening detection rate ranged from 5% to 15% of siblings screened. Prevention of dissection by identification of BAV in siblings over a 20-year period ranged from 60% to 100%. Mortality for a dissection episode ranged from 16% to 30%. Data are reported as mean and SD or median and range as appropriate. Confidence interval of a proportion was calculated.

RESULTS

There were 207 siblings of 181 children with BAV who underwent echocardiography screening. The median age at screening was 7 years (range 3–22 years). BAV was newly diagnosed in 21 (10.1%; 95% CI, 6.5%–15.3%) of siblings screened, with a male to female ratio of 2.5:1. The characteristics of these patients are summarized in Table 1. The median peak Doppler gradient was 18 mm Hg. Aortic insufficiency was mild or less in all. Abnormal physical findings were documented in 18 of the 21 patients. An ejection click was documented in 14 patients, and a systolic murmur was documented in 15 patients. There were 2 patients with normal physical examinations. There was 1 patient with no documented physical examination, who had outpatient echocardiography only without an office visit. There were 2 patients who were noted to have additional family members with BAV. No patients were restricted from physical activity by the cardiologist at the time of diagnosis. One of the patients identified via sibling screening needed surgical repair of the aortic valve 10 years after diagnosis because of progression of aortic insufficiency. No other patients needed any type of intervention.

TABLE 1 Characteristics of Siblings Who Screened Positive for BAV (n = 21)

Male:female ratio	15:6
Median age at screening	7 y
Physical examination findings	
Murmur	15 (71%)
Click	14 (67%)
Any physical finding	18 (86%)
Severity	
Median peak gradient	18 mm Hg

Given a cost of $213.08 for 1 screening echocardiogram, the cost of screening to identify 1 new BAV was $2109. Under baseline estimates, 1089 siblings would need to be screened to avert 1 dissection. The estimated mean cost of echocardiogram screening to prevent 1 aortic dissection was $363 911. The estimated cost to prevent 1 death between ages 20 and 40 years was $712 237. With 3% discounting, the cost per life-year saved was $74 884. Sensitivity analyses are shown in Table 2. Sensitivity analysis revealed a range of estimated cost per life-year saved of $17 461 to $1 136 536.

DISCUSSION

Screening of siblings of children with BAV has a high yield, with almost 10% of siblings having BAV. Routine echocardiographic screening of siblings of those with BAV appears to be a reasonable use of resources assuming that early detection may avert adverse events early in adulthood.

Prevalence of BAV is estimated to be 1% to 2% in the general population, but prevalence is greater in people with a first-degree relative with a left heart defect. Therefore, siblings of patients with known BAV are a high-yield population for screening for BAV. In a 2004 study of probands with BAV and their relatives, BAV was shown to be highly heritable, with a prevalence of 24% in the study population.[3] BAV is also more common in first-degree relatives of patients with LVOTO malformations; a 2004 study detected BAV in 13 of 278 first-degree relatives of children with LVOTO malformations.[12] Most of these published studies have included analysis of all left heart lesions and have been performed in the context of a research study. A recent study sought to explore the practicality of such screening, confirmed the high prevalence of BAV in first-degree relatives of patients with BAV, and advocated for familial screening of relatives of patients with BAV.[13] The present analysis represents screening as applied in routine clinical practice, with consideration for costs. It should be noted that our practice saw >800 children with isolated BAV during this study period. In light of US census data on children per household, one would have expected a higher proportion of siblings to have undergone screening.[14] The low screening rate may be related to a number of factors. Undoubtedly, practice variation exists, perhaps because of both practice variation and insufficient counseling about the inherited risks. In addition, it is possible that economic factors that might pose a barrier to screening.

Early detection of BAV is important because patients with BAV are at elevated risk for complications such as aortic valve stenosis or insufficiency, aortic root dilation, aortic dissection, and endocarditis. BAV is typically asymptomatic until adulthood. The first manifestation of BAV may be a serious complication.[15] There are physical examination findings that may raise the suspicion for BAV; the most specific finding is an ejection click best heard at the apex. Physical examination may also reveal murmurs of aortic stenosis, aortic incompetence, or coarctation of the aorta, if present. Previous studies have shown that routine clinical practice detected BAV in only about 50% of patients.[16] In our study, even with examination by an experienced pediatric cardiologist, an ejection click was detected in only 67% of the siblings diagnosed with BAV. In contrast, echocardiography has excellent sensitivity for BAV, detecting 92% to 96% of cases.[15]

Patients with BAV have a lifelong risk of various complications. The most common complication is mild aortic stenosis or insufficiency,[17] but the most dangerous complication is dilation of the ascending aorta. Patient with BAV have a risk of aortic dissection 6 times greater than in the general population.[18] Presence of a BAV is an independent risk factor for aortic dilation, aneurysm, and dissection; a dysfunctional (stenotic or insufficient) BAV is not necessarily thought to cause aortic root dilation because >50% of patients with a normally functioning BAV still have aortic dilation.[17] A 2004 study detected BAV in 4 of 817 apparently healthy children, and the aortic root was found to be significantly dilated in children with BAV compared with those with a normal trileaflet aortic valve.[19]

Because of the elevated risk of aortic root pathology, it is recommended that patients with BAV be followed by serial transthoracic echocardiograms to monitor the diameter of the aortic root and function of the valve. Depending on the

TABLE 2 Sensitivity Analysis for Cost per Life-Year Saved

Parameter	Lower Estimate	Base Estimate	Upper Estimate
Screening detection rate	15%	10.1%	5%
	$50 422	$74 884	$151 265
Detection rate without routine screening echocardiography	35%	50%	65%
	$57 603	$74 884	$106 977
Cost for screening echo		$213.08	$319.02
		$74 884	$110 438
Dissection rate per 1000 patient-years	1.4	0.9	0.4
	$47 365	$74 884	$177 976
Prevention of dissection with early detection	100%	80%	60%
	$71 511	$74 884	$80 506
Mortality from dissection	30%	22%	16%
	$54 915	$74 884	$102 965
Entire model	$17 461	$74 884	$1 136 536

dimensions of the ascending aorta, children and young adults with BAV may be restricted from some forms of sports participation. In adults, the risk of aortic dissection increases significantly with ascending aorta diameter of 6 cm or descending aorta diameter of 7 cm. Thus, surgical intervention is recommended before the aorta dilates to this extent.[20]

Based on our assumptions, the cost-effectiveness ratio of BAV sibling screening is reasonable and within the bounds of acceptable screening costs. Generally, interventions with a cost of <$50 000 per life-year saved are universally accepted as appropriate. Interventions with a cost of <$100 000 per life-year saved, such as our BAV screening model, may be a reasonable use of resources in many circumstances. Sensitivity analysis suggests that if the risks of aortic dissection are lower than our baseline estimate, the benefits of screening are less favorable but still reasonable from a cost-effectiveness perspective. A number of other echocardiographic screening strategies have been examined in children. These include universal screening for congenital heart disease and echocardiographic screening for young athletes. Both of these strategies appear less cost-effective than screening siblings for BAV, with cost exceeding $200 000 per life-year saved.[21]

There is potential for negative consequences of screening patients to identify BAV, such as psychological stress on the parent or child with newly diagnosed BAV. However, we believe these risks are outweighed by the benefit of identifying these children so they may be monitored to prevent rare but serious adverse events. In addition, periodic surveillance may be costly. Our model includes the cost of routine outpatient cardiology consultation and echocardiography.

Limitations

Although we recommend echocardiography screening of all siblings of patients with BAV, not all siblings may present for screening. Charges for echocardiography screening usually exceed costs as published by Centers for Medicare & Medicaid Services and may be prohibitive for some families. It is unknown what percentage of total siblings of patients with BAV underwent screening. Selection bias may be a confounding factor. Although it is our practice to recommend echocardiographic screening for all BAV siblings, it is possible that the families or primary physicians may have selectively referred siblings.

Compared with previous studies, a large proportion of the siblings newly diagnosed with BAV in our study were noted to have physical examination findings of an ejection click or systolic ejection murmur. This difference may be caused by unblinding of the examiners. Some patients may have been initially referred for echocardiography only, and only then had a full examination by a pediatric cardiologist.

CONCLUSIONS

Echocardiography detects BAV in siblings of patients with BAV with satisfactory yield. The cost of detecting a new case of BAV in this high-prevalence population compares favorably with that of other screening methods used in pediatrics. Therefore, it is reasonable to incorporate echocardiography screening of siblings with BAV into clinical practice. This screening may avert catastrophic consequences in rare cases of young adults. Such screening could also improve genetic counseling in families with a strong history of left heart defects.

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