

Cryptogenic Stroke in a Patient With a PFO: A Decision Analysis

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ABSTRACT: *Background:* Octogenarian Israeli prime-minister Ariel Sharon recently sustained a mild, reversible stroke. A patent foramen ovale (PFO) was detected and anticoagulants were given pending PFO closure. A few days later, he sustained major intracerebral hemorrhage and has since remained in vegetative state. The events triggered serious criticism in the mass media, experts promoting one management option over others. Because knowledge of outcome and hindsight bias evaluation of appropriateness of care, we sought to systematically review the clinical case. *Methods:* We performed a formal decision analysis to identify the preferred management between anticoagulation, antiplatelets, PFO closure, or no treatment. Using the best evidence available, we built a decision tree. Main outcomes: recurrent stroke and treatment complications within 1 year. *Results:* Optimal decision was found to be critically sensi-

tive to assumptions about etiology, efficacy and safety of treatments, recurrence risk, and to small changes in utilities. In multiway sensitivity analysis, when the risk of recurrent stroke was <0.12 per year, no treatment was the best management. PFO closure is dominant only when the risk of recurrent stroke is >0.12 per year closure effectiveness is assumed to be <0.28 . When closure effectiveness is >0.6 , it is inferior to anticoagulation and antiplatelet management. *Conclusions:* Uncertainties precluded a clear-cut answer and choice was found to be a “toss-up,” often associated with much controversy. Use of novel therapies, such as PFO closure, outside clinical trials will not reduce uncertainty about efficacy. **KEY INDEXING TERMS:** Stroke; Patent foramen ovale; Decision analysis. [*Am J Med Sci* 2008; 335(6):457–464.]

Prevalent causes of stroke in elderly patients are athero-thromboembolism, intracranial vascular disease (“lacunar” stroke), and atrial fibrillation. When investigations are negative, it is classified as “cryptogenic” stroke.

A potential association between patent foramen ovale (PFO) and cryptogenic stroke has been described.¹ PFO is a congenital abnormality allowing blood flow from the right atrium to the left, found in approximately 15% to 35% of adults.¹ A proposed mechanism of stroke is that venous emboli pass through this aperture and then to the cranial circulation. PFO closure of aperture and/or anticoagula-

tion are associated with adverse events and may not necessarily reduce stroke recurrence.^{2,3}

In December 2005, the news media reported that Israeli Prime Minister Ariel Sharon, aged 78 years, sustained mild stroke, resolving within 24 hours. It was later reported that imaging studies were consistent with cerebral amyloid angiopathy (CAA) and that a significant PFO was detected by echocardiography. Except for age, obesity, sedentary lifestyle, and some aortic atherosclerosis, there were no other risks for vascular disease (according to media reports). Mr. Sharon was treated by anticoagulants pending closure of PFO. Was this an optimal decision?

The 2006 guidelines by the American Academy of Neurology currently recommend antiplatelet therapy for patients with ischemic stroke and PFO, regardless of age.⁴ This recommendation is not based on randomized trials comparing aspirin, anticoagulants, and/or closure of PFO. Little data are available on elderly patients. Facing this uncertainty, we examined optimal choice by formal decision analysis.

Methods

Figure 1 describes a decision tree with following options: no treatment, antiplatelets (AP) with Aspirin, anticoagulation (AC) with Warfarin, and transcatheter PFO closure (TC). Patients in TC arm were also given periprocedural AC and Aspirin. TC may

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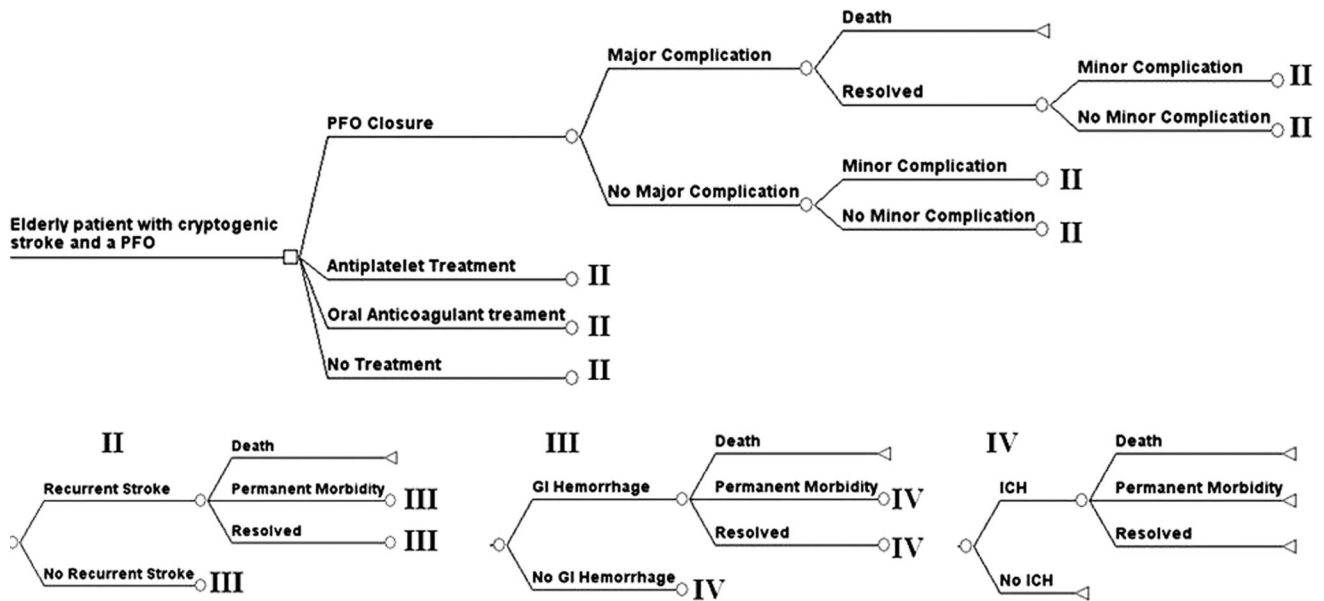


Figure 1. Decision tree modeling the presented clinical scenario. The entire tree has been split into several sub-trees (I-IV). I: Initial tree showing, at the first square node, a decision to be made between different management options. All subsequent nodes are probability nodes describing various outcomes. For example, patent foramen ovale closure can result in a major complication or not. A major complication can result in death or can resolve. Except for death, all initial options lead to sub-tree II: either recurrent stroke occurs or not. Stroke can result in death, permanent morbidity or can resolve. Except for death, all options lead to III: GI hemorrhage and recurrent stroke can either occur or not, with outcomes of death, permanent morbidity or resolution. Except for death, all options lead to IV: intracerebral hemorrhage can occur or not, with similar outcomes as GI hemorrhage and stroke. This is the final sub-tree.

lead to immediate complications of treatment (such events are rare for AP and AC). After treatment, patients may sustain recurrent ischemic stroke, intracerebral hemorrhage (ICH) or extracranial major hemorrhage. Each event may resolve or lead to permanent incapacitation or death. The time horizon of our model was set to 1 year. Major complications were considered to lead to death or resolve after 3 months. Minor complications were defined as resolving after 1 month. Results of the analysis are presented as expected utilities or survival in Monte-Carlo simulations.

Gastrointestinal hemorrhage was defined as bleeding requiring blood transfusions. Major complications of PFO closure included device embolization or fracture, pericardial effusion/tamponade, sinus node dysfunction, seizure, need for re-intervention or surgery. Minor PFO closure complications included air embolism, fever, ST segment elevation or arrhythmias, access site difficulties or hematoma, minor stroke, and scotomata. We did not include drug complications such as rash or skin necrosis because of very low probabilities (Warfarin induces skin necrosis in 1 of 10,000 patients).⁵

Probabilities and utilities of events and outcomes were derived from the literature. We searched Medline using key words: Patent (or Perforated) Foramen Ovale: PFO, stroke, cryptogenic, device, Aspirin, Coumadin or Warfarin, AC, and “randomized controlled trial.” Because of scant publications, we did not discriminate for size of PFO and/or presence of atrial septal aneurysm. In some cases, we extrapolated (for example when abstracting data of secondary prevention of stroke from meta-analyses of primary and secondary prevention studies^{6,7}) using PEPI program for calculations.⁸ We used TreeAge Pro 2006 Healthcare to create the model (Release 0.1, TreeAge Software Inc., Williamstown, MA).

Model Assumptions

We made the following assumptions: (1) Risk of recurrent stroke, hemorrhage, major and minor complications are independent of each other; (2) Treatment effectiveness and risk of hem-

orrhage is constant over time; (3) All closure devices and cardiology interventionists are equally effective and safe; and (4) All outcomes last a whole year except for TC complications.

Results

Current literature provided no conclusive evidence that treating elderly patients with PFO and cryptogenic stroke decreases stroke recurrence or mortality. There have been no publications of randomized trials evaluating this clinical scenario. Evidence was therefore, derived from observational studies⁹⁻¹² and case series.^{9,13-39}

Table 1 presents event probabilities and ranges entered into the decision model. Table 2 presents estimated utilities for various outcomes and ranges used in analysis.

Rational For Values Not Directly Quoted from the Medical Literature

Risk of Recurrent Stroke among Patients Not Treated. This risk was not directly taken from literature because we did not find studies estimating this risk for untreated elderly patients after stroke. Our estimation was calculated from the following formula:

$$x * RR_{AC} * 0.38 + x * RR_{AP} * (1 - 0.38) = 13.8\%$$

Where *x* is risk of recurrent stroke among untreated patients; RR_{AC} and RR_{AP} are relative risks (RRs) of recurrent stroke among patients treated

Table 1. Probabilities of Events in the Decision Tree

	Baseline Rate	Range
Risk for recurrent stroke with no treatment	0.24 ¹²	0.13–0.5
Death from recurrent stroke	0.14 ⁴⁵	0.1–0.5
Permanent morbidity after recurrent stroke	0.24 ^{61,62}	0.1–0.5
Risk for extracranial hemorrhage with no treatment	0.005 ^{6,7,40}	0.0038–0.0069
Risk for intracranial hemorrhage with no treatment	0.01 ⁴⁰	0.004–0.056
Death from extracranial hemorrhage	0.2 ²⁵	0.1–0.5
Permanent morbidity from extracranial hemorrhage	0.18 ⁶³	0.1–0.5
Death from intracranial hemorrhage	0.3 ⁴⁰	0.2–0.43
Resolution of intracranial hemorrhage	$(1-0.35) \times 0.37^{41}$	
Probability of major complications after TC	0.044 ^a	0.036–0.053 ^a
Death from major complications after TC	0.038 ^a	0.01–0.094 ^a
Probability of minor complications after TC	0.035 ^a	0.028–0.043 ^a
Relative risks Compared with No treatment	Baseline effectiveness	Range
RR for recurrent stroke with AP treatment	0.8 ^{6,9,11,45,46}	0.63–1
RR for recurrent stroke with AC treatment	0.4 ^{6,9–11}	0.4–1
RR for recurrent stroke after TC	^b	0.28 ⁹ –1
RR for extracranial hemorrhage with AP	27 ⁴⁰	1–4
RR for intracranial hemorrhage with AP	2 ⁶⁴	1–4
RR for extracranial hemorrhage with AC	3 ⁶	1–4
RR for intracranial hemorrhage with AC	7 ⁴⁹	3–10 ^{6,40,48}

^a See Table 3.

^b Values used ranging from 0.28 to 1.

TC indicates transcatheter device closure of patent foramen ovale; AP, antiplatelet treatment; AC, anticoagulation treatment; RR, relative risk.

with Warfarin and Aspirin, respectively (Table 1); 13.8% is annual rate of stroke recurrence above age 65 in article by Homma et al¹² where 38% of patients were on Warfarin and remainders on Aspirin.

Risk for Extracranial Hemorrhage among Patients Not Treated. We abstracted risk from meta-analysis by Derry and Loke,⁷ which includes data about gastro-intestinal bleeding in patients

treated with Aspirin compared with no treatment. We calculated risk using only patients from placebo group who had suffered stroke. Similar results were found in other meta-analyses.^{6,40}

Probability of Resolving Intracranial Hemorrhage. Navarrete-Navarro et al⁴¹ predicted 37% complete resolution after 1 year among patient surviving an ICH. We multiplied this number by 70% (proportion of patients surviving ICH).⁴⁰

Major and Minor Complications of PFO Closure. We found 2 nonsystematic reviews of literature^{1,42} and therefore undertook additional search of literature. All publications were case series.^{9,13–39} We systematically reviewed methods of recruitment and excluded duplicate publications, according to years and center of enrollment.^{9,34–39} One study was excluded because we were not able to derive specific data relating to percutaneous TC.⁴³ Table 3 shows that 2417 patients underwent TC, 106 had suffered major complications (4.4%, 95%CI 3.6%–5.3%) and 84 suffered minor complications (3.5%, 95%CI 2.8%–4.3%). Four patients suffering major complications died (0.16% of all patients undergoing TC and 3.8% of patients with major complications, 95%CI 1%–9.4%). We found one study reporting a similar complication rate among older patients.⁴⁴

Aspirin Effectiveness. Estimated effectiveness of Aspirin was derived from several sources and expressed as RR for recurrent stroke with Aspirin compared with no treatment. We used meta-analy-

Table 2. Utilities in the Decision Tree

	Baseline utility	Range
Death	0	
Permanent morbidity after recurrent stroke	0.5 ^{49,65}	0.3–0.6
Resolution of recurrent stroke	0.8 ^{49,65}	0.7–0.9
Permanent morbidity after ICH	0.5 ⁶⁵	0.3–0.6
Resolution of ICH	0.76 ^{49,65}	0.5–0.91 ⁶⁵
Permanent morbidity after extracranial hemorrhage	0.5 ⁶⁵	0.3–0.6
Resolution of extracranial hemorrhage	0.84 ⁴⁹	0.8–0.9
AP treatment	0.998 ⁶⁵	0.96–1 ⁶⁵
AC treatment	0.99 ^{49,65}	0.92–0.99 ⁶⁵
TC procedure	0.985	0.98–0.995
Major complications from TC	0.90 for 3 month ⁶⁵	0.7–0.99
Minor complications from TC	0.981 for 1 month ⁶⁵	0.8–0.99

ICH indicates intracerebral hemorrhage; TC, transcatheter device closure of patent foramen ovale; AP, antiplatelet treatment; AC, anticoagulation treatment; RR, relative risk.

Table 3. Case Series of Percutaneous PFO Closure^a

Article	Year	Patients, n	Complications, n		
			Total	Minor	Major (Deaths)
Bridges et al ¹³	NA	36	0	0	0
Ende et al ¹⁴	NA	10	1	0	1
Sideris et al ¹⁵	NA	12	1	0	1
Bohm et al ¹⁶	1996	8	6	0	6
Z'Brun et al ¹⁷	NA	1	1	0	1
Pfeiffer et al ¹⁸	NA	16	0	0	0
Rickers et al ¹⁹	NA	25	0	0	0
Beitzke et al ²⁰	NA	162	10	8	2
Butera et al ²¹	NA	35	0	0	0
Sievert et al ²²	From 1994	281	57	5	45 (1)
Wahl et al ²³	NA	152	17	7	10 (1)
Bruch et al ²⁴	1997–2001	66	3	3	0
Du et al ²⁵	1995–2000	18	0	0	0
Martin et al ²⁶	1995–2001	110	23	2	21
Schwerzmann et al ²⁷	1998–2001	100	10	6	3
Onorato et al ²⁸	1999–2002	256	28	23	5 (2)
Anzola et al ²⁹	2001–2004	140	15	14	1
Braun et al ³⁰	1998–2002	307	13	11	4
Kay et al ³¹	1995–1998	8	1	0	1
Khositseth et al ³²	1998–2002	81	7	5	2
Krummsdorf et al ³³	1992–2003	593	18	0	3
Total		2417	210	84	106 (4)

^a Patent foramen (PFO) excluding duplicate publications (see text).

sis of randomized controlled trials comparing Warfarin, Aspirin, and placebo for prevention of recurrent stroke after cardio-embolic stroke by Hart et al.⁶ The estimate is derived from Windecker et al.,⁹ Petty et al.,⁴⁵ Mas et al.,⁴⁶ and Homma et al.,¹¹ all including data unique for cryptogenic stroke.

Warfarin Effectiveness Compared with No Treatment. Computed by multiplying estimated effectiveness of Warfarin compared with Aspirin,^{6,10} by estimate of Aspirin effectiveness for secondary prevention of stroke (Table 1).^{6,25,47}

PFO Closure Effectiveness. We could find only 1 article, by Windecker et al.⁹, comparing TC with medical treatment. It was a nonrandomized cohort suggesting nonsignificant, slightly better outcome for patients undergoing TC compared with medical treatment, apparent after 1 year (see Figure 1 of Windecker et al.⁹). Recognizing study biases, we used these results as most optimistic boundary for range of estimated effectiveness. We performed sensitivity analysis for varying estimates ranging from 0.28 to 1 for RR of recurrent stroke with TC compared with no treatment.

RR of ICH with Warfarin. Hart et al.,⁶ Torn et al.,⁴⁸ and Antithrombotic Trialists' Collaboration⁴⁰ estimated that Warfarin tripled the risk for ICH compared with no treatment. Eckman et al.⁴⁹ suggested higher estimate, with RR of 10. We used for a RR range from 3 to 10, with a base estimate of 7 to account for an increased risk of cerebral bleed in an elderly patient with probable CAA although no study has directly examined this question (S. Greenberg, personal communication).

Primary Analysis

The model using baseline probabilities and utilities shown in Tables 1 and 2 indicated TC as the preferred option when RR of recurrent stroke with this treatment was 0.62 or below, compared with no treatment. When this RR was set higher, model preferred Aspirin. In other words, to recommend TC, we need evidence showing that it reduces the RR for recurrent stroke by nearly 40% and absolute risk by 9.6%).

Monte-Carlo simulation of 10,000 patients, on each treatment, estimated the number of patients who would die, become permanently disabled or recuperate. Mortality for AP, AC, and no treatment was 3.48%, 3.8%, and 3.67%, respectively. Rates of permanent morbidity for AP, AC, and no treatment were 5.82%, 5.81%, and 6.42%, respectively. If TC effectiveness is 0.6 (RR for recurrent stroke), 3.15% would die and 4.78% would remain with permanent morbidity, with this treatment option. If effectiveness is 0.75, 3.59% would die and 5.08% would remain with permanent morbidity. These small differences in rates of morbidity and mortality between treatment options would translate, at age 78, into survival differences of less than 2 weeks.

Using "Tornado" diagrams, with decision model utilities and Monte-Carlo simulations, the following variables were found to be of most influence: risk of recurrent stroke with no treatment, probability of ICH, probability of death from recurrent stroke, RR of ICH with AC treatment, TC effectiveness and utility.

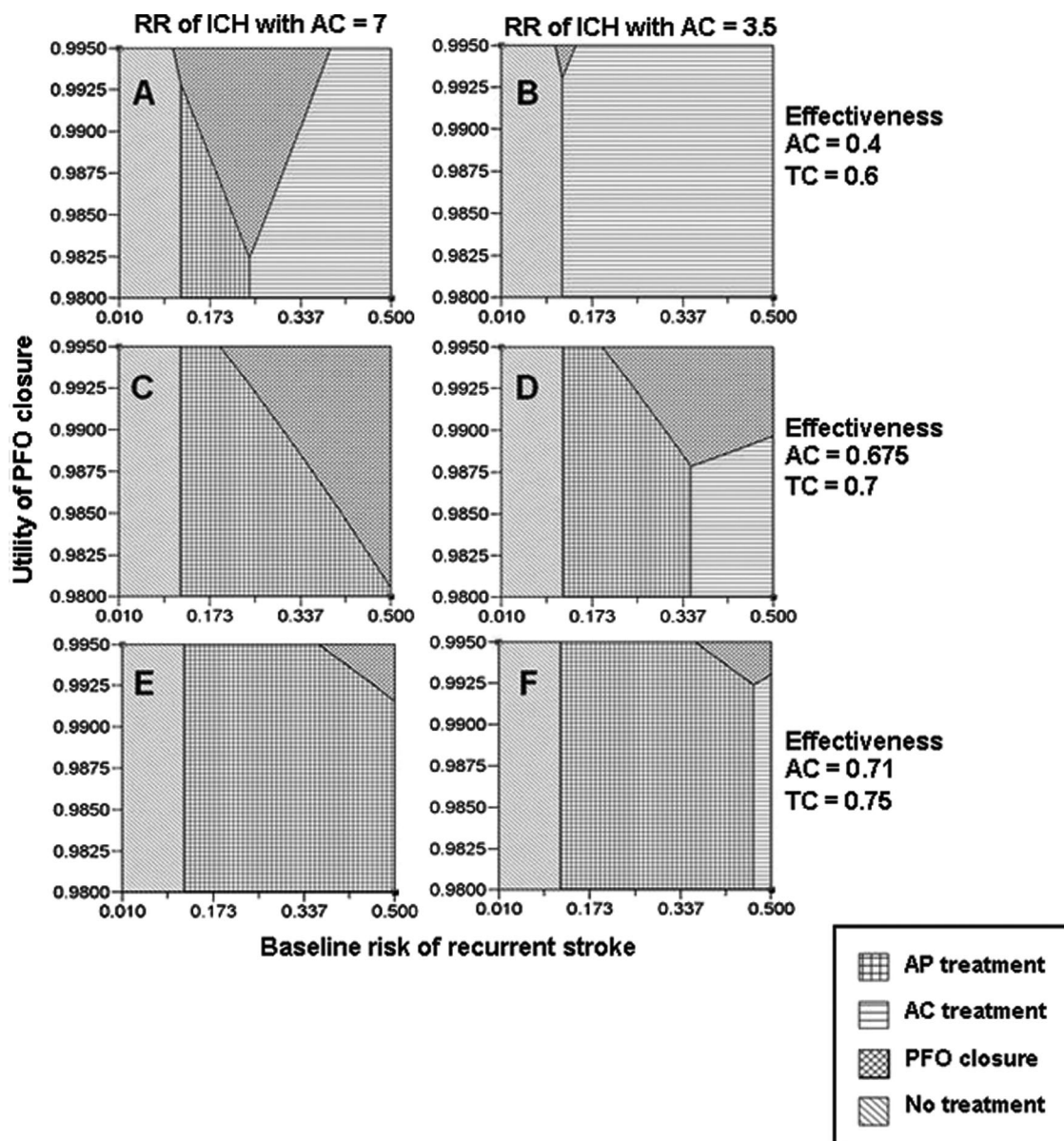


Figure 2. Multiple-way sensitivity analysis. In all 4 diagrams, x axis shows baseline risk for recurrent stroke and y axis shows utility for PFO closure. In the 3 diagrams on the left (A, C, and E), RR of ICH with AC, compared with no treatment, is set at 7, whereas it is 3.5 on the right diagrams (B, D, and F). In the upper diagrams (A and B), effectiveness of AC (measured as RR for stroke recurrence) is set at 0.4, in the middle diagrams (C and D) at 0.675, and in the lowest diagrams (E and F) at 0.71. In the upper diagrams, effectiveness of TC is set at 0.6, in the middle panels at 0.7, and in the lowest at 0.75. Example: assuming that paradoxical emboli caused initial stroke and that TC and AC are moderately effective (middle panels), if risk of recurrent stroke in following year is 0.17 and if TC utility is 0.985, preferred treatment would be AP such as Aspirin. PFO, patent foramen ovale; AP, antiplatelets; AC, anticoagulation; TC, transcatheter device closure of PFO; ICH, intracerebral hemorrhage.

Further Sensitivity Analyses

We examined changes in model preferences after concomitant changes in risk of recurrent stroke, TC effectiveness, and utility. When risk of recurrent stroke is small (less than 0.12 per year), preferred management is no treatment regardless of TC effectiveness and utility. If TC is very effective (RR = 0.28), it is the preferred option, when baseline risk of recurrent stroke is above 0.12. When TC effectiveness

is 0.6, other options become attractive. As TC effectiveness decreases, AP and AC become preferable in low and high risks of recurrent stroke, respectively.

As shown in Figure 2A, these results are further modulated by TC utility. Even in absence of any complication, utility of having to undergo a TC might be less than 1 (= perfect health), for instance because of perceived distress from an invasive procedure and/or its inconvenient timing. If utility of

this treatment option is set at 0.9825 and its effectiveness is 0.6—TC is no longer preferred in any circumstances. Choice between AC and AP is then mostly determined by risk of recurrent stroke, and by safety and efficacy of AC, as shown below.

Figure 2 illustrates results of multiple-way sensitivity analysis with varying assumptions about etiology of initial stroke and about risk of ICH from AC. In Figures 2(A) and 2(B), assuming embolic etiology for initial stroke, effectiveness of TC and AC (measured by the RR for recurrent stroke with these options) is set at 0.6 and 0.4, respectively. In the middle [Figures 2(C) and 2(D)] and lower diagrams [Figures 2(E) and 2(F)], assuming lesser chance for embolic etiology, effectiveness of both TC and AC is gradually reduced to 0.7 and 0.675, respectively (in middle diagrams) and then further to 0.71 and 0.75, respectively (in lowest diagrams).

In 3 diagrams on left [Figures 2(A), 2(C), and 2(E)], RR of ICH with AC is 7 (higher than average because of increased risk of bleeding in presence of CAA), whereas on the right, RR of ICH for patients treated with AC is 3.5 (average risk for AC).

Figure 2(B) shows that AC would be preferred option if assumed to be highly effective and associated with an average risk of ICH, provided risk of recurrent stroke is higher than 0.12 per year. In Figures 2(C) and 2(D) the choice between AP and TC is determined by baseline risk of recurrent stroke and utility given to TC. In Figures 2(E) and 2(F) the best choices become AP or no treatment.

In short, Figure 2 shows that optimal decision is very sensitive to assumptions about embolic etiology, efficacy and safety of treatments, risk of stroke recurrence, and to small changes in the utility of PFO closure.

Discussion

Israeli Prime Minister's ICH triggered major criticism of his management in the mass media. Experts questioned Sharon's management after his first neurological event and some stated decisively that one management option would have been undoubtedly better than another. Knowledge of outcome, however, influences reviewers about appropriateness of care,⁵⁰ as hindsight bias seriously restricts our ability to learn from the past.⁵¹

Our findings support a general policy when facing medical uncertainty: (1) acknowledge ignorance; (2) involve the patient and assess personal preferences; (3) prioritize good clinical trials before adopting unproven therapies, as recently discussed by others⁵²; and (4) caution should be practiced when extrapolating from results of low-grade evidence because of their inherent biases.

Optimal decision was found critically sensitive to assumptions about embolic etiology, efficacy and safety of treatments, risk of stroke recurrence and

utilities. We examined the question using formal decision analysis and literature review. We found no clear-cut preferred treatment for cryptogenic stroke associated with PFO in general and even more so in the elderly. Lack of clinical trials is the foremost reason for this uncertainty and we found no studies dealing with octogenarians.

Threshold values of PFO closure utility were very similar to those of either medical treatment (AC utility = 0.99 and AP utility = 0.998). Small changes in utility, in the order of a fraction of a percent, have major impact on preferred option. Such a reduction in utility may derive from perceived discomfort of an invasive procedure occurring at a critical time for a major politician leading a new party during a national election campaign. On the other hand, in such a situation, utility might rise if perception is that a one-shot procedure would restore personal and public image of health. Utility could therefore be affected by public expectations when a leading politician's health is at stake. Although future studies will probably determine more accurately effectiveness and safety of treatments, personal preference will always be case specific.

Our multiple-way sensitivity analysis examined 2 competing (but not mutually exclusive) hypotheses to explain the first neurological event: paradoxical embolization and microbleeds due to CAA. If both hypotheses are considered viable, all management modalities can be justified [Figure 2(A)]. Monte-Carlo simulation illustrated small absolute differences in rates of morbidity and mortality between options, in the order of a fraction of a percent, translating into an average survival difference (at age of 80) of less than 2 weeks. Such situations, in which consequences of different choices are very close, have been called "toss-ups" because a decision based on flipping a coin may not be less correct than one based on cognitive efforts.⁵³

Discussing toss-ups, Pauker and Kassirer said: "Determining whether decisions like these are toss-ups and, if they are, identifying them publicly as such could be important to patients. When 2 or more choices are a toss-up and the key elements of the outcomes (usually death and serious morbidity) are equivalent in value, patients can focus on other, more personal considerations in making their decisions." Remarkably, toss-ups often cause much controversy: "A loud and contentious public debate, with respected public organizations holding conflicting positions, creates confusion and anxiety. When we discover that 2 courses of action are roughly equivalent in value, we should calm our patients by explaining that either choice is reasonable."⁵⁴

Limitations

Our results are limited due to sources from which we abstracted data. Appropriate randomized clinical trials including elderly patients are scarce. Further-

more, our underlying assumptions, although allowing a simplified model, do not reflect reality's complexity. Also, we ignored in the analysis different PFO attributes: size, characteristic, presence or absence of inter-atrial aneurysm and of elevated right-sided heart pressures. Issues of cost and longer time horizons were not examined. Neither did we ask the question of whether nor when to obtain echocardiography for stroke evaluation.

Nobel Laureate D. Kahneman and A. Tversky have shown that the human mind has very limited capacity at combining probabilities, a frequent task for physicians.⁵⁵ Decision analysis enables systematic computation of probabilities and allows identification of most pertinent issues. In absence of strong evidence, choice is influenced by assumptions, in turn influenced by framing of clinical problem. Cardiologists or neurologists may recommend AC until fixing anatomical defects, while experts suspecting amyloid angiopathy would abstain from any treatment. Sophistication of medicine with imaging and thrombolysis options lead us to frame clinical uncertainties toward new directions departing from existing knowledge. Yet unproven therapies are often costly and may be shown, after years of use, to cause more harm than good. Our obsession with medical advances, fueled by physicians, patients, and industry, is probable cause for the spiraling rise in healthcare costs.⁵⁶ Change, begins by acknowledging ignorance,⁵² a profound departure from our too common medical narcissism.⁵⁷

After a transient neurological event, common practice might simply prescribe aspirin or, as United States' President George W. Bush told Prime Minister Ariel Sharon "eat less and exercise more" in concordance with published recommendations.⁵⁸ Intuitive and unelaborated decisions may not be necessarily less correct^{59,60} especially when facing so much incertitude. Our formal decision analysis shows the remarkable extent of unknowns in the index clinical scenario.

In conclusion, our study demonstrates that the correct treatment for an elderly patient with cryptogenic stroke and PFO is a toss-up. Patient preference is paramount when assessing management options. Use of novel therapies outside well-designed clinical trials will not reduce our uncertainty regarding their efficacy.

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