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Guglielmi Detachable Coil Embolization for Unruptured Aneurysms in Nonsurgical Candidates: A Cost-effectiveness Exploration

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PURPOSE: **We calculated the incremental cost-utility ratio for Guglielmi detachable coil (GDC) embolization versus no therapy for unruptured intracranial aneurysms considered inappropriate for surgical clipping procedures.**

METHODS: **Decision tree and Markov analyses that employ cohort simulation were applied to determine the incremental cost-utility ratio of GDC embolization versus no therapy for unruptured cerebral aneurysms. Clinical values required as input data were estimated from the literature for the following variables: relative frequencies of complete aneurysmal occlusion, partial aneurysmal occlusion, and attempted coiling (no coils detached); morbidity and mortality of GDC embolization; frequency, morbidity, and mortality of spontaneous aneurysmal rupture in untreated and GDC-embolized aneurysms; annual rate of recanalization of GDC-embolized aneurysms; quality of life when knowingly living with untreated or GDG-embolized aneurysms and of living with fixed neurologic deficit; costs of GDC embolization, spontaneous aneurysmal rupture, stroke, and rehabilitation; and discount rate. Cost-utility ratios below $50 000 per quality-adjusted life year saved were considered acceptable. Sensitivity analyses were performed for all relevant input variables.**

RESULTS: **Baseline input values resulted in acceptable cost-utility ratios for GDC embolization of unruptured intracranial aneurysms. These ratios remained within acceptable limits across wide ranges of various input parameters. Cost-effectiveness was markedly affected by the natural course of unruptured, untreated aneurysms; rates of spontaneous rupture greater than 2% per year resulted in favorable cost-utility ratios that were relatively unaffected by variation in GDC efficacy, while rates of rupture less than 1% per year resulted in unfavorable ratios that were highly dependent on GDC efficacy. Many of the GDC efficacy indexes, such as rate of failed coiling, early recanalization, and progressive aneurysmal thrombosis, have mild effects on the cost-utility ratios. GDC complication rate as well as life expectancy had moderate effects on the analysis. The influence of late aneurysmal recanalization was mild unless high rates of rupture for partially coiled aneurysms were applied. Suboptimal clip placement resulting from the presence of GDC coils within a ruptured aneurysm had no demonstrable consequence on cost-utility ratios.**

CONCLUSIONS: **The single most influential variable determining the cost-effectiveness of GDC embolization in our analysis was the natural course of untreated aneurysms. Other important variables included GDC-related morbidity and life expectancy at the time of GDC embolization.**

Guglielmi detachable coils (GDCs) represent a major advance in the endovascular approach to cerebral aneurysms. Approved by the Food and Drug Administration in September 1996 for the therapy of unclippable aneurysms, the coils are being used by an increasing number of practitioners worldwide (1–7). However, long-term outcomes data for the GDC are relatively sparse: hence, the precise role for the coils among the various therapies available for treatment of cerebral aneurysms remains to be defined.

Cost-effectiveness analyses are being applied to numerous medical and surgical interventions to determine the most rational allocation of health care expenditures, including those associated with various

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neurovascular disorders (8–12). For example, a recent article reports that surgical clipping of asymptomatic, unruptured cerebral aneurysms may be cost-effective only if the quality of a patient's life is in great measure adversely affected by the knowledge of an unruptured aneurysm (8). Such cost-effectiveness analyses rely upon the availability of exquisite input parameters derived from clinical outcomes information, since the results of these analyses are only as valid as the data used in their construction.

An alternative application of cost-effectiveness analyses is in the evaluation of emerging technologies. Decision trees (13) and Markov models (14) are constructed on the basis of the clinical algorithm containing the new technology, and cost-effectiveness is estimated through cohort simulation applying the best-available information about the new technology. The input data are then varied in sensitivity analyses to identify the clinical descriptors with the greatest influence on cost-effectiveness ratios, thereby isolating the clinical data that must be most precisely defined before the cost-effectiveness of the new technology can be specified with confidence.

GDC embolization of cerebral aneurysms represents an emerging technology that can benefit from cost-effectiveness analysis. The input variables necessary to define the cost-effectiveness of GDC embolization are myriad, and include rates of failed coiling and of partial and complete aneurysmal occlusion; types and frequencies of procedural complications; rates of aneurysmal recanalization after GDC embolization; efficacy of complete and partial aneurysmal occlusion in diminishing rates of aneurysmal rupture; and costs of the procedure.

We present a cost-effectiveness analysis of GDC embolization of unruptured, asymptomatic cerebral aneurysms. Our primary goal is not to determine the cost-effectiveness of GDC embolization precisely but rather to explore the input variables of greatest importance in determining the cost-effectiveness of the device, in order that future health economics research can focus on the most relevant clinical parameters of this treatment.

Methods

Derivation of Cost-effectiveness Ratios

We determined the incremental cost-effectiveness ratio of GDC embolization versus no therapy for unruptured, asymptomatic cerebral aneurysms in nonsurgical candidates. The calculation of incremental cost-effectiveness proceeds as follows:

Incremental cost-utility ratio, GDC embolization versus no therapy =

(cost of GDC embolization − cost of no therapy)/

(utility of GDC embolization − utility of no therapy)

Utility is applied as a metric of *effectiveness*, such that *cost-utility ratio* may be considered a measure of cost-effectiveness for our analysis. The calculation of costs and utilities for both treatment options requires specification of Markov chains to define states and possible transitions, formulation of decision tree algorithms to determine the initial conditions of the patient cohorts, and simulation of the model to determine discounted costs and weighted, discounted utilities. Utilities are quantified by using quality factors, which range from 1.0 (perfect health) to 0.0 (dead) (15). Quality factors and time spent within a given health state are used to calculate quality-adjusted life years (QALYs) saved with GDC embolization versus no treatment. We use a societal perspective for costs and utilities, and apply a discount rate of 5% in our baseline analysis (16–18). Microsoft Excel version 5.0 (Microsoft Corp, Redmond, Wash) is used for the simulation and all computation.

Markov Models

The evolution of a patient's disease and treatment can be modeled by a discrete-time Markov chain, defined by a set of states with given initial conditions and specified state-to-state transition probabilities. Separate models are developed for the no treatment and GDC embolization cohorts (Fig 1).

No Treatment Cohort.—The no treatment cohort is modeled as a four-state Markov chain (Fig 1A). The states are as follows: I, unruptured, untreated aneurysm; II, full recovery after aneurysmal rupture during the cohort simulation; III, neurologic deficit after aneurysmal rupture during the cohort simulation; and IV, death. For purposes of orientation we place within the Markov chain a transition event (subarachnoid hemorrhage) to model the occurrence of aneurysmal rupture in a given cycle. State I may transition via subarachnoid hemorrhage to states II, III, or IV. The portion of the cohort in state II (postoperative, intact) is considered cured, without risk of subsequent aneurysmal rupture. Similarly, patients in state III are without risk of subsequent hemorrhage. States I, II, and III may transition to state IV via age- and comorbid disease-adjusted death rates unrelated to aneurysmal rupture. The self-loops in the Markov diagrams account for the times when no transition is made in a given year.

GDC Embolization Cohort.—The GDC embolization cohort is modeled as a six-state Markov chain (Fig 1B). The states are as follows: 1, unruptured, untreated aneurysm; 2, completely coiled aneurysm; 3, partially coiled aneurysm; 4, full recovery after aneurysmal rupture during the cohort simulation; 5, fixed neurological deficit after complication during the GDC procedure or after aneurysmal rupture during the cohort simulation; and 6, death.

The following transitions are allowed in the GDC embolization cohort. States 1 through 4 may transition via subarachnoid hemorrhage to states 4 through 6. Note that patients in state 4 (postoperative, intact) may suffer rehemorrhage, since we hypothesize that the presence of coils may lead to suboptimal aneurysmal clip placement. Patients in states 1 through 5 may also transition to state 6 according to age- and comorbid disease-adjusted death rates unrelated to aneurysmal rupture.

Decision Tree Analysis and Initial Conditions

Initial conditions are determined by using decision tree analysis (Fig 2). Neurologically intact patients enter the decision tree after having undergone diagnostic cerebral angiography to identify unruptured cerebral aneurysms. The cost and morbidity of the initial diagnostic angiogram are excluded from our analysis because they are identical in the GDC embolization and no treatment cohorts. Aneurysms deemed inappropriate for attempted GDC embolization on the basis of anatomic considerations are also excluded from the analysis.

Determination of initial conditions for the no treatment cohort is trivial, since all patients enter the analysis intact and harboring an unruptured, untreated, asymptomatic cerebral aneurysm. For the GDC embolization cohort, calculation of initial conditions is complex, as shown in Figure 2. All patients in the GDC embolization cohort undergo attempted GDC embolization, with one of four results: complete coiling (100% aneurysmal occlusion), partial coiling (less than 100% aneurys-

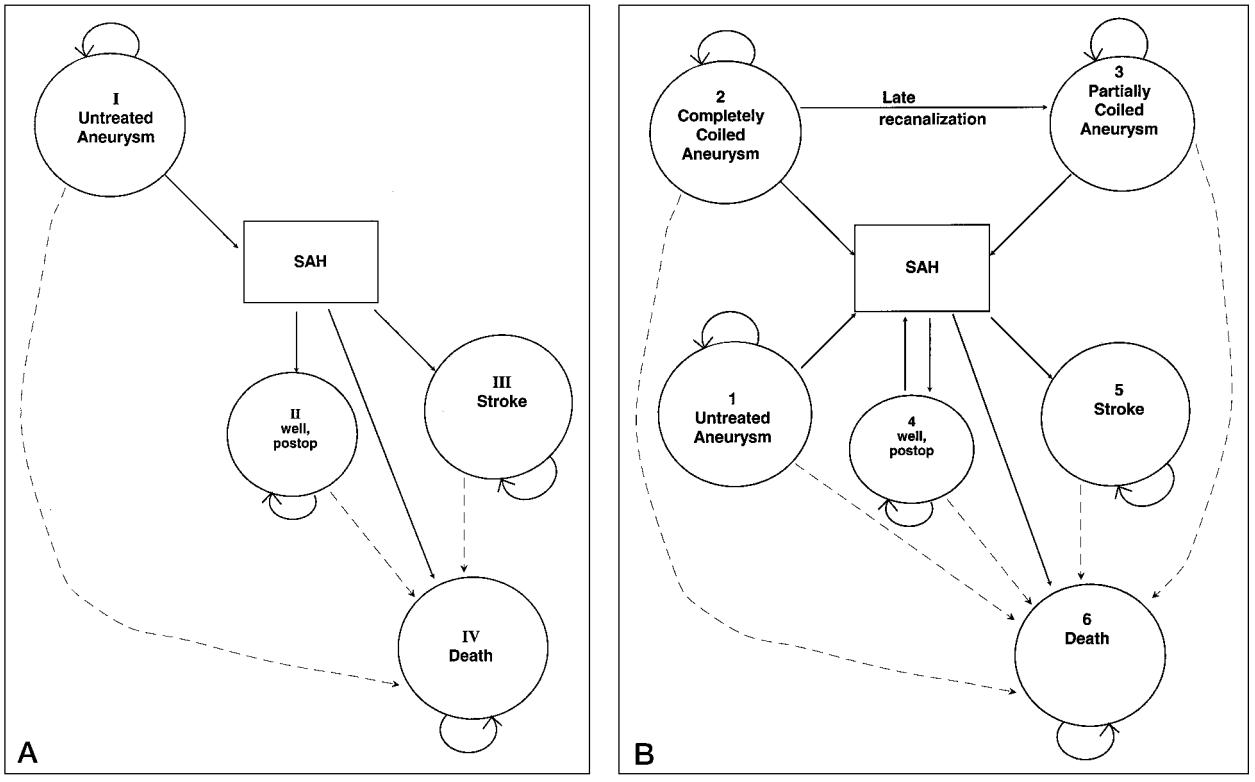

FIG 1. Markov transition diagrams.

A, No treatment cohort. Four Markov states are defined, as described in the text. Transitions occur once each year, at the 6-month point in the cycle. Transitions resulting from the effects of acute aneurysmal rupture are denoted by *solid lines*. Transitions to the death state from causes other than acute aneurysmal rupture are denoted by *dashed lines*. The self-loops for each Markov state represent the fraction of the cohort within a state that undergoes no transition in a given year. *SAH* indicates subarachnoid hemorrhage resulting from aneurysmal rupture.

B, Guglielmi detachable coil (GDC) embolization cohort. The six Markov states for this cohort are described in detail in the text. Note that, unlike the Markov chain for the no treatment cohort, transition from the postoperative, healthy state back to SAH is allowed in the GDC embolization cohort. This models the potential deleterious effects on the efficacy of surgical aneurysmal clipping by the presence of GDCs within a ruptured aneurysm.

mal occlusion, or neck remnant), attempted coiling (no coils detached), or procedural complication. Patients who suffer a procedural complication, including thromboembolism, aneurysmal perforation, or death, enter the appropriate Markov state (state 5 or 6) at that time, and are not considered for further aneurysmal treatment. Patients in whom GDC coiling is attempted but not performed enter Markov state 1 at that time, without further treatment.

Patients who undergo GDC coil embolization, with either complete or partial aneurysmal occlusion, return for reevaluation with cerebral angiography in 6 months. Those patients in whom coil configuration is stable (either completely or partially occluded aneurysms) are then entered into the appropriate Markov state (state 2 or 3). Patients in whom repeat angiography shows interval growth of the aneurysmal lumen undergo attempted repeat coil embolization, with efficacy rates altered in relation to the initial sitting.

See the Appendix for details regarding the formulas used to determine initial state probabilities.

Cohort Simulation

Cohort simulations of the Markov chains are used to calculate visit ratios for each state as well as discounted costs and discounted, weighted utilities. We apply discrete-time chains with annual state transitions occurring at the 6-month point in the yearly cycle. The simulations are carried out until greater than 99.9% of the cohort is dead (state 6).

Clinical Indications for GDC Embolization

The current standard of care for treatment of unruptured cerebral aneurysms reserves GDC embolization for patients deemed nonsurgical candidates, either because the size, morphology, or location of the aneurysm is unfavorable for a surgical approach or because the patient's coexisting medical condition precludes surgery. These two scenarios must be evaluated separately, because input data differ between them. For instance, aneurysms that are difficult to approach surgically because of size or morphology may also be difficult to treat effectively with GDC embolization, so that data regarding GDC efficacy should be modified appropriately. Conversely, patients who are refused surgery because of coexisting medical conditions may harbor aneurysms that are easily and effectively treated with GDC embolization. The model used in the latter situation must be modified, however, to reflect the comorbid disease state.

We offer two separate clinical scenarios for use as models for GDC embolization of unruptured aneurysms. Scenario A evaluates the cost-effectiveness for patients refused surgery on the basis of size, morphology, or location of the aneurysm, while scenario B focuses on patients in whom surgery is considered unduly risky owing to coexisting medical conditions. The configuration of the decision tree and Markov chain is identical for the two scenarios, but input data differ in several instances, which are highlighted in the following paragraphs.

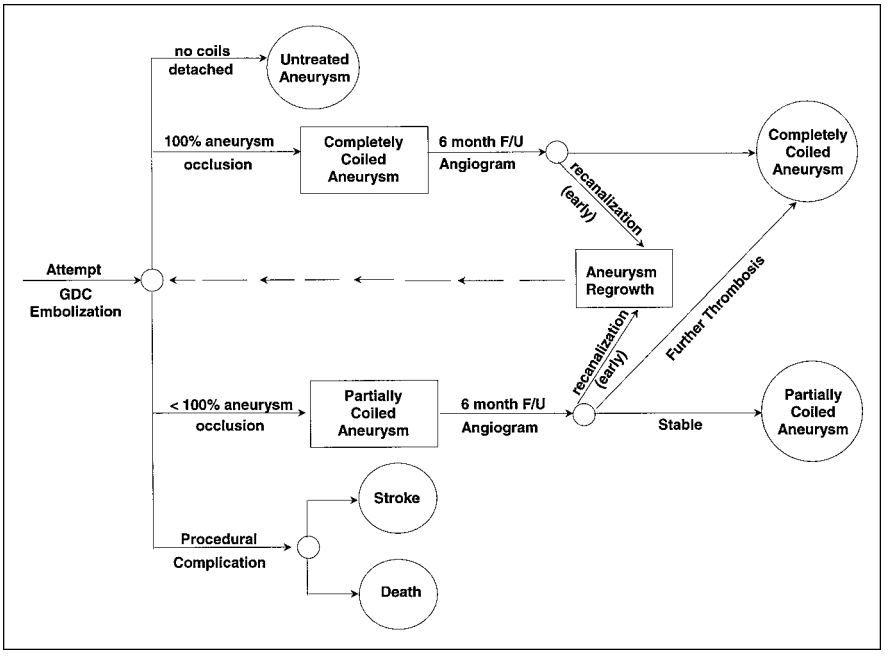

FIG 2. Decision tree. The cohort enters the decision tree from the far left, with the *upper line* entering the Guglielmi detachable coil (GDC) embolization cohort and the *lower line* entering the no treatment cohort. The *circles* along the right aspect of the figure represent Markov states used in the cohort simulation. See text for details.

Input Data

Inputs to the cohort simulation are used to specify the initial conditions of the Markov states, the transition probabilities among states, the costs associated with transitions and states, and the quality factors associated with the states. All input data as well as ranges used for sensitivity analyses are listed in the Table and are further discussed below.

Quality Factors.—States I and 1 (unruptured, untreated aneurysms from the no treatment and GDC embolization cohorts, respectively) both have baseline quality factors of 1.0, but sensitivity analysis utilities range from 0.9 to 1.0 to account for the potential decrease in quality of life resulting from knowingly living with an unruptured aneurysm (8). States 2 and 3 from the GDC embolization cohort also have baseline factors of 1.0, but sensitivity analysis utilities range from 0.95 to 1.0, since patients may suffer diminished quality of life from awareness that GDC-embolized aneurysms may undergo late recanalization with resultant risk of aneurysmal rupture. States II and 4 (postoperative, full recovery: no treatment and GDC embolization cohort, respectively) are both assigned a quality factor of 1.0. States III and 5 (stroke: no treatment and GDC embolization cohorts, respectively) are both assigned a quality factor of 0.76 (8, 19), and states IV and 6 (death: no treatment and GDC embolization cohorts, respectively) have a quality factor of 0.0. Aneurysmal morbidity unrelated to acute rupture, such as that from mass effect, is not modeled in our analysis.

Natural Course of Unruptured, Untreated Aneurysms.—A vast literature exists concerning the annual rate of rupture of unruptured, asymptomatic cerebral aneurysms (20–31), with reported annual rates of hemorrhage ranging from 1 to 6.5%. Most recent reports, however, state annual rates of rupture of approximately 1.4% to 1.6%. As such, our baseline analysis uses an annual rate of rupture of 1.4%. Annual rates of rupture may also be related to aneurysmal size and to time elapsed since aneurysmal formation (20, 25, 26, 28, 29). As such, sensitivity analysis is performed in which the annual rate of spontaneous rupture ranges from 0.5% to 2.5%.

Efficacy of GDC Embolization.—Data regarding GDC efficacy are derived from the USA Multicenter GDC Study Group for Treatment of Intracranial Aneurysms (F. Viñuela, "Review of the USA Multicenter GDC Study Group for Treatment of Intracranial Aneurysms," presented at the annual meeting of the American Society of Neuroradiology, Chicago, Ill, April 1995), which detailed results in 715 patients treated with GDC embolization. Efficacy parameters reported in this series were initial rates of aneurysmal occlusion (reflected in rates of attempted embolization, partial embolization, and complete embolization); GDC-related morbidity and mortality; and rates of early of early (<6 months) aneurysmal recanalization.

GDC efficacy parameters not included in the USA Multicenter GDC Study Group for Treatment of Intracranial Aneurysms study include annual rate of late (>6 months) aneurysmal recanalization and spontaneous, progressive thrombosis of partially coiled aneurysms; annual rate of rupture of partially coiled and completely coiled aneurysms; and efficacy of surgical clipping in the setting of previous coil embolization. For each of these variables we apply our best estimate for the baseline analysis. Because of inherent limitations in these estimates, extensive sensitivity analyses are presented for these variables. If results are stable in the face of broad changes in a given input variable within a sensitivity analysis, then one may conclude that precise determination of that clinical descriptor is relatively unimportant.

For our analysis, we consider that partially coiled aneurysms rupture with a frequency similar to that of partially clipped aneurysms. Unfortunately, the natural course of rests in unruptured aneurysms after surgical clipping is not well defined. Multiple studies have documented the growth and rupture of postoperative aneurysmal rests (32–36); however, most of these studies, including that by Lin et al (33), represent case series from which it is impossible to calculate annual rates of aneurysmal rehemorrhage. One series offers data from which an annual rate of rupture can be calculated (35). This series estimated an annual rate of 0.5% per year, which we use as our baseline rate of rupture for partially coiled aneurysms. We note, however, that this figure is based on a series that included both unruptured and ruptured aneurysms. As such, the potential effect of less protection from GDC embolization relative to surgical clipping is partially offset by lower expected rupture rates in our hypothetical cohorts.

We consider that completely coiled aneurysms are cured, without risk of future hemorrhage. Statistically significant decreases in rate of rehemorrhage after GDC embolization in ruptured aneurysms have been reported (7). However, since the background rates of hemorrhage in unruptured aneurysms is low, it is extremely difficult to prove decreased rupture rates after GDC embolization in such aneurysms.

TABLE 1: Simulation input data and ranges for sensitivity analysis

	Baseline		Sensitivity Analysis			
			Lower Limit		Upper Limit	
	Scenario A	Scenario B	Scenario A	Scenario B	Scenario A	Scenario B
Age, y	40	40				
Failure rate of GDC embolization, %	20	10	10	5	30	20
Morbidity rate of GDC embolization, %	4	4	2	2	8	8
Mortality rate of GDC embolization, %	1	1	0	0	3	3
Rate of complete aneurysmal obliteration with GDC embolization, %	38	62				
Rate of partial aneurysmal obliteration with GDC embolization, %	38	22				
Early (<6 mo) rate of recanalization, %	15	8				
Annual rate of rupture, untreated aneurysm %/y	1.4	1.4	0.5	0.5	2.5	2.5
Annual rate of rupture, completely coiled aneurysm, %/y	0	0				
Annual rate of rupture, partially coiled aneurysm, %/y	0.5	0.5	0.4	0.4	1.2	1.2
Annual rate of late (>6 mo) recanalization, %/y	3	2	0	0	10	10
Spontaneous progressive thrombosis of partially coiled aneurysm, %	8	8				
Quality factor, living with neurologic deficit	0.76	0.76				
Quality factor, living with GDC-embolized aneurysm	1	1	0.95	0.95	1	1
Quality factor, living with unruptured, untreated aneurysm	1	1	0.9	0.9	1	1
Annual discount rate, %/y	5	5	0	0	10	10
Morbidity from aneurysmal rupture, %	20	30				
Mortality from aneurysmal rupture, %	50	50				
Comorbid disease-adjusted death rate (/1000)	0	30				
Cost of GDC embolization, $	10 000	10 000	5000	5000	15 000	15 000
Cost of follow-up angiography, $	1500	1500				
Cost of stroke, $	20 000	20 000				
Cost of subarachnoid hemorrhage from aneurysmal rehemorrhage, $	30 000	30 000				
Cost of rehabilitation, $	15 000	15 000				

Note—Baseline values are listed for all variables. Where appropriate, separate values are listed for scenario A and scenario B. Boundary values (lower and upper limits) are listed for those input variables subjected to sensitivity analysis. Labels in *italics* denote data derived from the USA Multicenter GDC Study Group for Treatment of Intracranial Aneurysms.

In the Table we have denoted with italics the data taken from the USA Multicenter GDC Study Group for Treatment of Intracranial Aneurysms. Separate baseline values for scenarios A and B are listed in the Table for some of these data. For instance, in scenario A (unfavorable aneurysmal morphology) we apply less favorable initial GDC efficacy data, including higher failure rate and lower rate of complete aneurysmal obliteration compared with scenario B (comorbid disease). Conversely, we apply higher rates of death from comorbid disease in scenario B than in scenario A.

Outcome after Aneurysmal Rupture.—We apply separate baseline values of morbidity and mortality after aneurysmal rupture in scenarios A and B, since it is likely that these values will be elevated in scenario B (22, 37).

Cost Estimates.—Costs are estimated on the basis of physicians' current procedural terminology (CPT) codes from the American Medical Association for 1996. The CPT code for "aneurysm embolization, intrasaccular electrothrombosis" is 61708, with a professional charge of $7175. We add technical charges for this CPT code as well as short-stay intensive care unit charges based on institutional data, for a baseline total cost of $10 000 for GDC embolization. For follow-up angiography we apply CPT codes 36217 (catheterization) and 75665 (interpretation) for a single second-order vessel cerebral arteriogram. The professional charges for these codes are $1002 and $188, respectively. We add technical charges for these CPT codes based on institutional data, for a baseline total cost of $1500 for follow-up angiography. We acknowledge that these values represent charges rather than societal costs (38), but we consider them appropriate for this initial analysis.

A recent report details costs associated with specific cerebrovascular events at academic medical centers (39). From these data we estimate the cost of aneurysmal rupture to be $30 000. We estimate the acute-care cost of a cerebral infarction resulting from GDC procedure-related morbidity to be $20, 000 (39). Annual rehabilitation costs for cerebral infarction are estimated to be $15 000 (40).

Acceptable Cost-Utility Ratios.—Acceptable incremental cost-utility ratios below $50 000/QALY are considered by any investigators to be acceptable in terms of comparisons with ratios reported for other medical interventions (41–44). However, the absolute value of the ratio is of limited importance in a given series (45), especially one using such preliminary data as in this analysis. However, reference to an acceptable limit not only allows a basis for comparison between our data and that of prior published reports but also defines a general ceiling for acceptable ratios as a given input variable is changed within a sensitivity analysis.

Results

Baseline Input Data

The incremental cost-utility ratio calculated by using baseline input data for scenario A is $23 000/QALY (incremental cost = $13 000, incremental QALY = 0.56). For scenario B, using baseline values, the incremental cost-utility ratio is $19 000/QALY (incremental cost = $10 100, incremental QALY = 0.53).

Sensitivity Analyses

Results of the sensitivity analyses are listed in the Table, and selected sensitivity analyses are shown graphically in Figures 3 through 7.

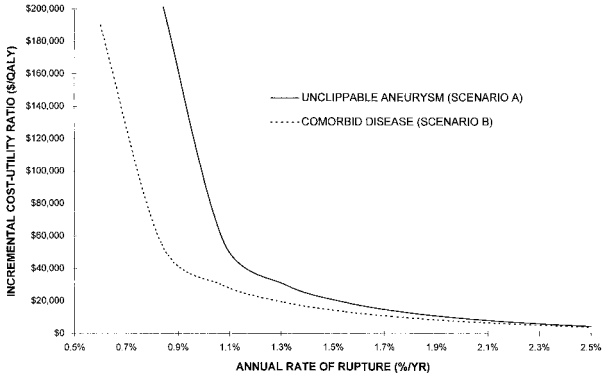

FIG 3. Sensitivity analysis for annual rate of rupture of untreated aneurysms. Incremental cost-utility ratio is plotted versus annual rate of rupture of untreated aneurysms for scenario A (*solid line*) and scenario B (*dotted line*). See text for details.

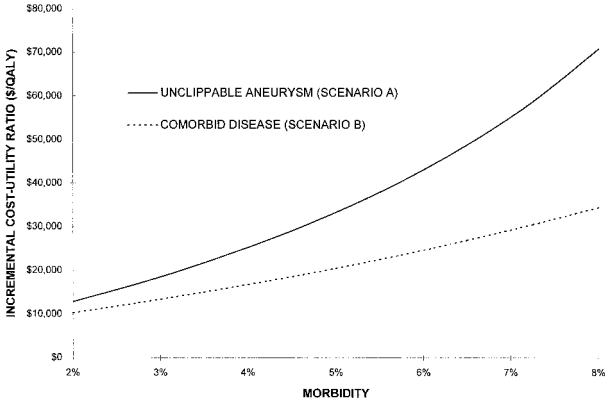

FIG 4. Sensitivity analysis for morbidity of Guglielmi detachable coil (GDC) embolization. Incremental cost-utility ratio is plotted versus GDC morbidity for scenario A (*solid line*) and scenario B (*dotted line*). See text for details.

Natural Course of Unruptured, Untreated Aneurysms.—Figure 3 illustrates influence of the annual rate of rupture of untreated aneurysms on the cost-utility ratios. Separate curves are presented for scenarios A and B. For both scenarios there is marked increase in the cost-utility ratio with small decreases in annual rates of rupture of untreated aneurysms below 1%. Conversely, for annual rates of rupture greater than 1.5% there is minimal change in the ratio with relatively large increases in rupture rate. Unfortunately, the best available estimates for annual rate of rupture are on the order of 1% to 1.6%, which represent values along the transition between the steep and shallow portions of the sensitivity analysis (Fig 3). These results indicate that highly reliable data regarding natural course of unruptured aneurysms is required before precise estimates of the cost-effectiveness of GDC embolization of such aneurysms can be determined.

GDC Efficacy.—Failure rate. Sensitivity analysis shows that the cost-utility ratios remain relatively constant regardless of GDC failure rate for scenario B, while those of scenario A undergo an increasing rise as failure rates approach 30%. Even so, the variation seen with changes in the GDC failure rate is much less striking than those seen in changes in the natural history of unruptured aneurysms.

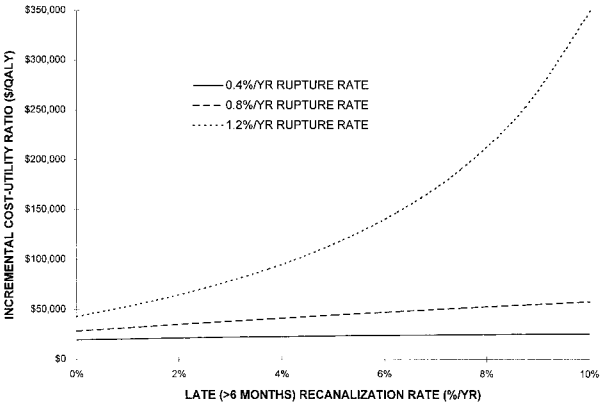

FIG 5. Two-way sensitivity analysis for late recanalization rate and annual rate of rupture of partially coiled aneurysms. Incremental cost-utility ratio is plotted versus late recanalization rate for scenario A. Three separate curves are shown, each representing a different annual rate of rupture of partially coiled aneurysms (0.4%, *solid line*; 0.8%, *dashed line*; 1.2%, *dotted line*). See text for details.

GDC procedural morbidity. Figure 4 shows the effect of procedural morbidity on the cost-utility ratio. As above, separate curves are presented for the two clinical scenarios under consideration. As morbidity increases from 2% to 8% there is only mild change in the cost-utility ratio for scenario B, while that of scenario A increases by greater than $60 000/QALY with small changes in morbidity rate. The difference between the two scenarios is partially related to the high baseline GDC failure rate in scenario A, which results in a large fraction of the cohort being exposed to the cost and morbidity of the procedure without gaining benefit in the form of decreased rates of aneurysmal rupture.

Recanalization of completely coiled aneurysms and rate of rupture of partially coiled aneurysms. The significance of aneurysmal recanalization after GDC embolization is intimately related to the rate of rupture of partially coiled aneurysms. Figure 5 is a two-way sensitivity analyses that reflects the influence on the cost-utility ratios of the rates of late (>6 months) aneurysmal recanalization in conjunction with rupture rates of partially coiled aneurysms in scenario A. For aneurysms with low (0.4%) and moderate (0.8%) annual rates of rupture relative to untreated aneurysms, there is minimal change in the cost-utility ratio when increasing late recanalization rates to as high as 10% per year. However, the importance of aneurysmal recanalization steadily increases with increasing rates of rupture of partially coiled aneurysms. For an annual rate of rupture that is nearly as high as that of untreated aneurysms (1.2% versus 1.4%), there is marked increase in the cost-utility ratio with increasing rates of recanalization. Specifically, increasing the annual recanalization rate in this latter setting from 6% to 8% results in an increase of more than $200 000/QALY in the cost-utility ratio.

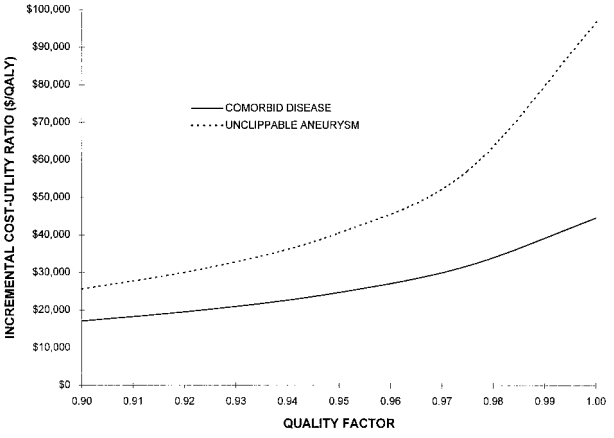

FIG 6. Sensitivity analysis for quality of life when knowingly harboring an unruptured, untreated aneurysm. For this analysis, quality of life when harboring an embolized aneurysm is also changed in linear fashion, from 0.95 to 1.0. Incremental cost-utility ratio is plotted versus quality of life when knowingly harboring an unruptured, untreated aneurysm for scenario A (*solid line*) and scenario B (*dotted line*). See text for details.

Early changes in aneurysmal morphology (early recanalization and further thrombosis rates). Both these factors are found to have only mild effects on the cost-utility ratios (not shown).

Quality of Life when Knowingly Harboring an Unruptured Aneurysm.—Figure 6 shows the effect on the cost-utility ratio of varying the quality factor when knowingly living with an unruptured aneurysm. For this analysis, the quality of life with a previously coiled aneurysm is varied as well, from 0.95 to 1.0, since these same patients may also suffer diminished quality of life knowing that GDC-embolized aneurysms may recanalize and rupture. For scenario B, the effect of varying the quality factor is mild. However, steep increases in the cost-utility ratio are noted in scenario A when the quality factor is diminished from 1.0 to 0.97.

Life Expectancy.—The influence of life expectancy at entry to the model is shown in Figure 7. For this sensitivity analysis we applied life-table data for a 50-year-old patient, and increased death rates from comorbid disease to yield diminished life expectancies. This analysis shows that the cost-utility ratios undergo mild change when varying life expectancy above 15 years, but that small decreases in life expectancy below 10 years result in marked increases in the ratio.

Adverse Influence of Coils on Surgical Efficacy after Aneurysmal Rupture.—Partial coiling of aneurysms may not eliminate completely the risk of subsequent aneurysmal rupture. As such, neurosurgeons may be required to clip acutely ruptured, previously coiled aneurysms. In our model, we have assigned diminished surgical efficacy to these cases, such that previously coiled, ruptured aneurysms are not considered cured after clipping. However, across wide ranges of risk of future hemorrhage in these cases, there is essentially no change in the cost-utility ratio (not shown).

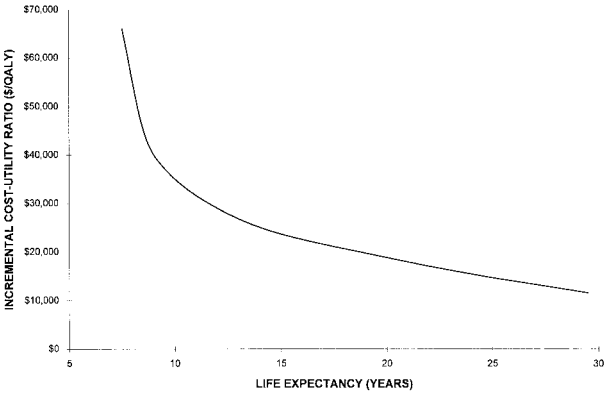

FIG 7. Sensitivity analysis for life expectancy at time of entry into the algorithm. Incremental cost-utility ratio is plotted versus life expectancy for scenario B. Life expectancy was altered by changing the death rate from comorbid disease, so this analysis was limited to scenario B.

Cost of GDC Embolization.—Increases in procedural costs yield linear increases in the cost-utility ratio (not shown).

Discount Rate.—A steep increase in the ratio is noted for rates greater than 5% (not shown), but below this level the rate of change in the ratio with increasing discount rates is small.

Discussion

This study elucidates the factors that have the greatest influence on the cost-effectiveness of GDC embolization of unruptured, intracranial aneurysms considered inappropriate for standard surgical clipping procedures. Baseline cost-effectiveness ratios are within acceptable limits for both scenario A (unclippable aneurysms) and scenario B (comorbid disease precluding surgery).

Our results indicate that precise determination of the natural course of unruptured aneurysms is of overwhelming importance in determining the cost-effectiveness of GDC embolization. Indeed, for annual rates of rupture above 1.5% there is little change in the cost-utility ratios across wide ranges of other input variables, and the absolute value of the ratio is well within the acceptable range based on a comparison with other medical interventions. However, as noted above, recent data suggest that the annual rate of aneurysmal rupture is between 1% and 1.6%. In this range of rupture rates, wide variation in cost-utility ratios results from small changes in other input variables.

Our analysis shows that rates of early (<6 months) aneurysmal recanalization and early, spontaneous, progressive thrombosis have minimal effect on the cost-utility ratios. The influence of late recanalization is highly dependent on the rupture rate of partially coiled aneurysms, such that late recanalization rates have minimal effect on the analysis if the rate of rupture of partially coiled aneurysms is less than 0.8% per year. Unfortunately, the rate of hemorrhage of partially coiled aneurysms is not well defined. Indeed, the rate of rupture of partially clipped aneurysms has

yet to become well established, and surgical clipping has been performed for decades.

Variation in life expectancy has its predominant impact on the cost-utility ratios when life expectancy is 10 years or less. This results from the nature of treatment of unruptured aneurysms, since most of the benefit from the procedure is accrued in delayed fashion resulting from decreased rates of aneurysmal rupture. If the patient cohort dies from unrelated illness within several years of aneurysmal treatment, then there is less benefit to gain from the intervention.

The quality of life experienced by patients harboring unruptured aneurysms had moderate effect on cost-utility ratios in our analysis. We noted a disparity in the relative effect of this variable between the two scenarios considered in our analysis, such that in the unclippable aneurysm scenario the rate of change of cost-utility ratios was steep, with small changes in the quality factor. This disparity may be explained by noting that alteration in the quality factor results in greater aggregate change in total utility for the unclippable aneurysm scenario relative to the comorbid disease scenario.

Our analysis shows that the presence of coils within a partially coiled, acutely ruptured aneurysm had minimal effect on cost-utility ratios. It is possible that surgical clipping may be difficult in the presence of GDC coils, although several reports have noted reasonable surgical results in previously coiled aneurysms (5, 6). However, even when we modeled marked decreases in surgical efficacy by changing rehemorrhage rates, there was essentially no change in the cost-utility ratio. Because only a small portion of the cohort suffered spontaneous aneurysmal rupture, changes in outcome in this subgroup did not affect overall results.

Similar analyses to our own have been performed for surgical intervention in unruptured aneurysms (8). These studies, like ours, found profound changes in cost-effectiveness with small variation in the natural course of unruptured aneurysms, discount rates, quality factors associated with knowingly harboring an unruptured aneurysm, and life expectancy. Compared with GDC embolization, surgery carries greater initial cost but offers more assured efficacy. However, because we focused on nonsurgical candidates, direct comparisons between GDC embolization and surgery are difficult.

Limitations of Our Analysis

This analysis represents an investigation into the clinical variables that have the most profound effect on the cost-effectiveness of GDC embolization in unruptured aneurysms. As such, we made several simplifying assumptions. We did not account for a second follow-up angiogram or a potential third GDC procedure, since this would have resulted in further increases in complexity in our decision tree analysis, and only 2.6% of patients in the North American series underwent a third GDC procedure. Also, we applied constant values for annual rate of rupture for untreated aneurysms as well as age-independent morbidity and mortality rates for spontaneous aneurysmal rupture. Time-dependent variance of each of these input variables could be easily added to our analysis, but the added complexity probably would not add useful information at this stage of investigation, given uncertainty surrounding many other input variables. Also, we applied a zero rate of rupture for completely coiled aneurysms, although nonzero rupture rates for completely coiled aneurysms could easily be modeled in our analysis. We chose to focus instead on the complex interaction between the rate of rupture of partially coiled aneurysms with the rate of recanalization of completely coiled aneurysms.

We imply in our analysis that all aneurysms can be pooled into a single group regarding annual rate of rupture, even though this critical input variable may also depend on the size of a given aneurysm. For instance, most giant aneurysms rupture within 5 years (28, 29). However, there is some debate regarding the influence of aneurysmal size on rupture rate (27) for nongiant aneurysms. At any rate, the purpose of our analysis was not to supply data that would be useful in a given case but rather to explore cost-effectiveness issues for general policy and health resource allocation decisions.

We did not include morbidity of the follow-up cerebral angiogram in our analysis. The morbidity of diagnostic cerebral angiography is approximately 0.3% to 0.5% (46, 47). However, essentially all morbidity in the most recent large, prospective series was in patients being evaluated for transient ischemic attacks (47). Thus, it is likely that morbidity of follow-up angiography would be vanishingly small, so it was excluded from this analysis.

The data used for the cost of GDC embolization represent charge information rather than actual societal cost data (38). We acknowledge this limitation, and note that, since charges are generally greater than societal costs, the ratios reported in our analysis may systematically overestimate the actual cost-utility ratios.

The GDC efficacy data used in our analysis was derived from the initial cohort of 715 patients treated in the USA Multicenter GDC Study Group for Treatment of Intracranial Aneurysms. This database represents the best available efficacy data, but its use introduces several limitations. Our analysis focuses on a hypothetical cohort of unruptured, asymptomatic aneurysms, while the database was composed predominantly of ruptured or otherwise symptomatic aneurysms; only 21.5% of the cohort in that study represented incidental aneurysms. Also, safety and efficacy might be expected to improve with experience, so the database may underestimate these factors. However, the practitioners who performed the early procedures were highly skilled, so that extrapolation of these data to other physicians may not be accurate.

We do not include lost wages as part of our analysis, even though we used the societal perspective. There is debate in recent literature regarding the most appropriate manner in which lost wages should be addressed. Some authorities suggest that the true indirect costs should be limited to the costs associated with replacing or retraining workers (48). Also, in-

cluding lost wages in addition to assigning lower quality factors may lead to "double jeopardy," since the societal impact is at least partially taken into account by the quality-of-life issues (49).

We did address the use of noninvasive imaging techniques, such as computed tomography, angiography, and magnetic resonance angiography, in the workup of unruptured cerebral aneurysms in our analysis. We considered that all patients entered the cohort with known aneurysms, discovered either by noninvasive or invasive means, and limited our incremental cost-benefit analysis to the impact of different therapeutic options.

Conclusions

Baseline input values result in acceptable cost-utility ratios for GDC embolization of unruptured intracranial aneurysms. Cost-effectiveness is markedly affected by the natural course of unruptured, untreated aneurysms. Many of the GDC efficacy indexes, such as rate of failed coiling, early recanalization, and progressive aneurysmal thrombosis, have mild effects on the cost-utility ratios. GDC complication rate as well as life expectancy have moderate effects on the analysis. The influence of late aneurysmal recanalization is mild unless high rates of rupture for partially coiled aneurysms are applied. Suboptimal clip placement resulting from the presence of GDC coils within a ruptured aneurysm has no demonstrable consequence on cost-utility ratios.

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Appendix

The formulas used to determine the proportion of patients in the various Markov states at the entry into the model are provided below for the GDC embolization cohort.

Untreated aneurysm (state 1): U

Complete aneurysmal coiling (state 2): (1−RR)
[R(1−F−MB−MT)]/(1+R)+(FT)
(1−F−MB−MT)/(1+R)+(1−MB−MT)((1−FT)
[(1−F−MB−MT)/(1+R)]+(RR)
[R(1−F−MB−MT)]/(1+R))(EFF)(1−RR)
[R(1−F−MB−MT)]/(1+R)

Stroke (state 4): MB+(1−FT)[(1−F−MB−MT)/
(1+R)]+(RR)[R(1−F−MB−MT)]/(1+R)
(EFF)[R(1−F−MB−MT)]/(1+R)+
(1−F−MB−MT)/(1+R)](RR)(MB)

Death (state 6): MT+(1−FT)[(1−F−MB−MT)/
(1+R)]+(RR)[R(1−F−MB−MT)]/(1+R)
(EFF)[R(1−F−MB−MT)]/(1+R)+
(1−F−MB−MT)/(1+R)](RR)(MT)

where

U = untreated aneurysms

C = completely coiled aneurysms, initial GDC procedure

cP = partially coiled aneurysms, initial GDC procedure

cF = attempted (failed) coiling, Tinitial GDC procedure

MB = morbidity of GDC embolization

MT = mortality of GDC embolization

cR = ratio of complete: incomplete coiling procedures

RR = rate of early (<6 months) recanalization

FT = further thrombosis rate

EFF = relative efficacy of repeat GDC embolization

Partially coiled aneurysm (state 3) is calculated as the remaining fraction of the cohort after calculating fractions in states 1, 2, 4, and 6.

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