Prognosis After Aortic Valve Replacement With the Carpentier-Edwards Pericardial Valve: Use of Microsimulation

John P. A. Puvimanasinghe, MD, PhD, Johanna J. M. Takkenberg, MD, PhD, Marinus J. C. Eijkemans, PhD, Ewout W. Steyerberg, PhD, Lex A. van Herwerden, MD, PhD, Gary L. Grunkemeier, PhD, J. Dik F. Habbema, PhD, and Ad J. J. C. Bogers, MD, PhD

Departments of Cardiothoracic Surgery and Public Health, Erasmus Medical Center, Rotterdam, the Netherlands, and Providence Health System, Portland, Oregon

Background. The second-generation Carpentier-Edwards pericardial valve (Edwards Lifesciences LLC, Irvine, CA) is widely used for aortic valve replacement. However, knowledge on the long-term outcomes of patients after valve implantation is incomplete. We used microsimulation to calculate the long-term outcome of any given patient after aortic valve replacement with the Carpentier-Edwards pericardial valve.

Methods. A meta-analysis of 8 reports on aortic valve replacement with the Carpentier-Edwards pericardial valve (2,685 patients; 12,250 patient years) was used to estimate the hazards of valve-related events other than structural valvular deterioration. Structural valvular deterioration was described by age-dependent Weibull curves calculated from 18-year follow-up, premarket approval, Carpentier-Edwards pericardial primary data. These estimates provided the input data for the parameters of the microsimulation model, which was then used to calculate the outcomes of patients of different ages after valve implantation. The model estimates of survival were validated using two external data sets.

Results. The Weibull analysis estimated a median time to reoperation for structural valvular deterioration ranging from 18.1 years for a 55-year-old male to 23.2 years for a 75-year-old male. For a 65-year-old male, microsimulation calculated a life expectancy and event-free life expectancy of 10.8 and 9.1 years, respectively. The lifetime risk of at least one valve-related event was 38% and that of reoperation due to structural valvular deterioration 17%, respectively, for this patient. The model estimates of survival showed good agreement with external data.

Conclusions. Microsimulation provides detailed insight into the long-term prognosis of patients after aortic valve replacement. The Carpentier-Edwards pericardial valve performs satisfactorily and offers a low lifetime risk of reoperation due to structural valvular deterioration, especially for elderly patients requiring aortic valve replacement.

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Stented bovine pericardial bioprosthetic heart valves, which offer an alternative to the glutaraldehyde-treated porcine valves, have been used for aortic valve replacement (AVR) for over 30 years. After disappointing results with the first-generation Ionescu-Shiley valve (Shiley, Inc, Irvine, CA) [1, 2], the second-generation Carpentier-Edwards (Perimount) pericardial bioprosthesis (Edwards Lifesciences LLC, Irvine, CA) was introduced in 1982 and obtained US Food and Drug Administration (FDA) approval in 1991. It is currently the most widely used pericardial valve worldwide and the only pericardial valve approved by the FDA [3].

Compared with its predecessors, the Carpentier-Edwards pericardial valve incorporates significant design modifications including improved tissue fixation and a sophisticated method of mounting leaflets on a flexible elgiloy metal stent [4]. This has resulted in the reported excellent hemodynamics and durability of the valve [5, 6]. However, knowledge on the long-term outcome of patients after valve replacement with Carpentier-Edwards pericardial valves and the lifetime risk of valve-related events is still incomplete. This information would be useful for comparison of the Carpentier-Edwards pericardial valve with other bioprostheses, especially the more commonly used porcine valves, and in the choice of a valve for the individual patient.

We combined a meta-analysis and other data with microsimulation to provide insight into the age-related life expectancy and lifetime risks of valve-related events after AVR with the Carpentier-Edwards pericardial valve.

Material and Methods

Meta-Analysis

The estimates of hazards of valve-related events, other than structural valvular deterioration (SVD), were obtained from a meta-analysis of selected literature. For this

purpose, we conducted a literature search of the Medline database using the PubMed interface for the period January 1995 to December 2002, to identify reports that examined the outcomes of patients after AVR with the Carpentier-Edwards pericardial valve. The text words used for the search were "Carpentier-Edwards" and the terms "bioprosthesis" and "tissue heart valves" in combination with "bovine" and "pericardial," respectively. The titles and abstracts of the search results were screened for reports that contained data on valve-related events, their consequences, and long-term survival of patients after AVR. The references in these reports were cross-checked for other potentially relevant studies, which finally resulted in 30 published reports.

We then applied six criteria to these reports in order to obtain a similar group of studies. These criteria were the following: (1) valve sizes 19–31 mm, not focusing on a particular size or range; (2) patients greater than 15 years of age, not focusing on a particular age group; (3) predominantly first time AVR; (4) AVR with or without coronary artery bypass grafting (CABG), excluding other valve replacements; (5) predominantly patients who do not require long-term anticoagulation; and (6) no overlapping patient populations. This excluded 22 reports, leaving 8 reports for further analysis [6–13]. Valve-related events in these reports were defined according to the guidelines of Edmunds and colleagues [14, 15]. The 8 reports were reviewed in detail to obtain data required for calculation of the input parameters of the microsimulation model.

Assuming a constant hazard over time, weighted mean estimates of linearized annual occurrence rates were calculated for valve thrombosis, thromboembolism, hemorrhage, and nonstructural dysfunction, respectively. The risk of endocarditis was assumed to take 2 phases of constant hazard, the hazard within six months of implantation greater than in the subsequent period. Hence, a 2-period exponential model was fitted to the pooled freedom-from-endocarditis curve obtained by combining the individual curves in the selected reports [16]. The combined mortality and reoperation rates were also calculated.

Analysis of Primary Data to Estimate Hazard of SVD

The risk of SVD in a bioprosthesis depends on the age of the patient at implantation and on the time elapsed since valve replacement. The risk decreases with implantation age, but increases with time since implantation. The estimate of the hazard of SVD was obtained by fitting age-dependant Weibull curves on primary data [17, 18]. The Weibull formula for the freedom from SVD is:

$$S(t) = e^{-(t/\sigma)^{\beta}},$$

where S(t) indicates the freedom from SVD at time t while σ and β denote the scale and shape parameters of the model. The shape parameter reflects the changing risk of SVD over time. We used a data set of 267 patients, implanted with Carpentier-Edwards pericardial prostheses between 1981 and 1984, to calculate the parameters of

the Weibull model. The SVD was diagnosed at explant for this analysis. The mean age of the patients at implantation was 65 ± 12 years, 64% were men, and the follow-up extended to 18 years. These patients formed part of the original four-center premarketing clinical investigation conducted for the US FDA.

The Microsimulation Model

The microsimulation model is a computer application that simulates the life of a patient after AVR with a given valve type, taking into account the morbidity and mortality events that the patient may experience. The mortality of a patient is composed of the mortality experience of the general population, mortality due to valve-related events and an "additional mortality" component that is associated with underlying valve pathology, left ventricular function, and valve replacement procedure, respectively [19].

The mortality experience of the general population was incorporated into the model by means of the life table of the relevant population; American males in this analysis. Mortality due to valve-related events was incorporated using the data obtained from the meta-analysis. We previously estimated age-specific and sex-specific hazard ratios to represent the effect of additional mortality. They were 2.9, 1.8, 1.2, and 0.8 for male patients aged 45, 55, 65, and 75 years, respectively [20]. Operative mortality was estimated at 1.5% for a 40-year-old patient, increasing with odds ratios of 1.022 per additional year of age and 1.7 per reoperation. The model calculates patient outcomes by superimposing the morbidity and mortality estimates of valve-related events on the other two mortality components. For each calculation, 10,000 simulations were performed. In principle, the model can be applied for any valve type and for a patient of either sex. For this analysis, the model was used to calculate outcomes of male patients after AVR with the Carpentier-Edwards pericardial valve. A detailed account of the microsimulation structure and methodology has been given previously [21, 22].

Validation

To assess the validity of the microsimulation model calculations, we compared the age-specific and sex-specific survival calculations of the microsimulation model with two separate data sets; the Carpentier-Edwards pericardial valve data set and the Carpentier-Edwards standard valve data set, both from the Providence Health System, Portland, Oregon. The pericardial data contain 1,021 patients who were implanted with the prosthesis between 1991 and 2002. The mean age of the patients was 74.3 years. We also compared the age-specific and sex-specific model outputs with the Portland 25-year follow-up data on patients who underwent AVR with the Carpentier-Edwards "standard" bioprosthesis [23].

Sensitivity Analysis

A one-way sensitivity analysis was performed to investigate the effect of uncertainty in the parameter estimates. This was done by varying each individual parameter,

Table 1. Pooled Incidence of Valve-Related Events and Their Outcomes After Aortic Valve Replacement With Carpentier-Edwards Pericardial Valves

Valve-Related Events	Events (n)	Hazard Rate (per 100 Patient Years)	Outcome	
			Death Rate	Reoperation Rate
Valve thrombosis	2	0.03	0.50	0.50
Thromboembolism	166	1.35	0.23	0
Hemorrhage	53	0.43	0.41	0
Endocarditis	70	1.76/0.54[a]	0.38	0.17
Nonstructural dysfunction	4	0.13	0	0.50
Structural valvular deterioration	55	[b]	0.09	0.85

[a] A two-period exponential model was constructed for the risk of endocarditis during and after the first six months after aortic value replacement;
[b] An age-dependent Weibull model was constructed using the original premarketing clinical investigation data set.

while keeping the other estimates fixed. Variation of the estimates of valve-related events by their 95% confidence intervals yielded only very small changes in the long-term outcomes. Therefore, for this analysis we defined larger ranges by increasing and decreasing the baseline estimates by 25%. A plausible range was also considered for the hazard ratio representing the additional mortality component.

Results

Meta-Analysis

The eight reports selected for the meta-analysis comprised 2,685 Carpentier-Edwards pericardial valve recipients and 12,250 patient-years of follow-up, respectively. Sixty-two percent of the patients were male and the mean age at implantation was 67 years. Concomitant CABG was performed on about 30% of the patients, although differences between the component studies were noted. The pooled incidence of valve-related events and their outcomes are given in Table 1. As depicted in Table 1, thromboembolism occurred with an annual incidence of 1.35% per patient-year while the incidence of endocarditis was 1.76% per patient-year in the first 6 months after implantation, decreasing threefold in the subsequent period.

Structural Valvular Deterioration

The value of the scale (σ) parameter of the Weibull model, fitted to represent SVD in the pericardial valves, depends on age: $\sigma = e^{2.31 + 0.0124 * age}$. Extension of the model with a quadratic function for age was found to be not significant and hence, a linear function for age was assumed. The shape parameter (β) = 3.76. With these parameters, the median time to reoperation due to SVD in the pericardial valves was 18.1, 20.5, and 23.2 years, respectively, for 55-, 65-, and 75-year-old male patients.

Microsimulation Model Output

The microsimulation model calculated actuarial patient survival, reoperation-free survival, and event-free survival of male patients of different ages at valve implantation. The areas under the respective curves give the life expectancy (LE), reoperation-free life expectancy (RFLE),

and the event-free life expectancy (EFLE). For a 65-year-old male patient for example, the LE was 10.8 years, RFLE was 10.0 years, and the EFLE was 9.1 years, respectively, after implantation with a Carpentier-Edwards pericardial valve. The LE, RFLE, and EFLE for men at different ages of valve implantation are given in Figure 1.

The microsimulation model also calculates the "actual" or lifetime risks of valve-related events and reoperation after valve implantation (Fig 2). The lifetime risk of a reoperation due to SVD reduced with advancing age of implantation and was 17% and 5%, respectively, for 65- and 75-year-old males.

We further compared the LE of male patients who received Carpentier-Edwards prostheses with that of corresponding males of the general American population. As depicted in Figure 3, the relative LE increased with advancing age of implantation from 61% at 50 years to about 95% for a 75-year-old patient. The relative LE of a hypothetical valve recipient who was immune from valve-related events was also analyzed. It too increased with advancing age of implantation and was greater than 100% that of a person in the general population at 75 years. The difference between the two curves represents
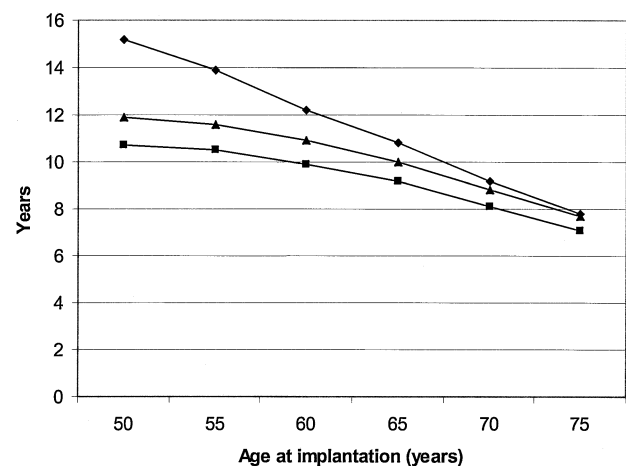

Fig 1. Life expectancy (LE; ◆), reoperation-free LE (▲), and event-free LE (■) for men after aortic valve replacement with the Carpentier-Edwards pericardial valve.
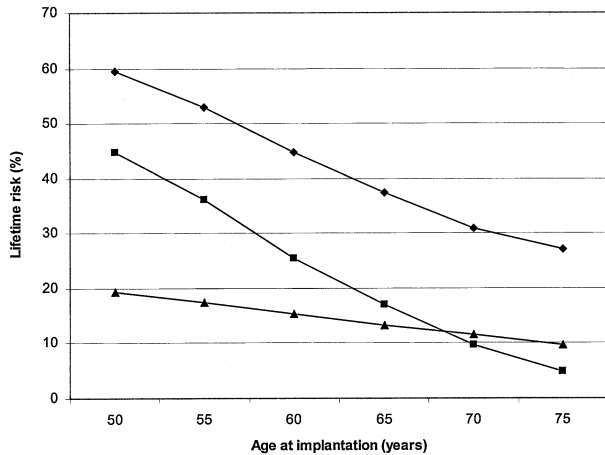
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Fig 2. Lifetime risk of at least one valve-related event (♦), reoperation due to structural valvular deterioration (■), and thromboembolism (▲) for males after aortic valve replacement.

Fig 4. Comparison of microsimulation model (MSM) outputs and corresponding Portland Carpentier-Edwards standard valve survival for 55- (top), 65- (middle), and 75- (bottom) year-old males after isolated aortic valve replacement. ♦ = MSM; - = Portland.

the mortality associated with valve-related events. The difference between the curve for the hypothetical patient and the general population standard (ie, 100%) represents the additional mortality component, which was incorporated into the microsimulation model by way of hazard ratios.

Validation

The actuarial 7-year survival of 60- to 69-year-old males in the Portland pericardial data, who survived the AVR procedure, was 69%. The corresponding microsimulation estimate for a 65-year-old male was 68%. The actuarial 8-year survival of 70- to 79-year-old males was 54%, compared with the 8-year estimate of 47% calculated by the microsimulation model. The small numbers at risk and the absence of events precluded comparison up to 10 years and in the 50- to 59-year-old age group, respec-

tively. Further, the survival outputs of the microsimulation model for males of different ages compared favorably with the corresponding curves of the Carpentier-Edwards standard Portland experience, through 25 years postimplantation (Fig 4).

Sensitivity Analysis

The LE and EFLE of a 65-year-old male patient, on individually increasing and decreasing the baseline valve-related event estimates by 25%, are given in Table 2. Variation in the median time to SVD and the hazard ratio representing additional mortality had the most effect on the life expectancies.

Comment

The pericardial bioprostheses, which have been in use for more than 30 years [4], are considered an important alternative to the porcine valves. The pericardial bioprostheses are fabricated using bovine pericardium, which is sewn into a valvular configuration on a stented frame. The first commercially available pericardial valve, the Ionescu-Shiley valve was abandoned in 1988 due to a high incidence of valvular deterioration characterized by leaflet tears and valve incompetence [2, 24]. Of the second-generation pericardial valves, the Carpentier-Edwards pericardial valve has shown better results than the other valve in its class, the Pericarbon pericardial bioprosthesis (Sorin Biomedica, Italy) [8]. The former, which received FDA approval in 1991 and is widely implanted in many centers at present, was chosen to represent the pericardial valves in this analysis.

We used a microsimulation model to provide insight into the age- and sex-related life expectancy and lifetime risks of valve-related events after AVR with the Carpentier-Edwards pericardial valve. Simulation techniques, by modeling complex outcome paths that result from many competing risks, provide a useful adjunct to stan-
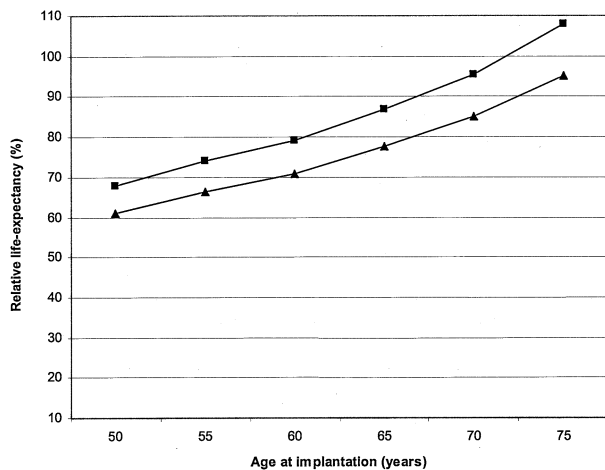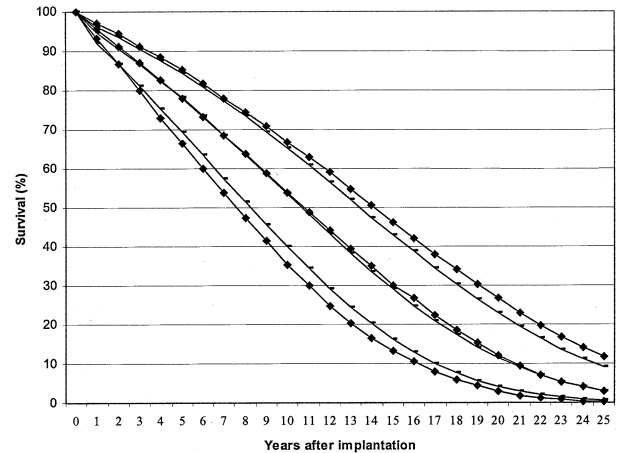

Fig 3. Life expectancy of males after aortic valve replacement, as a proportion of the life expectancy of comparable males in the general population. ▲ = with valve-related events; ■ = immune from valve-related events.

Table 2. Summary of Sensitivity Analysis for a 65-Year-Old Male Patient After Aortic Valve Replacement

Parameter	Baseline Estimate	Plausible Range[a]		Life Expectancy (Years)		Event-Free Life Expectancy (Years)	
		Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable
Valve thrombosis	0.03	0.02	0.04	10.8	10.8	9.1	9.1
Thromboembolism	1.35	1.01	1.69	10.9	10.7	9.3	8.9
Hemorrhage	0.43	0.32	0.54	10.9	10.7	9.2	9.0
Endocarditis	1.76/0.54	1.32/0.41	2.2/0.68	10.8	10.7	9.2	9.0
Nonstructural dysfunction	0.13	0.10	0.16	10.8	10.8	9.1	9.1
SVD[b]	20.5 years	25.6 years	15.4 years	10.9	10.6	9.4	8.4
Additional mortality (hazard ratio)	1.2	1.1	1.3	11.2	10.4	9.4	8.8

[a] The baseline estimates (except for the hazard ratio) were increased and decreased by 25% to estimate the plausible range; [b] Median time to structural valvular deterioration.

(The Life Expectancy and Event-free life Expectancy were 10.8 and 9.1 years for a 65 year-old male patient.)

SVD = structural valvular deterioration.

dard statistical methods in calculating the outcomes of patients after AVR. Data required to parameterize the microsimulation model were obtained by two methods. Estimates of the occurrence of valve-related events were obtained by a meta-analysis of published reports. An advantage of pooling data was that it represented the experience of many centers. The SVD was incorporated into the microsimulation model by age-dependent Weibull curves. Grunkemeier and colleagues [25] have shown that the Weibull distribution was efficient in summarizing SVD in biological valves. However, they stressed that at least 12 years of follow-up was needed to provide reliable estimates. We used data on the Carpentier-Edwards pericardial valve, with an 18-year follow-up, to calculate the Weibull parameters. Accordingly, the median time to reoperation due to SVD for 55-, 65- and 75-year-old males implanted with pericardial valves was 18.1, 20.5, and 23.2 years, respectively. These estimates may be used to compare the durability of pericardial valves with the porcine valves and with newer bioprostheses.

The LE, RFLE, and EFLE for males of different ages as estimated by the microsimulation model, are depicted in Figure 1. Mortality of an AVR patient who survives the operation is greater than that of a matched person in the general population. This excess mortality is due to valve-related mortality and an additional mortality. The additional mortality, which may be related to underlying valve pathology, left ventricular residual hypertrophy, and functional abnormality and the valve replacement procedure, is not clearly defined and estimated at present. Hence, we had previously estimated age- and sex-specific hazard ratios to represent the effect of additional mortality in the model, using data from a follow-up study on stented porcine bioprostheses [26]. Kvidal and colleagues [27], who investigated the excess mortality after heart valve replacement, described an increasing excess hazard during follow-up and a decreasing excess hazard with advancing age of implantation. This supports a "multiplicative" excess mortality, which was a

structural assumption in our model. The use of an "additive" model may increase LE estimates, especially in patients under 70 [28, 29].

We have not addressed the possibility that the additional mortality component may vary with different valve types and valve sizes, which would necessitate different hazard ratios to represent that component. In this regard, the Carpentier-Edwards pericardial valve has been shown to be less obstructive in the aortic position than the Carpentier-Edwards standard and supraannular valves [5, 30]. This may translate to greater and more rapid regression of left ventricular hypertrophy after AVR with a pericardial valve [31], thus conferring a higher survival benefit than presently calculated by the microsimulation model. Hence, we have used sensitivity analysis to underscore the importance of excess mortality on the outcomes of patients after AVR. The effect on LE and EFLE of a 65-year-old male, caused by lowering of the hazard ratio, is given in Table 2.

Actuarial analysis is commonly used for the analysis of valve-related events that are not necessarily fatal. Such analysis describes the risk for patients provided they were immortal. Hence, actuarial analysis overestimates the risk of SVD, this error being magnified with increasing age. A more relevant estimate is the cumulative incidence, termed actual analysis, which calculates the percentage of patients who will experience an event before they die [32, 33]. It provides a better estimate of the durability of a bioprosthesis, especially in the elderly. The microsimulation model calculates the actual lifetime risk of valve-related events. For a 65- and 75-year-old male for example, the lifetime risk of reoperation due to SVD is 17% and 5%, respectively.

The American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease [34] recommends a bioprosthesis for those older than 65 years, based on the major reduction in SVD and the increased risk of hemorrhage in this age group. Birkmeyer and colleagues [28], who used a Markov state-transition model to simulate the

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outcomes after AVR with a mechanical valve, calculated a 20% or more lifetime risk of hemorrhage in a 65-year-old patient. Considering our model calculation for the lifetime risk of reoperation, a lowering of the 65-year age threshold for implantation of a pericardial valve may be considered, especially in younger patients whose life expectancy is reduced by concomitant disease.

Limitations of this study included certain structural assumptions in the microsimulation model and the uncertainty associated with the input parameters. For example, a constant hazard was assumed for valve thrombosis, thromboembolism, hemorrhage, and nonstructural dysfunction. However, these hazards may vary with increasing age and age at implantation. Based on a previous study [35], we assumed endocarditis to take two phases of constant risk, the initial risk up to 6 months after implantation, greater than in the subsequent period. However, comparisons of different time periods of implantation have shown a significant decline in early prosthetic endocarditis in recent years [36]. Many other patient-related and surgery-related factors have been shown to influence overall survival after AVR [37–40]. However, at present the model calculates outcome for an average risk profile only. The moderate numbers of events for some valve-related events and possible publication bias give a degree of uncertainty to the input parameters of the model.

In conclusion, we have described the use of microsimulation in providing detailed insight into outcomes after AVR with the Carpentier-Edwards pericardial valve. This information can be useful for patient counseling and in selecting the optimal valve prosthesis for a given patient.

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Online Discussion Forum

Each month, we select an article from the *The Annals of Thoracic Surgery* for discussion within the Surgeon's Forum of the CTSNet Discussion Forum Section. The articles chosen rotate among the six dilemma topics covered under the Surgeon's Forum, which include: General Thoracic Surgery, Adult Cardiac Surgery, Pediatric Cardiac Surgery, Cardiac Transplantation, Lung Transplantation, and Aortic and Vascular Surgery.

Once the article selected for discussion is published in the online version of *The Annals*, we will post a notice on the CTSNet home page (**http://www.ctsnet.org**) with a **FREE LINK** to the full-text article. Readers wishing to comment can post their own commentary in the discussion forum for that article, which will be informally moderated by *The Annals* Internet Editor. We encourage all surgeons to participate in this interesting exchange and to avail themselves of the other valuable features of the CTSNet Discussion Forum and Web site.

For September, the article chosen for discussion under the Pediatric Cardiac Dilemma Section of the Discussion forum is:

Randomized Comparison Between Normothermic and Hypothermic Cardiopulmonary Bypass in Pediatric Open-Heart Surgery
Massimo Caputo, MD, Simon Bays, FRCS, Chris A. Rogers, PhD, Ash Pawade, FRCS, Andrew J. Parry, FRCS, Saadeh Suleiman, PhD, and Gianni D. Angelini, FRCS

Tom R. Karl, MD
The Annals *Internet Editor*
UCSF Children's Hospital
Pediatric Cardiac Surgical Unit
505 Parnassus Ave, Room S-549
San Francisco, CA   94143-0118
Phone: (415) 476-3501
Fax: (212) 202-3622
e-mail: karlt@surgery.ucsf.edu