



# Decision analysis to define the optimal management of athletes with anomalous aortic origin of a coronary artery

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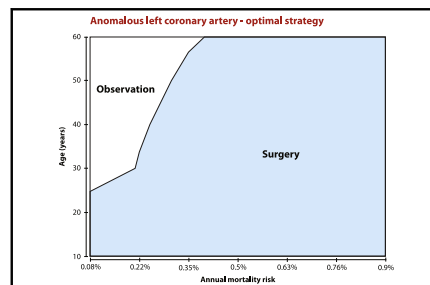
## ABSTRACT

**Objectives:** The goal of this study was to use decision analysis to evaluate the impact of varying uncertainties on the outcomes of patients with anomalous aortic origin of a coronary artery.

**Methods:** Two separate decision analysis models were created: one for anomalous left coronary artery (ALCA) and one for anomalous right coronary artery (ARCA). Three strategies were compared: observation, exercise restriction, and surgery. Probabilities and health utilities were estimated on the basis of existing literature. Deterministic and probabilistic sensitivity analyses were performed.

**Results:** Surgery was the optimal management strategy for patients <30 years of age with ALCA. As age increased, observation became an equivalent strategy and eventually surpassed surgery as the treatment of choice. The advantage on life expectancy for surgery over observation ranged from  $2.6 \pm 1.7$  years for a 10-year-old patient to  $-0.03 \pm 0.1$  for a 65-year old patient. In patients with ARCA, observation was the optimal strategy for most patients with a life expectancy advantage over surgery of  $0.1 \pm 0.1$  years to  $0.2 \pm 0.4$  years, depending on age. Surgery was the preferred strategy only for patients <25 years of age when the perceived risk of sudden cardiac death was high and the perioperative mortality was low. Exercise restriction was a suboptimal strategy for both ALCA and ARCA in all scenarios.

**Conclusions:** The optimal management in anomalous aortic origin of a coronary artery depends on multiple factors, including individual patient characteristics. Decision analysis provides a tool to understand how these characteristics affect the outcomes with each management strategy and thus may aid in the decision making process for a particular patient. (*J Thorac Cardiovasc Surg* 2016;152:1366-75)



Optimal strategy for anomalous left coronary artery based on age and annual mortality risk.

### Central Message

Decision analysis explains how different factors affect the optimal management of a particular patient with an anomalous coronary.

### Perspective

The risk of sudden cardiac death and the optimal management for patients with anomalous aortic origin of a coronary artery are unclear. Decision analysis provides a valuable tool to make a more informed decision on what the best management strategy (surgery, observation, and exercise restriction) is for a particular patient, taking into account the varying effects of different uncertainties.

See Editorial Commentary page 1376.

Anomalous aortic origin of a coronary artery (AAOCA) with an interarterial segment is the second-leading cause of sudden cardiac death (SCD) among young athletes in

the United States and it is responsible for 17% of cases of SCD.<sup>1</sup> The risk of SCD is reportedly greater for patients with anomalous left coronary artery from the right sinus of Valsalva (ALCA) than for patients with anomalous right coronary artery from the left sinus of Valsalva (ARCA).<sup>2</sup>

An estimated 0.12% to 0.70% of the general population has AAOCA.<sup>3-7</sup> The detection of this anomaly seems to be increasing as the result of improved imaging technology, increased frequency of imaging studies performed for

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### Abbreviations and Acronyms

AAOCA	= anomalous aortic origin of a coronary artery
ALCA	= anomalous left coronary artery from the opposite sinus of Valsalva
ARCA	= anomalous right coronary artery from the opposite sinus of Valsalva
CI	= confidence interval
QALY	= quality-adjusted life year
SCD	= sudden cardiac death

other abnormalities, and screening initiatives for children and young athletes.<sup>6,7</sup> The true risk and mechanisms responsible for SCD in patients with AAOCA are unclear. Several strategies (ie, exercise restriction and different surgical interventions) have been devised in an attempt to decrease the risk of SCD. The effect of these strategies on the prevention of SCD also is unclear.<sup>2</sup> Because of these uncertainties, there is no consensus on how to best manage AAOCA, leaving physicians with a difficult task when counseling patients and families with this anomaly.<sup>8-10</sup>

Decision analysis is a formal quantitative approach that analyzes different management strategies under conditions of uncertainty. The goal of this study was to use decision analysis to provide the clinician with a tool to better understand the impact of various uncertainties on the optimal management strategy for a particular patient with AAOCA and an interarterial segment.

## METHODS

### Decision Analysis Models

Two identically structured decision analysis models with different probabilities were created: one for ALCA and another for ARCA (Figure 1). Patients diagnosed with AAOCA can undergo 1 of 3 management strategies: observation (without exercise restriction), exercise restriction, or surgical intervention. Patients who undergo surgery can die from surgery (perioperative mortality), develop nonlethal complications secondary to surgery (short-term or long-term) with a subsequent impact on quality of life, or survive surgery without any complications. After the initial decision, hypothetical patients enter a Markov state-transition model that simulates the life of each hypothetical patient. For all management strategies, during each annual cycle of the model, patients can die from SCD related to AAOCA, die from other unrelated causes, or survive and go on to the next yearly cycle. The likelihood of patients moving through these different health states is defined by transition probabilities.

### Transition Probabilities

Initial transition probabilities were defined on the basis of estimates obtained from the literature, when available. Probabilities were then widely varied within a plausible range for sensitivity analyses (Table 1).<sup>1-7,11-29</sup>

**Risk of SCD from AAOCA.** The exact risk of SCD in young athletes with AAOCA currently is not known. Therefore, the risk probabilities were extrapolated from existing literature by the use of estimates of the prevalence of AAOCA in the general population<sup>3-7</sup> and

observed mortality rates from AAOCA in several studies.<sup>1,11,12,30</sup> The details of these calculations are shown in the Appendix. The estimates used for the annual mortality risk from AAOCA for athletes and the range of values for sensitivity analyses were 0.35% (0.08%-0.9%) for ALCA and 0.02% (0.0035%-0.06%) for ARCA.

**Risk of SCD from AAOCA and age.** According to the literature, the risk of SCD appears to vary by age. The majority (80%) of cases of SCD from AAOCA occur in patients 10 to 30 years of age with scant reports of mortality events in patients <10 years of age.<sup>13</sup> Therefore, a distribution variable was created to determine the annual mortality risk from AAOCA based on age (Table 1). The risk was increased progressively from nearly zero at 10 years old to reach its full value at 14 years of age. The risk was then decreased after 26 years and kept at 10% of the corresponding full value after 30 years of age.

**Perioperative surgical outcomes.** No perioperative deaths have been reported in several case series of surgery for AAOCA with an aggregate of approximately 200 patients<sup>16</sup>; however, for the purpose of our analyses and biasing the results in favor of a nonsurgical approach, a perioperative mortality rate of 0.5% (0%-2% for sensitivity analyses) was assumed. The risk of nonlethal perioperative complications in the literature ranges from 0% to 14%; an estimate of 10% (5%-20% for sensitivity analyses) was used. The probability of these complications being long-term complications was modeled at 10% (0%-20% for sensitivity analyses).

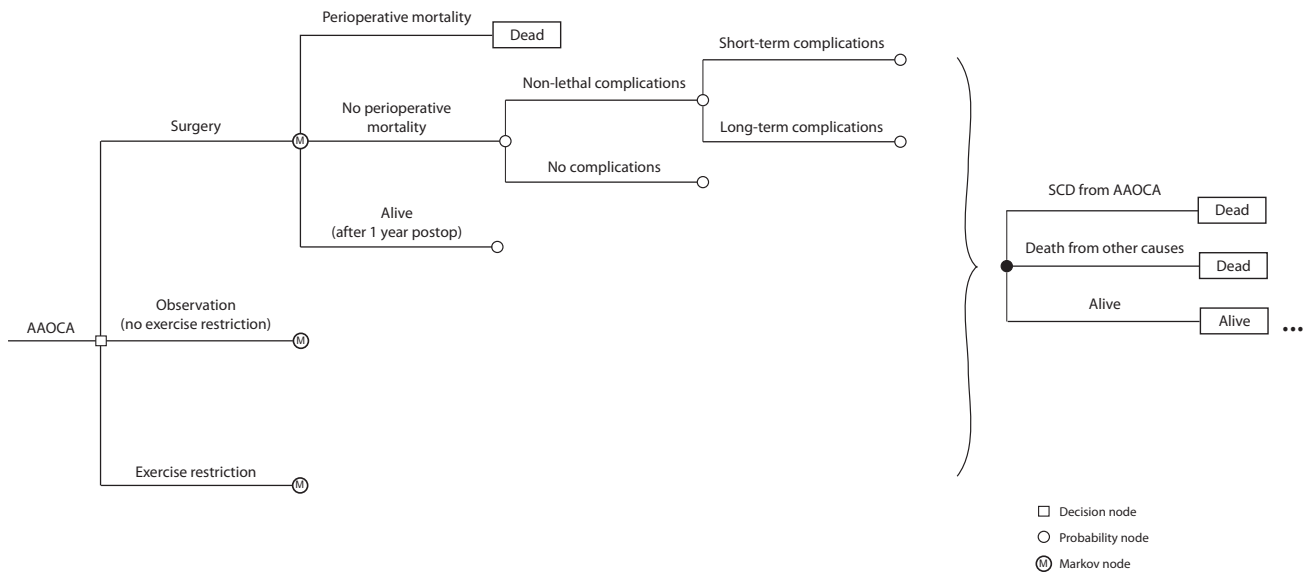
**Reduction in risk with intervention.** No reliable data are available regarding the effect of surgery or exercise restriction on the risk of SCD from AAOCA. Therefore, the reduction in risk resulting from these 2 strategies varied from 70% to 100%. For the base decision analysis, surgery and exercise restriction were each assumed to reduce the risk of SCD by 90%.

**Mortality from non-AAOCA causes.** The annual risk of mortality from non-AAOCA causes was calculated from US life tables that provide age-specific death rates for the general population.<sup>24</sup> Large population-based studies have shown that a lack of exercise increases all-cause mortality.<sup>31</sup> Guidelines from the US Department of Health and Human Services recommend at least 150 minutes per week of moderate-intensity activity for adults and 60 minutes of daily physical activity for children and adolescents.<sup>17</sup> A meta-analysis of cohort studies with almost 978,000 patients showed that compliance with these guidelines was associated with a 19% reduction in annual mortality risk when compared with no activity.<sup>18</sup> Because the study focused on athletes, it was assumed that all individuals allowed to exercise would meet exercise guidelines. Mortality rates for athletes were calculated using the US life tables,<sup>24</sup> the age-specific likelihood that individuals on the general population included in the life tables are compliant with exercise recommendations (Table 1),<sup>19-23</sup> and the assumed reduction in all-cause mortality with exercise.<sup>18</sup> These data also were used to calculate age-specific increases in mortality risk for patients who were under exercise restriction.

### Health Utilities

Health utilities are weights that represent individual preferences for different health states and are used to calculate quality-adjusted life expectancy. Utilities range from 0 (death) to 1 (perfect health) and are multiplied by the years spent in the corresponding health states to calculate quality-adjusted life years (QALYs). Athletes who were disqualified from exercise were assumed to have a utility score equivalent to that of adolescents diagnosed with heart disease (0.89)<sup>26</sup> for the first 5 years, an approach similar to the one used by Wheeler and colleagues<sup>29</sup> in a recent cost-effectiveness analysis of electrocardiography screening for prevention of SCD in athletes.

Patients without complications after cardiac surgery were assumed to have a health utility of 0.94 (0.7-1 for sensitivity analyses) for the first 2 months after surgery,<sup>25</sup> with normal quality of life thereafter. Patients



**FIGURE 1.** Monte Carlo simulation model. The model starts with a decision node and 3 management strategies. Each subtree enters a Markov cycle that repeats itself annually until all patients in the simulation have died. The first 2 branches within the “Surgery” strategy only occur during the first year after surgery. The circular nodes represent probability nodes; the likelihood of a patient moving into each of the branches depends on the assigned transition probabilities at that particular cycle. At the end of each branch is a terminal node with a health state contained in a rectangle (“Dead” or “Alive”). This represents the state at which a patient moving through the model will start his or her next yearly cycle. The “Dead” state is an absorbing state; a patient in this state does not continue to travel through the model. If a patient finishes the iteration in the “Alive” state, the patient will then go on to the next Markov cycle. *AAOCA*, Anomalous aortic origin of a coronary artery; *SCD*, sudden cardiac death.

who suffered a short-term complication from cardiac surgery were assumed to have a health utility of 0.87 (0.5-1 for sensitivity analyses) for the first 4 months after surgery.<sup>25</sup> The health utility for patients with long-term complications was assigned after we analyzed several sources in the literature for patients with 2-3 simultaneous chronic conditions, dysrhythmias, stroke, and congestive heart failure.<sup>26-28</sup> The health utility for these patients was assumed to be 0.85 (0.65-0.95 for sensitivity analyses) through the remainder of their lifetime.

**Analyses**

The models were constructed and analyzed with TreeAge Pro 2012 (TreeAge Software, Inc, Williamstown, Mass). Because the main outcomes were life expectancy and quality-adjusted life expectancy, outcomes were not discounted with time (ie, gains in life expectancy were considered the same whether they occurred early after diagnosis or later in life).

We calculated long-term prognosis in terms of life expectancy and quality-adjusted life expectancy for each strategy by performing a first-order Monte Carlo simulation using a cohort of 10,000 hypothetical identical patients entering the model at diagnosis and followed until death. The management strategy was kept constant throughout the lifetime of the patient. The base case assumed a diagnosis of AAOCA in a patient 15 years of age, although the model was analyzed for ages between 10 and 65 years. Results are reported as means and 95% confidence intervals (CIs) of remaining years of life expectancy and QALYs.

One-, two-, and three-way deterministic sensitivity analyses were performed to vary key model assumptions and determine the thresholds of those variables at which the preferred treatment strategy changed for each of the models. Probabilistic sensitivity analyses were performed for various ages at diagnosis by simultaneously varying all parameters of the model (except for age) using uniform, beta, or triangular distributions, as appropriate (Table 1). These analyses were performed using second-order Monte Carlo simulations with 10,000 unique iterations (ie, the values of each variable were varied for each iteration according

to the defined distribution types and ranges for each variable) to yield a mean residual life expectancy that incorporates the uncertainty of all parameters simultaneously. In addition, the percentage of all simulations that favored each of the different strategies by age (in 5-year increments) was calculated.

**RESULTS**

**Anomalous Left Coronary Artery**

Under the base assumptions, surgery was the preferred strategy for a 15-year-old patient with ALCA; future life expectancies were 64.5 years (95% CI, 64.2-64.8) for surgery, 62.5 years (95% CI, 62.2-62.8) for exercise restriction, and 62.0 years (95% CI, 61.7-62.4) for observation with no exercise restriction. The results were similar when analyzing quality-adjusted life expectancy: 64.4 QALYs (95% CI, 64.0-64.7) for surgery, 62.0 QALYs (95% CI, 61.7-62.3) for exercise restriction, and 62.0 QALYs (95% CI, 61.7-62.4) for observation.

Surgical intervention remained the preferred management strategy for a 15-year-old patient even if the annual mortality risk from SCD was as low as 0.08% (Figure 2, A); however, the results of the model varied by age. For patients >30 years of age, if the annual mortality risk from SCD was <0.2% to 0.4% depending on age, observation was the preferred strategy (Figure 2, B). The results were similar regardless of the degree of reduction in AAOCA-related mortality risk conferred by surgery within the predetermined range (Figure 2, C). The risk of

TABLE 1. Initial assumptions and ranges used for sensitivity analyses

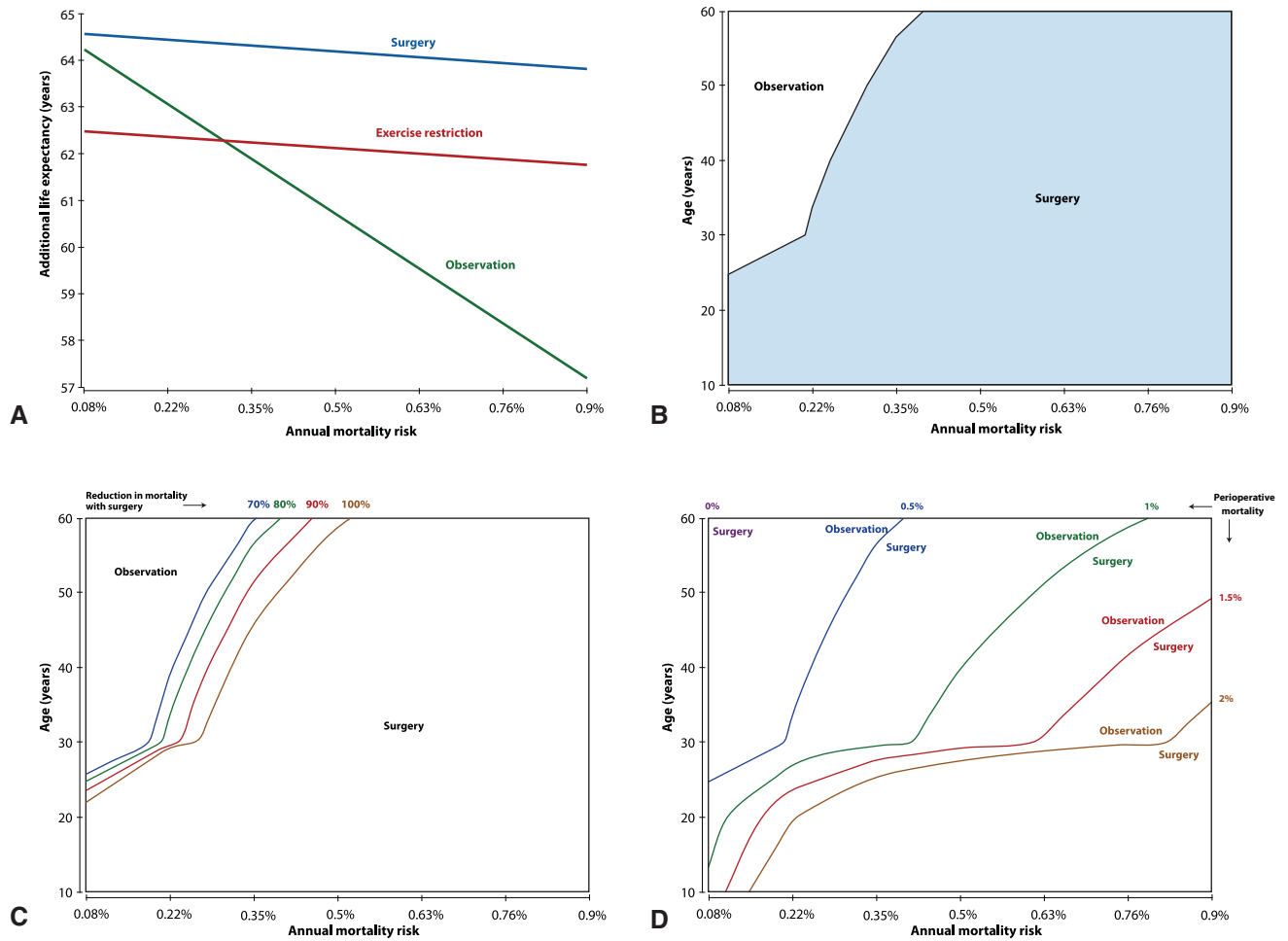
Parameters	Value	Range/95% CI	Distribution used for probabilistic sensitivity analysis
Annual probability of SCD <sup>1,3-7,11,12,*</sup>			
ALCA	0.35%	0.08%-0.9%	Beta
ARCA	0.02%	0.0035%-0.06%	Beta
Age at presentation, y	15	10-65	Stratified by age
Variation in mortality risk from AAOCA by age, y <sup>2,13-15,*;†</sup>			Not varied
0-10	0.00001 * risk		
11	0.25 * risk		
12	0.5 * risk		
13	0.75 * risk		
14-26	1 * risk		
27	0.75 * risk		
28	0.5 * risk		
29	0.25 * risk		
30 and older	0.1 * risk		
Outcomes after surgical intervention <sup>16</sup>			
Perioperative mortality	0.5%	0%-2%	Beta
Perioperative major complication rate	10%	0%-20%	Beta
Probability of a major complication being a long-term complication	10%	0%-20%	Beta
Reduction in risk with intervention			
Surgery	90%	70%-100%	Triangular
Exercise restriction	90%	70%-100%	Triangular
Reduction in all-cause mortality risk with recommended nonvigorous moderate physical activity <sup>17,18</sup>	19%	15%-24%	Beta
Percentage of individuals who exercise according to guidelines			
5-8 y of age <sup>19</sup>	76%	70%-82%	Beta
9-11 y of age <sup>20</sup>	65%	60%-70%	Beta
12-14 y of age <sup>21</sup>	72%	70%-74%	Beta
15-17 y of age <sup>22</sup>	29%	27%-30%	Beta
18-24 y of age <sup>23</sup>	61%	59%-63%	Beta
25-44 y of age <sup>23</sup>	54%	53%-55%	Beta
45-54 y of age <sup>23</sup>	46%	44%-48%	Beta
55-64 y of age <sup>23</sup>	43%	41%-45%	Beta
65-74 y of age <sup>23</sup>	41%	39%-43%	Beta
75 y and older <sup>23</sup>	27%	25%-29%	Beta
Annual mortality from other causes <sup>24</sup>	US Life Tables, 2006		Not varied
Health utilities			
Utility value for the first 2 mo after surgery with no complications <sup>25</sup>	0.94	0.7-1.0	Uniform
Utility value for the first 4 mo after surgery with short-term perioperative complications <sup>25</sup>	0.87	0.5-1.0	Uniform
Utility value for lifetime after surgery with long-term complications <sup>26-28</sup>	0.85	0.65-0.95	Uniform
Utility value with no exercise restriction	1		Not varied
Utility value for the first 5 y for athletes being exercise restricted <sup>26,29;‡</sup>	0.89	0.7-0.95	Uniform

CI, Confidence interval; SCD, sudden cardiac death; ALCA, anomalous left coronary artery from the opposite sinus of Valsalva; ARCA, anomalous right coronary artery from the opposite sinus of Valsalva; AAOCA, anomalous aortic origin of a coronary artery. \*See text for explanation of values. †Ratio multiplied by the incremental mortality risk. ‡Utility value was assumed to be normal after 5 years.

perioperative mortality changed the preferred treatment strategy (Figure 2, D). As perioperative mortality increased, observation became the optimal strategy for older patients and those with a low risk of SCD from AAOCA. Exercise restriction was not a competing strategy unless exercising was assumed to have only a minimal effect on all-cause mortality (below the predetermined range, Figure E1). The results were similar when analyzing quality-adjusted

life expectancy. Changing other parameters, either individually or adjusted for age and annual risk of SCD, did not substantially change the results of these analyses (see Figures E2-E4 for selected analyses).

If exercise restriction was only limited to patients until they reached 30 years of age (with later liberalization of exercise), exercise restriction became an optimal strategy only if the annual mortality risk of SCD was <0.15%



**FIGURE 2.** Sensitivity analyses for life expectancy for ALCA. A, 1-way sensitivity analysis showing the future life expectancy for each of the strategies for a 15-year-old patient while varying the annual risk of SCD from ALCA. B, A 2-way sensitivity analysis shows the optimal strategy while simultaneously varying age at presentation and annual risk of SCD. The colored area represents the range of values where surgery is an optimal strategy, and the white area represents the range where observation is preferable. C, A 3-way sensitivity analysis simultaneously varying age at presentation (Y-axis), annual risk of SCD (X-axis), and reduction in risk achieved with surgery. Each colored line represents a different value for reduction in mortality risk with surgery. Any range of values for annual risk of SCD and age at presentation above and to the left of a particular line favors observation, whereas any range of values below and to the right of the line favors surgery. D, A 3-way sensitivity analysis varying age, annual risk of SCD, and perioperative mortality risk. Each colored line represents a particular perioperative mortality risk. The strategies immediately above and below each line represent the optimal strategy on each side of the line for the set of values for annual mortality risk and age at that level of perioperative mortality risk.

(Figure E5). This advantage disappeared when we took into account quality of life.

The results of probabilistic sensitivity analyses by age for ALCA can be found in Table 2. For these analyses, all other parameters besides age were simultaneously modified according to the distributions in Table 1. Surgery was the preferred strategy for younger patients, conferring about 2 more additional years of life expectancy than observation or exercise restriction. As the age at presentation increased, observation became equivalent to and eventually surpassed surgery as the treatment of choice. The vast majority of simulations favored surgical intervention for patients 25 years of age and younger, whereas a larger proportion

of simulations favored observation for older patients (Figure 3).

**Anomalous Right Coronary Artery**

Both surgery and observation were optimal strategies for a 15-year-old patient with ARCA. The future life expectancies were 64.8 years (95% CI, 64.5-65.1 years) for surgery and for observation, and 62.4 years (95% CI, 62.1-62.7 years) for exercise restriction. In terms of quality-adjusted life expectancy, the results were slightly greater for observation (64.8 QALYs, 95% CI, 64.5-65.1) than for surgery (64.7 QALYs, 95% CI, 64.3-65.0). Quality-adjusted life expectancy for exercise

**TABLE 2. Probabilistic sensitivity analysis for anomalous left coronary artery**

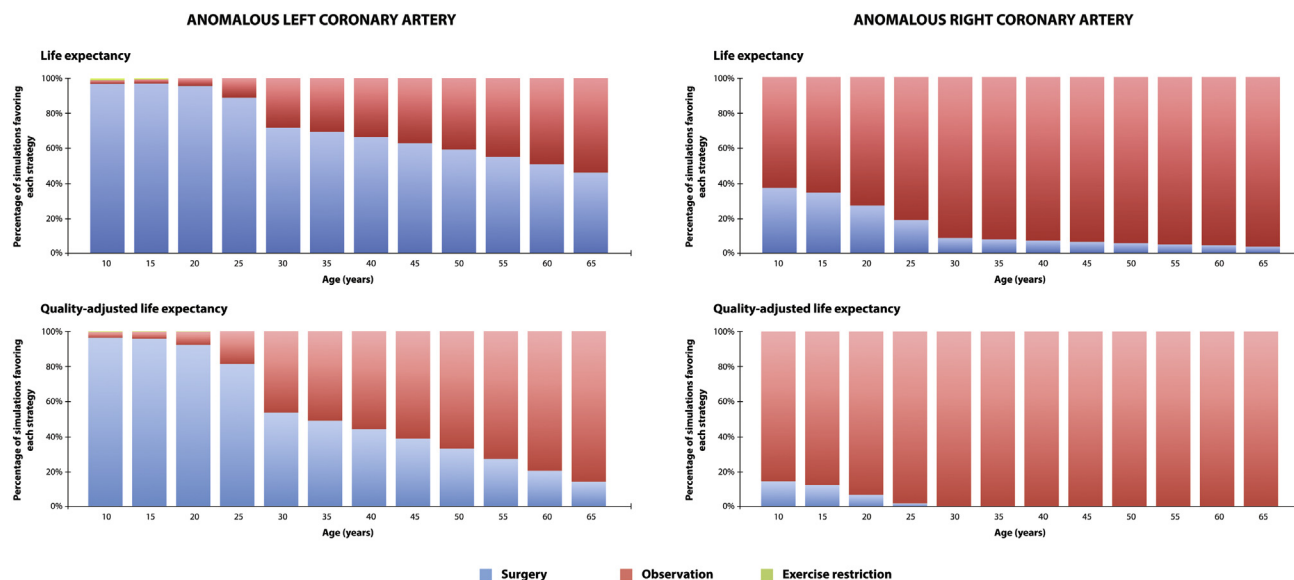
	Age at diagnosis, y							
	10	15	20	25	35	45	55	65
<b>Life expectancy</b>								
<b>Surgery</b>								
Life expectancy, y	68.8 ± 0.8	64 ± 0.7	59.4 ± 0.5	54.9 ± 0.4	45.6 ± 0.3	36.4 ± 0.3	27.6 ± 0.2	19.6 ± 0.2
<b>Observation (no exercise restriction)</b>								
Life expectancy, y	66.3 ± 2.1	61.8 ± 1.8	58.1 ± 1.2	54.3 ± 0.7	45.5 ± 0.3	36.3 ± 0.2	27.6 ± 0.2	19.6 ± 0.2
Incremental years*	-2.6 ± 1.7	-2.2 ± 1.5	-1.4 ± 1.0	-0.6 ± 0.6	-0.1 ± 0.3	-0.03 ± 0.2	+0.01 ± 0.2	+0.03 ± 0.1
<b>Exercise restriction</b>								
Life expectancy, y	66.8 ± 0.6	61.9 ± 0.5	57.4 ± 0.4	52.9 ± 0.2	43.6 ± 0.1	34.4 ± 0.1	25.8 ± 0.1	18.0 ± 0.1
Incremental years*	-2.1 ± 0.8	-2.1 ± 0.7	-2.1 ± 0.6	-2.1 ± 0.5	-2.0 ± 0.4	-2.0 ± 0.3	-1.8 ± 0.3	-1.6 ± 0.2
<b>Quality-adjusted life expectancy</b>								
<b>Surgery</b>								
Quality-adjusted life expectancy, QALYs	68.7 ± 0.8	63.9 ± 0.7	59.3 ± 0.5	54.8 ± 0.4	45.5 ± 0.3	36.3 ± 0.3	27.6 ± 0.2	19.5 ± 0.2
<b>Observation with no exercise restriction</b>								
Quality-adjusted life expectancy, QALYs	66.3 ± 2.1	61.8 ± 1.8	58.1 ± 1.2	54.3 ± 0.7	45.5 ± 0.3	36.3 ± 0.2	27.6 ± 0.2	19.6 ± 0.2
Incremental QALYs*	-2.4 ± 1.7	-2.0 ± 1.5	-1.2 ± 1.0	-0.5 ± 0.6	+0.03 ± 0.3	+0.1 ± 0.2	+0.1 ± 0.2	+0.1 ± 0.1
<b>Exercise restriction</b>								
Quality-adjusted life expectancy, QALYs	66.0 ± 0.7	61.2 ± 0.6	56.6 ± 0.5	52.1 ± 0.4	42.8 ± 0.3	33.6 ± 0.3	25.1 ± 0.3	17.2 ± 0.3
Incremental QALYs*	-2.7 ± 0.9	-2.7 ± 0.8	-2.7 ± 0.7	-2.7 ± 0.6	-2.7 ± 0.5	-2.6 ± 0.5	-2.5 ± 0.4	-2.3 ± 0.4

All numbers represent means ± standard deviation. QALYs, Quality-adjusted life years. \*Compared with surgery.

restriction was significantly lower at 61.9 QALYs (95% CI, 61.6-62.2).

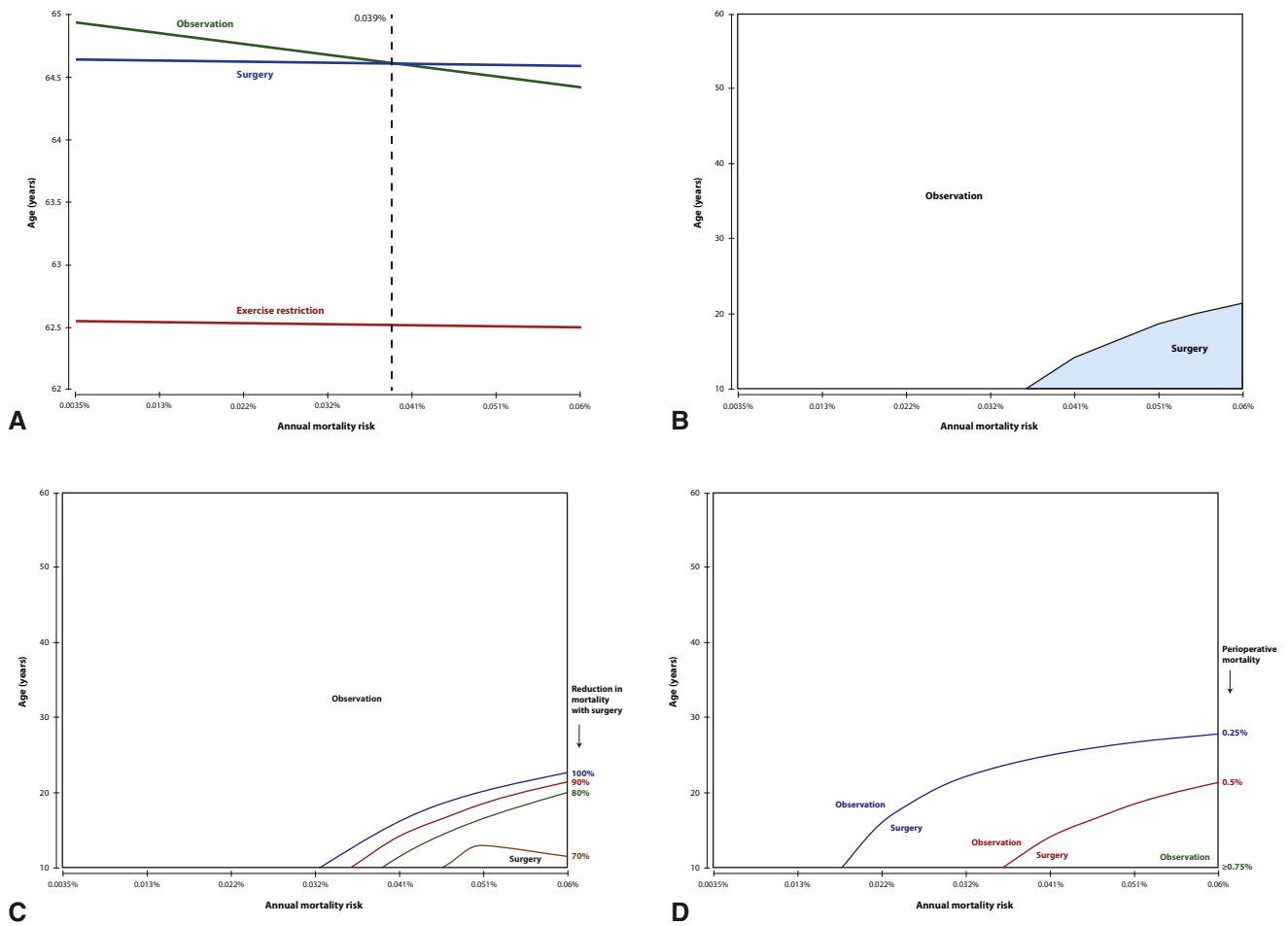
On life expectancy sensitivity analyses, observation was the preferred strategy unless the annual mortality risk from SCD was >0.039% (Figure 4, A). Exercise restriction remained a suboptimal strategy regardless of annual

mortality risk. As noted in Figure 4, B, observation was the preferred strategy for most patients, except for patients <20 years of age with >0.035% annual mortality risk of SCD. As the reduction in AAOCA-related mortality achieved with surgery decreased, observation became a more preferred strategy (Figure 4, C). As expected, a



**FIGURE 3.** Preferred treatment strategies by age using probabilistic sensitivity analysis. With a Monte Carlo simulation, remaining life years and QALYs were calculated for 10,000 different iterations for each lesion and age group while simultaneously varying all other parameters within the predetermined ranges. Each panel represents the percentage of those simulations that favored each strategy by age. The upper panels account only for life expectancy whereas the lower panels incorporate quality of life.

CONG



**FIGURE 4.** Sensitivity analyses for life expectancy for ARCA. A, A 1-way sensitivity analysis comparing the projected future life expectancy for a 15-year-old patient under each management strategy while varying the annual risk of SCD from ARCA. B, A 2-way sensitivity analysis, shows the optimal strategy while simultaneously varying the age at presentation (Y-axis) and the annual risk of SCD (X-axis). The *colored area* represents the range of values where surgery would be preferred, and the *white area* represents the values where observation would be optimal. C, A 3-way sensitivity analysis, shows the optimal strategy while varying the age at presentation (Y-axis), risk of SCD (X-axis), and the reduction in SCD mortality achieved with surgery. Each curve represents a different threshold for reduction in mortality with surgery. Values above and to the left of each curve favor observation whereas values below and to the right favor surgery. D, A 3-way sensitivity analysis, shows the optimal strategy while simultaneously varying age at presentation (Y-axis), annual risk of SCD (X-axis), and perioperative mortality risk. For each perioperative mortality risk threshold, all values above and to the left of the curves favor observation, and those below and to the right favor surgery. If the perioperative mortality risk is  $\geq 0.75\%$ , observation is the preferred strategy for all scenarios.

decrease in perioperative mortality increased the role of surgery to include older patients and those with lower risks of SCD (Figure 4, D). If the perioperative mortality risk was  $\geq 0.75\%$ , observation was the preferred strategy for all patients. Exercise restriction was not a competing strategy unless the reduction in all-cause mortality with exercise was assumed to be minimal (below the predetermined range, Figure E6). The results were largely unchanged after changing other parameters.

When we analyzed quality-adjusted life expectancy, observation was the preferred strategy for most scenarios. Surgery was the preferred strategy only for patients <30 years of age with a high risk of SCD if the perioperative

mortality rate was <0.4% (Figure E7). Exercise restriction was not a preferred strategy for any patient even if exercising according to guidelines was assumed not to have any impact at all in all-cause mortality. The results were largely unchanged after varying other parameters.

If exercise restriction was applied only until 30 years of age, exercise restriction became an optimal strategy for patients 10-28 years old with an annual mortality risk >0.02% to 0.04% depending on age (Figure E8). However, exercise restriction was a suboptimal strategy for all patients after taking into account quality of life.

Table 3 illustrates the results of the ARCA model by age when simultaneously accounting for the uncertainty of all

**TABLE 3. Probabilistic sensitivity analysis for anomalous right coronary artery**

	Age at diagnosis, y							
	10	15	20	25	35	45	55	65
Life expectancy								
Surgery								
Life expectancy, y	69.5 ± 0.4	64.6 ± 0.4	59.8 ± 0.4	55.1 ± 0.3	45.7 ± 0.3	36.4 ± 0.3	27.7 ± 0.2	19.6 ± 0.2
Observation (no exercise restriction)								
Life expectancy, y	69.7 ± 0.3	64.8 ± 0.2	60.0 ± 0.2	55.4 ± 0.2	45.9 ± 0.2	36.6 ± 0.2	27.8 ± 0.2	19.7 ± 0.2
Incremental years*	+0.2 ± 0.4	+0.2 ± 0.3	+0.2 ± 0.3	+0.2 ± 0.3	+0.2 ± 0.2	+0.2 ± 0.2	+0.1 ± 0.1	+0.1 ± 0.1
Exercise restriction								
Life expectancy, y	67.4 ± 0.1	62.5 ± 0.1	57.7 ± 0.1	53.1 ± 0.1	43.6 ± 0.1	34.5 ± 0.1	25.9 ± 0.1	18.0 ± 0.1
Incremental years*	-2.1 ± 0.5	-2.1 ± 0.5	-2.1 ± 0.4	-2.1 ± 0.4	-2.0 ± 0.4	-2.0 ± 0.3	-1.8 ± 0.3	-1.6 ± 0.2
Quality-adjusted life expectancy								
Surgery								
Quality-adjusted life expectancy, QALYs	69.4 ± 0.4	64.5 ± 0.4	59.7 ± 0.4	55.0 ± 0.4	45.6 ± 0.3	36.3 ± 0.3	27.6 ± 0.2	19.5 ± 0.2
Observation with no exercise restriction								
Quality-adjusted life expectancy, QALYs	69.7 ± 0.3	64.8 ± 0.2	60.0 ± 0.2	55.4 ± 0.2	45.9 ± 0.2	36.6 ± 0.2	27.8 ± 0.2	19.7 ± 0.2
Incremental QALYs*	+0.3 ± 0.4	+0.3 ± 0.4	+0.3 ± 0.3	+0.4 ± 0.3	+0.3 ± 0.2	+0.3 ± 0.2	+0.2 ± 0.1	+0.2 ± 0.1
Exercise restriction								
Quality-adjusted life expectancy, QALYs	66.7 ± 0.3	61.7 ± 0.3	57.0 ± 0.3	52.3 ± 0.3	42.9 ± 0.3	33.7 ± 0.3	25.1 ± 0.3	17.3 ± 0.3
Incremental QALYs*	-2.7 ± 0.6	-2.7 ± 0.6	-2.7 ± 0.6	-2.7 ± 0.5	-2.7 ± 0.5	-2.6 ± 0.5	-2.5 ± 0.4	-2.3 ± 0.4

All numbers represent means ± standard deviation. QALYs, Quality-adjusted life years. \*Compared with surgery.

parameters using probabilistic sensitivity analysis. Overall, observation was the preferred strategy in terms of life expectancy and quality-adjusted life expectancy for all ages, with a slight advantage over surgery. Among patients 20 years old and younger, a small percentage of simulations favored surgery (Figure 3). Otherwise, the vast majority of simulations favored observation alone. Exercise restriction was a suboptimal strategy throughout the entire age spectrum.

## DISCUSSION

It is widely accepted that AAOCA with an interarterial segment, and in particular ALCA, is associated with an increased risk of SCD. The exact mechanism of SCD in AAOCA is unclear and as such, there is a wide variability in the management of these patients.<sup>8</sup> Some authors recommend surgical intervention for patients with symptomatic AAOCA or asymptomatic ALCA but recommend only exercise restriction for asymptomatic patients with ARCA,<sup>9</sup> whereas others suggest intervention for all patients with AAOCA since its pathophysiologic mechanisms are unknown.<sup>32</sup>

The uncertainties surrounding AAOCA make managing and counseling of these patients extremely difficult. Regardless of the availability of data, however, the clinician is faced with a decision to make for a particular patient. The results of this decision analysis model are meant to provide a general tool for the clinician to understand how the different uncertainties surrounding AAOCA influence its

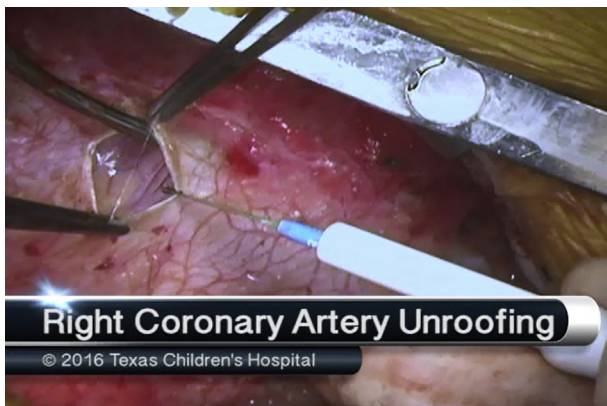
optimal management for a particular patient. Because of the large gaps in knowledge and resulting uncertainties, however, the model is not meant to provide a definitive answer.

According to the model, patients with ALCA would benefit from surgery unless they are >30 years of age, the perceived risk of SCD is lower than average, and the perioperative mortality risk is high. In those cases, observation becomes the preferred strategy.

The decision for patients with ARCA is more complex. Overall, observation is the preferred strategy for most patients. Surgery may play a role in patients <20 years of age with a greater-than-average perceived risk of SCD, provided that the perioperative mortality risk is kept low. The obvious difficulty lies in defining which patients are at the greater end of the spectrum of risk. The presence of symptoms possibly related to ischemia or the presence of anatomic abnormalities on imaging may potentially play a role in defining this subset of patients.

Some centers have recommended surgical treatment for all teenagers with AAOCA based on excellent outcomes and the uncertainty regarding which patients are at increased risk of SCD.<sup>32</sup> Even though this study does not support that approach, the risk of morbidity and mortality after surgery was intentionally kept high in the model. Surgery could therefore play an even larger role than specified in the model if morbidity and mortality rates are kept lower than the ones used.





**VIDEO 1.** Surgical technique for unroofing of an intramural anomalous right coronary artery arising from the left sinus of Valsalva (© 2016 Texas Children's Hospital, published with permission). Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(16\)31045-5/addons](http://www.jtcvsonline.org/article/S0022-5223(16)31045-5/addons).

The model provided is not intended as a substitute for clinical decision-making but as a tool to inform the clinician facing a difficult management decision. It is clear that the clinician will have to decide where in the spectrum of risk a particular patient falls depending on that patient's characteristics (eg, the presence of an intramural segment, the length of intramurality, the appearance of the ostium on imaging, the presence of symptoms, coronary dominance).

This model suggests that surgery increases the life expectancy of an average 15-year-old patient with ALCA by 2 years more than observation alone and 2.5 years more than exercise restriction. These are substantial benefits compared with those provided by other medical interventions. As frame of reference,  $\beta$ -blockers used after myocardial infarction translate into a 0.1- to 0.5-year gain in life expectancy<sup>33</sup> and smoking cessation in a 35-year-old man increases life expectancy by 0.8 years.<sup>34</sup>

An important finding of this analysis is the limited role that exercise restriction ought to play in the management of patients with AAOCA. The negative long-term effects of exercise restriction on all-cause mortality appear to be more significant than the low risk of SCD from AAOCA, even for ALCA. Exercise restriction had a positive impact in life expectancy only when limited to patients <30 years of age. This advantage completely disappeared, however, after taking into account quality of life. Furthermore, based on the authors' experience, the impact of exercise restriction in the quality of life of a young athlete can be even more significant than what we accounted for in the model using health utilities based on the literature. This would make exercise restriction an even less favorable strategy.

There are multiple inherent limitations to this study. The model is only as precise as the transition probabilities it is

based on. Because of the limited data available, these probabilities are not exactly known and are based mainly on retrospective studies and registries, with their associated flaws and biases. The use of sensitivity analyses with a wide variability was used to ameliorate this problem. For the sake of simplicity, some variables, such as perioperative mortality risk, were not modified as the patient aged, potentially introducing some bias.

The study did not account for differences in clinical presentation (ie, presence of symptoms) due to the unknown differential risk in SCD between patients with and without symptoms and to the difficulty ascribing symptoms, particularly in children and adolescents, to cardiac ischemia. The presence of symptoms suggestive of ischemia in a particular patient may imply that the patient is at the higher spectrum of SCD risk in the model for that particular lesion.

The study also did not account for differences in short-term and long-term outcomes between different surgical strategies (eg, coronary unroofing [Video 1], coronary translocation, pulmonary translocation) as there is not enough data in the literature to compare these techniques.

In general, the strategy chosen at clinical presentation was assumed to be followed for the lifetime of the patient, not allowing for cross-over in strategies. Thus, for most analyses, exercise restriction was assumed to last for the lifetime of the patient. To assess the effect that such an assumption would have on the results, a subanalysis was performed limiting exercise restriction to patients <30 years of age. The results were not substantially different.

The psychological impact of a diagnosis of AAOCA can be significant on a patient and the family. The model did not account for self-imposed limitations in exercise activity or the mere effects of an AAOCA diagnosis on quality of life. It could be hypothesized that taking these factors into account could make someone favor surgical intervention over observation. The effect of partial exercise restriction (allowing patients to exercise but not to participate in competitive sports) on mortality was also not analyzed. Most notably, because of the lack of appropriate data, the model does not have the necessary granularity to define the best management strategy for patients with different subtypes and anatomic characteristics of ALCA or ARCA.

Despite these limitations, however, we believe that this first attempt at using decision analysis modeling for AAOCA provides valuable information that can inform the decision by the clinician and the patient regarding the optimal management strategy for a given situation and contribute to the discussion regarding the best management of these patients. Ongoing population-based studies and multi-institutional registries such as the AAOCA registry by the Congenital Heart Surgeons' Society<sup>35</sup> may eventually provide the critically needed data to accurately estimate

the risk based on specific variables, and improve modeling of uncertainties and probabilities, which will in turn lead to more informed management decisions for these patients.

### Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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**Key Words:** anomalous aortic origin of a coronary artery, coronary anomaly, coronary disease, decision analysis, exercise restriction, sudden cardiac death, surgery

## APPENDIX. CALCULATIONS TO DETERMINE THE RISK OF SUDDEN CARDIAC DEATH (SCD)

The exact risk of SCD in anomalous aortic origin of a coronary artery (AAOCA) is unknown. Therefore, the transition probabilities used for the model were extrapolated from the literature as follows.

On the basis of various prevalence studies<sup>E1-E5</sup> and preliminary information from a cardiac magnetic resonance imaging screening study involving middle-school students by Angelini and colleagues,<sup>E6</sup> the prevalence of AAOCA in the general population was assumed to be between 0.12% and 0.7%, with anomalous right coronary artery from the left sinus of Valsalva (ARCA) being approximately 6 times more common than anomalous left coronary artery from the right sinus of Valsalva (ALCA).

Eckart and colleagues<sup>E7</sup> analyzed all deaths that occurred among 6.3 million military recruits undergoing basic military training from 1997 to 2001. Of the 277 deaths encountered, 21 were due to AAOCA, and all were from ALCA. On the basis of a prevalence of ALCA of 0.12%, one would assume that approximately 7,560 recruits were ALCA carriers at the time of military training, which would translate into a 0.27% mortality risk in recruits with AAOCA during the 6 weeks of military training. If the prevalence of AAOCA was 0.6%, then the mortality risk would be 0.05% in recruits with AAOCA during the 6 weeks of training. If this risk would remain constant for the entire year, if recruits were assumed to continue to have the substrate for mortality from AAOCA, and if people were exposed to the same conditions of military training throughout the year, then the annual mortality risk for ALCA could be as high as 0.48% to 2.4%.

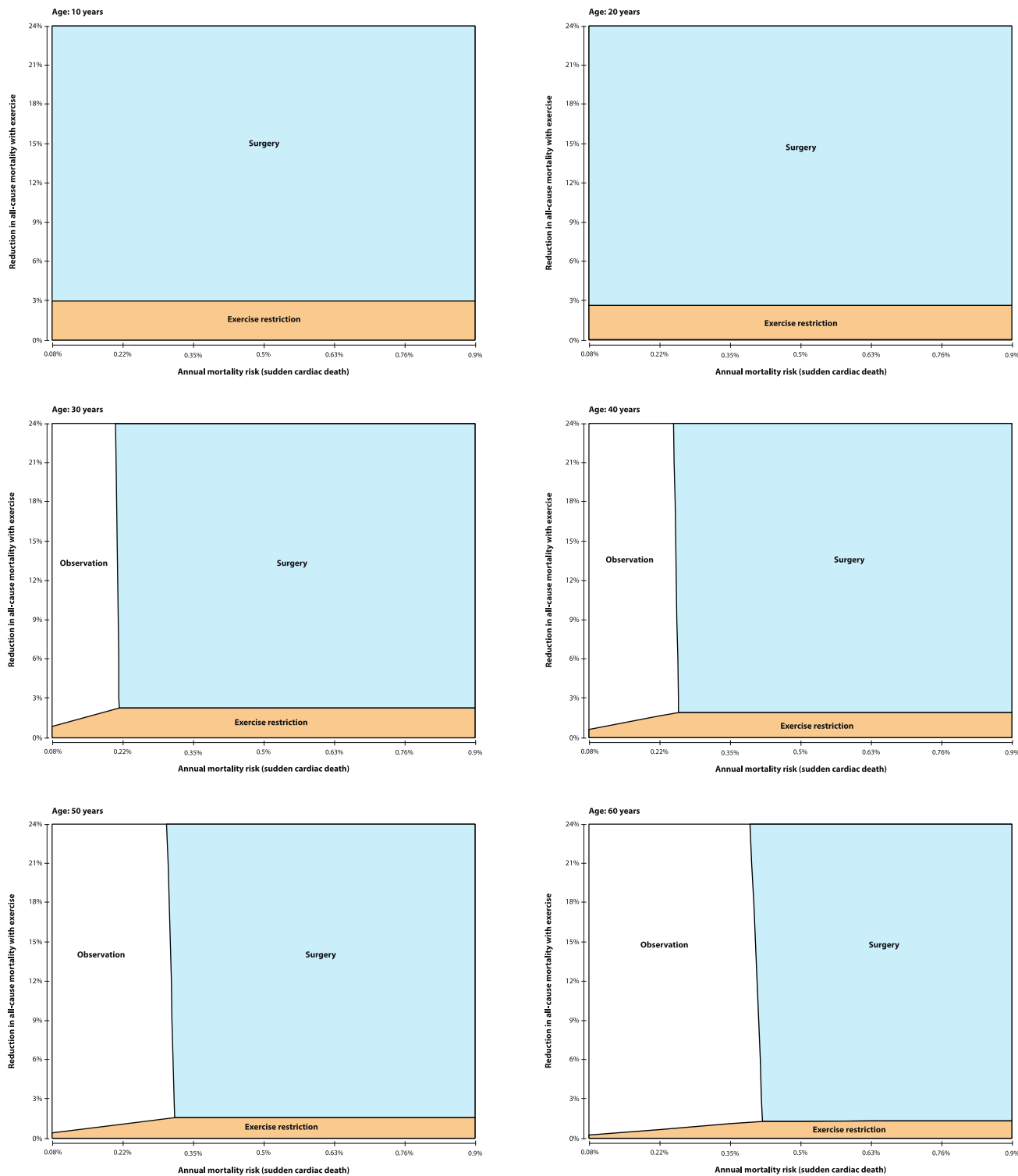
In a different study based on media reports, Maron and colleagues<sup>E8</sup> estimated the incidence of SCD in athletes to be 0.61 per 100,000 person-years, of which 17% were caused by AAOCA. Among deaths from AAOCA, ALCA was responsible for 4 times more deaths than ARCA. Using a similar analysis to the one performed by Brothers and colleagues<sup>E9</sup> and assuming a prevalence of AAOCA of 0.12%-0.7% and a prevalence ratio of ALCA to ARCA

of 1:6,<sup>E4,E10</sup> the annual mortality would be calculated at 0.08%-0.5% for ALCA and 0.0035%-0.02% for ARCA. However, in a different study by Harmon and colleagues<sup>E11</sup> among National Collegiate Athletic Association athletes, the risk of SCD was significantly greater (1:43,770 participants per year). When similar calculations are used, the annual risk of mortality from AAOCA would be as high as 0.26%-1.5% for ALCA and 0.011%-0.06% for ARCA.

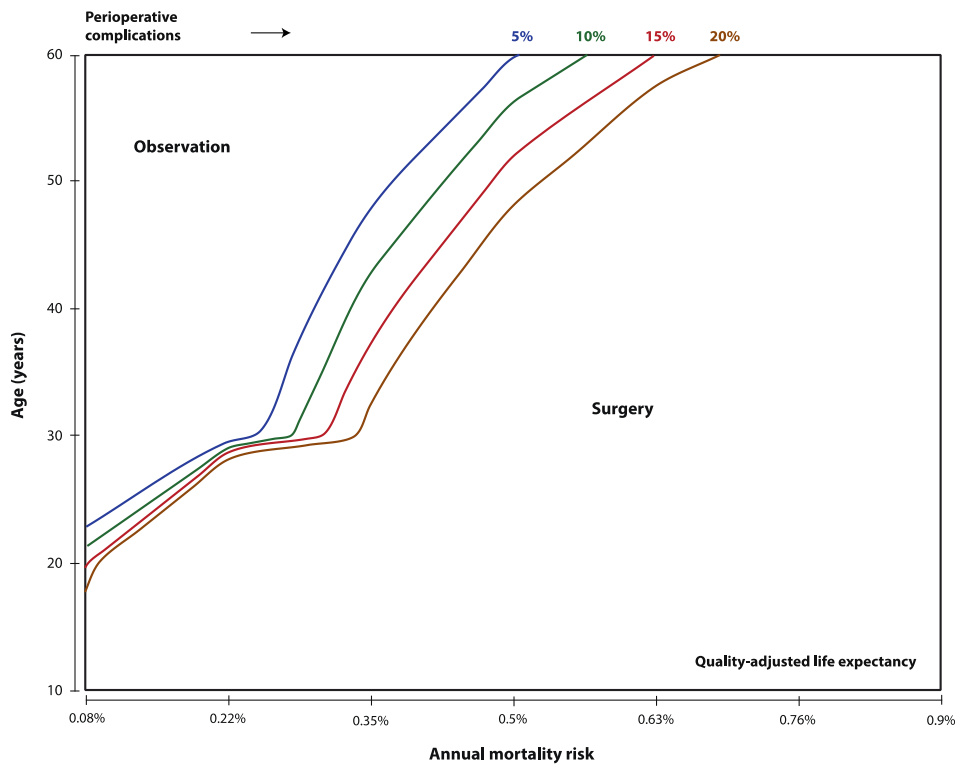
For the purpose of this study, conservative estimates with a wide variability for sensitivity analyses were used. The annual mortality risk used for the model and the range used for sensitivity analyses were 0.35% (0.08%-0.9%) for ALCA and 0.02% (0.0035%-0.06%) for ARCA.

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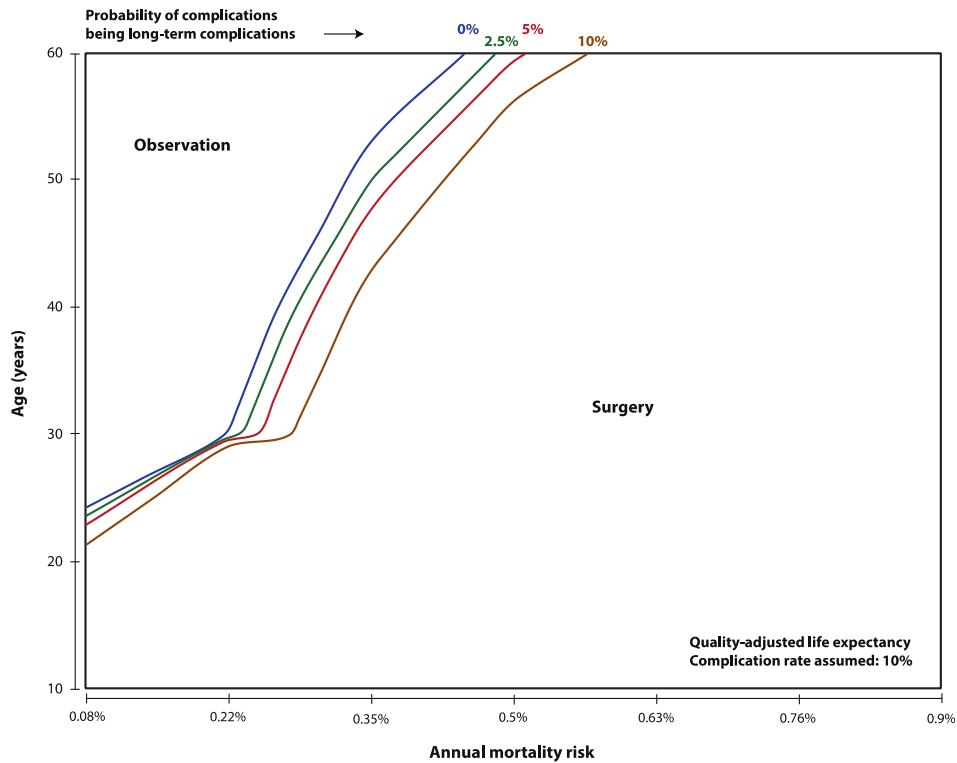


**FIGURE E1.** Effect of risk of sudden cardiac death and reduction in all-cause mortality by exercising according to guidelines on patients with anomalous left coronary artery by age. These panels illustrate how varying the risk of sudden cardiac death (X-axis) and the effect of exercising according to guidelines on all-cause mortality (Y-axis) have on life expectancy of patients with an anomalous left coronary artery. Each panel represents a different age group. The colored areas on each panel represent the optimal strategy given that set of values. For patients 10 years of age, surgery is the preferred strategy unless performing exercise according to guidelines is assumed to just have a minimal (<3%) effect on all-cause mortality, in which case exercise restriction becomes the preferred strategy. For older patients, either surgery or observation is the preferred strategy (depending on assumed risk of sudden cardiac death), unless exercise is assumed not to have a significant effect on all-cause mortality.



**FIGURE E2.** Sensitivity analysis for quality-adjusted life expectancy for anomalous left coronary artery based on annual risk of sudden cardiac death, age at presentation, and risk of developing perioperative complications. The Figure depicts the effect of annual risk of sudden cardiac death (X-axis), age at presentation (Y-axis), and risk of developing perioperative complications on quality-adjusted life expectancy. Each colored curve represents a different value for risk of developing perioperative complications. Observation is favored for the set of values that lie to the left and above the respective curve. Surgery is the preferred strategy for values that lie to the right and below each curve.

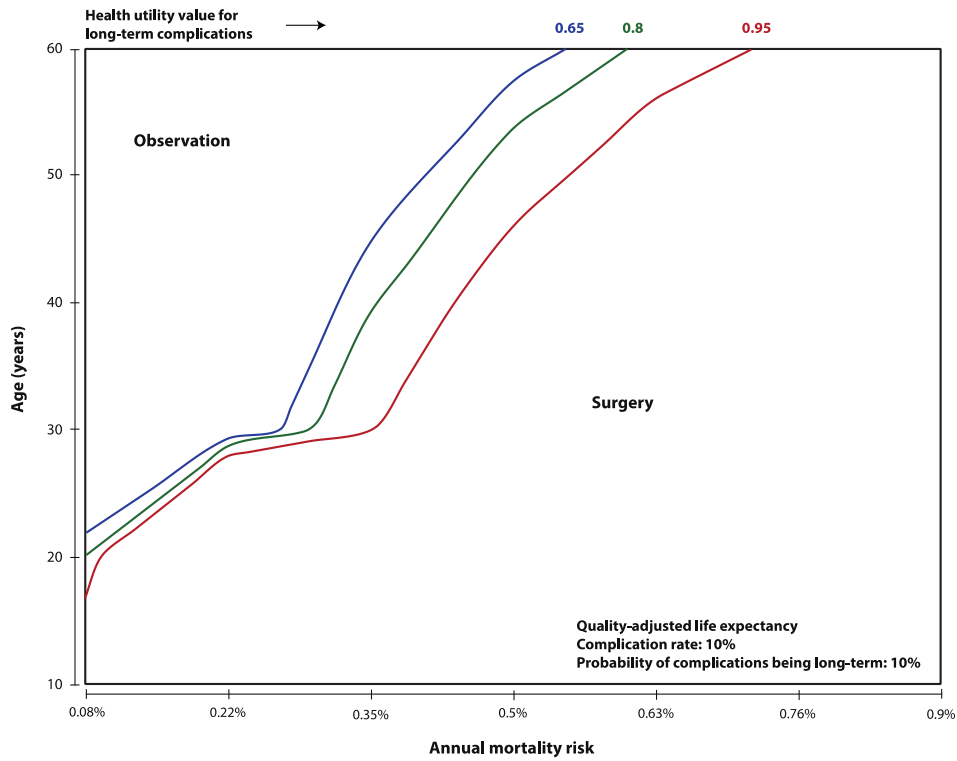
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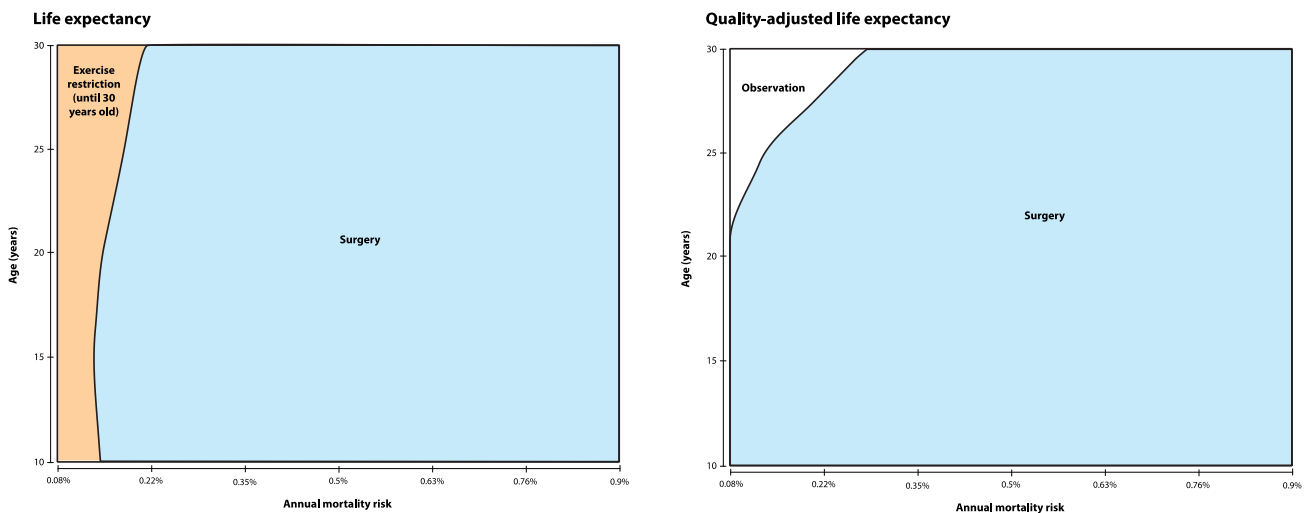
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**FIGURE E3.** Sensitivity analysis for quality-adjusted life expectancy for anomalous left coronary artery based on annual risk of sudden cardiac death, age at presentation, and the probability of long-term complications. This Figure assesses the effect of annual risk of sudden cardiac death (X-axis), age at presentation (Y-axis), and the probability that the complications developed by the patient after surgery are long-term complications (instead of short-term complications). The likelihood of developing perioperative complications after surgery was fixed at 10% for this analysis. The health utility for long-term complications was assumed to be 0.85 (see text for details). Values to the left and above each curve favor observation while values to the right and below the curve favor surgery.

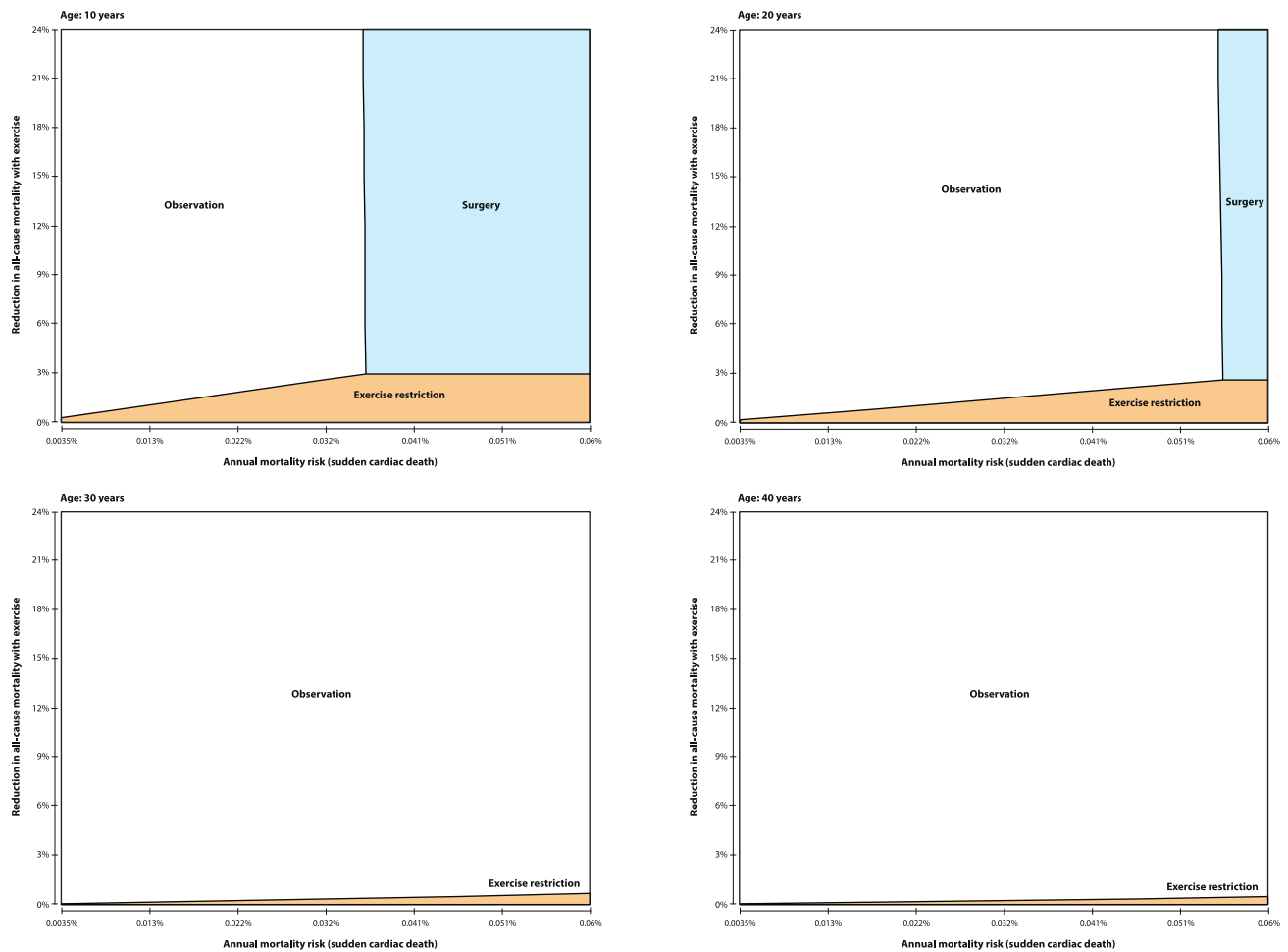
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**FIGURE E4.** Sensitivity analysis for quality-adjusted life expectancy for anomalous left coronary artery based on annual risk of sudden cardiac death, age at presentation, and quality of life after long-term complications. This Figure illustrates the effect of annual risk of sudden cardiac death (X-axis), age at presentation (Y-axis), and quality of life for long-term complications, as assessed by health utility values. To perform this analysis, the health utility after long-term complications was varied from 0.65 to 0.95 (a health utility of 1 is the equivalent of perfect health and a health utility of 0 is the equivalent of death). The perioperative complication rate was fixed at 10% and 10% of all complications were assumed to be long-term complications. Values to the left and above each particular curve favor observation while values to the right and below each curve favor surgery.

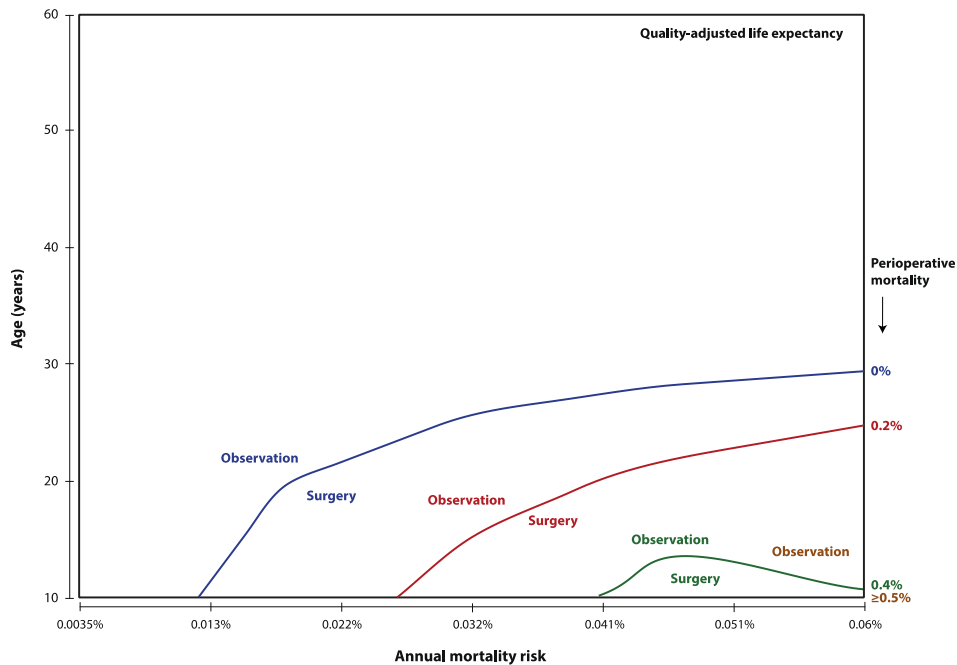


**FIGURE E5.** Sensitivity analysis for patients 10-30 years of age with anomalous left coronary artery if exercise restriction is applied only until 30 years of age. These panels represent the optimal strategy based on life expectancy (*left panel*) and quality-adjusted life expectancy (*right panel*) while varying the annual risk of sudden cardiac death and age at presentation for patients 10-30 years of age, if exercise restriction is only applied while patients are <30 years old. Each colored area corresponds to the optimal strategy for the particular set of values. Based on life expectancy, exercise restriction is the optimal strategy only for patients with the lowest annual mortality risk but the advantage disappears when taking into account quality of life.

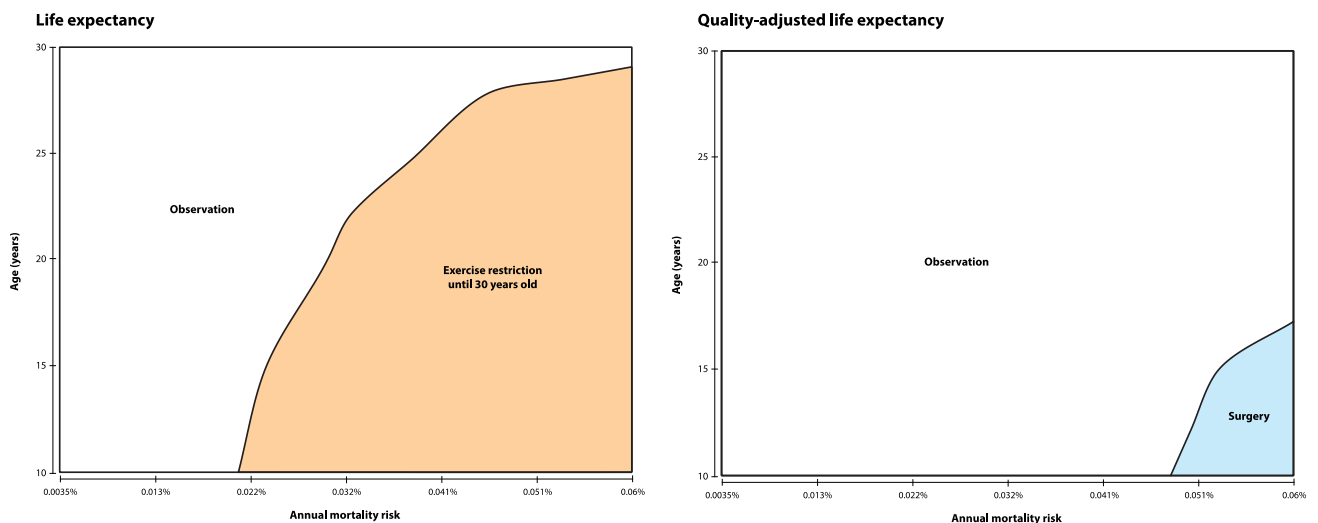


**FIGURE E6.** Effect of risk of sudden cardiac death and reduction in all-cause mortality by exercising according to guidelines on patients with anomalous right coronary artery by age. These panels represent the optimal strategy based on life expectancy while varying the risk of sudden cardiac death (X-axis), the effect of exercising according to guidelines on all-cause mortality (Y-axis), and age. Each panel represents a different age group from 10 to 40 years of age. Each colored area corresponds to the optimal strategy based on that set of values. Observation is the dominant strategy for most scenarios. Surgery is the optimal strategy for young patients if the risk of sudden cardiac death is assumed to be high. Exercise restriction is an optimal strategy only if exercise is assumed not to have a significant effect on all-cause mortality (significantly below the predetermined range).





**FIGURE E7.** Effect of risk of sudden cardiac death, age at presentation, and perioperative mortality on quality-adjusted life expectancy for patients with anomalous right coronary artery. This sensitivity analysis depicts the effect of risk of sudden cardiac death (X-axis), age at presentation (Y-axis), and perioperative mortality on quality-adjusted life expectancy for patients with anomalous right coronary artery. Each colored curve represents a different value of perioperative mortality. Values to the left and above the particular curve favor observation while values to the right and below the curve favor surgery. Observation is the preferred strategy for all patients if perioperative mortality is assumed to be  $\geq 0.5\%$ .



**FIGURE E8.** Sensitivity analysis for patients 10-30 years of age with anomalous right coronary artery if exercise restriction is applied only until 30 years of age. These panels represent the optimal strategy based on life expectancy (left panel) and quality-adjusted life expectancy (right panel) for patients 10-30 years old if exercise restriction is only applied while patients are  $< 30$  years of age. Each colored area corresponds to the optimal strategy for the particular set of values. When analyzing life expectancy, exercise restriction was the optimal strategy for patients with a higher annual mortality risk, while observation remained the optimal strategy for the rest of the patients. When taking into account quality of life, exercise restriction was not favored under any of the values, while observation and surgery were optimal strategies depending on the set of values used for annual mortality risk and age at presentation.