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ORIGINAL RESEARCH ARTICLE

Economic Evaluation of the Combined Use of Warfarin and Low-dose Aspirin Versus Warfarin Alone in Mechanical Valve Prostheses

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Abstract

Background The use of combined therapy of antiplatelet and anticoagulant versus anticoagulant alone to reduce instances of thromboembolic events in patients with heart valve prostheses is an established standard of care in many countries but not in Egypt. A previous Markov model cost-effectiveness study on Egyptian patients aged 50–60 years demonstrated that the combined therapy reduces the overall treatment cost. However, due to the lack of actual real-world data on cost-effectiveness and the limitation of the Markov model study to 50- to 60-year-old patients, the Egyptian medical community is still questioning whether the added benefit is worth the cost.

Objective To assess, from the perspective of the Egyptian health sector, the cost-effectiveness of the combined use of warfarin and low-dose aspirin (75 mg) versus that of warfarin alone in patients with mechanical heart valve prostheses who began therapy between the age of 15 and 50 years.

Methods An economic evaluation was conducted alongside a randomized, controlled trial to assess the cost-effectiveness of the combined therapy in patients with mechanical valve prostheses. A total of 316 patients aged between 15 and 50 years were included in the study and randomly assigned to a group treated with both warfarin and aspirin or a group treated with warfarin alone.

Results The patients in the combined therapy group exhibited a significantly longer duration of protection against the first event. Fewer primary events were observed in the patients treated with warfarin plus aspirin than in those treated with warfarin alone (1.4 %/year, vs. 4.8 %/year), and a higher mean quality-adjusted life-years (QALYs) value over 4 years was obtained for the group treated with warfarin plus aspirin (difference 0.058; 95 % CI 0.013–0.118), although this difference did not reach a conventional level of statistical significance. The total costs over a 4-year period were lower with the combined therapy (difference −US$244; 95 % CI −US$483.1 to −US$3.8), which yielded an incremental cost-effectiveness ratio of −US$4206 per QALY gained. Thus, the combined therapy was dominant. All costs were reported in US dollars (USD) for the financial year 2014.

Conclusions The results of this analysis indicate that from the perspective of the Egyptian health sector, the addition of aspirin to the typical warfarin therapy is more effective and less costly for patients with mechanical valve prostheses than treatment with warfarin alone. This combined strategy could be adopted to prevent the complications of mechanical valve prostheses. Our study adds to the body of evidence supporting the option of warfarin-plus-aspirin therapy for patients with mechanical valve prostheses.

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Key Points for Decision Makers

In patients with valve replacement, the combined use of aspirin and warfarin provides a longer duration of protection against blood clots and death than the use of warfarin alone.

The combined therapy also reduces the number of hospitalizations, improves quality of life, and reduces the overall cost of treatment.

1 Background

Valvular heart disease, which primarily affect young adults, is a growing problem because of the high incidence of rheumatic heart disease in developing countries [1, 2]. Approximately 4 million prosthetic heart valve replacements have been performed worldwide over the past 50 years [3], and this therapy remains the only definitive treatment for most patients with severe valvular heart disease. Patients who survive a heart valve replacement have a 13–20 % risk of dying within 1 year [4], a finding that substantiates the rationale for antithrombotic secondary prevention. Two categories of long-term antithrombotic therapy are generally used today: oral anticoagulant agents and platelet-inhibiting drugs.

Aspirin has been demonstrated to reduce the incidence of composite end points (valve thrombosis and systemic embolism) [5, 6]. The combined use of warfarin and aspirin may exert an additive effect by suppressing both the coagulation cascade and platelet function. Moreover, the combination may be effective with less intensive anticoagulation therapy [7, 8]. A previous Egyptian Markov-model study concluded that the combined use of warfarin and low-dose aspirin therapy is more effective and less costly than the use of warfarin alone [9]. However, the Egyptian medical community believes that the combined therapy has no added benefit and may increase cost, a belief that influences the treatment decisions of the Egyptian health sector [9]. To date, there are no local data available on the cost-effectiveness of the combined use of warfarin and low-dose aspirin in young adults with mechanical valve prostheses. Therefore, the cost-effectiveness of the combined therapy among young Egyptian patients needs to be studied from the perspective of the Egyptian health sector (public scheme).

2 Methods

An economic evaluation was conducted alongside a randomized, controlled trial of patients with mechanical valve prostheses for the prevention of thromboembolic complications. Patients were recruited within a 1-year time frame. The direct medical costs of thrombotic and hemorrhagic events, anticoagulation clinic visits, and physician visits were calculated. The economic evaluation took the form of a cost-utility analysis using quality-adjusted life-years (QALYs) based on avoidance of the primary and secondary events as the benefit measure. This study examined the potential for quality-of-life gains from a reduction in clinical events. All of the costs were converted using the purchasing power parity rate [10] and are reported in US dollars (USD) for the financial year 2014.

2.1 Clinical Study Design and Patient Population

An economic evaluation was conducted alongside a randomized, double-blind, double-arm, clinical study to assess the cost-effectiveness of the combined therapy for patients with mechanical valve prostheses. Both arms of the study received a warfarin regimen adjusted according to the international normalized ratio (INR) [two for aortic valve replacement (AVR), 2.5–3 for mitral valve replacement (MVR), and 2.5–3.5 for double valve replacement (DVR)] with one arm receiving 75-mg aspirin oral long-life tablets daily and the second arm receiving a placebo (matching dummy). The valve area, valve gradient, and INR were clinically monitored for both regimens. All other aspects of care were in accordance with local clinical practice.

The clinical benefits are expressed in terms of the avoidance of primary and secondary outcomes. The primary outcomes measured were the occurrence of valve thrombosis, which was defined as the occurrence of valve thrombosis that requires surgical intervention, and death from vascular causes. The secondary outcomes measured were major systemic embolism, non-fatal intracranial hemorrhage that requires hospital admission or blood transfusion, major extra cranial hemorrhage requiring transfusion or surgery, and all-cause mortality. The primary and secondary outcomes were recorded based on the diagnosis detailed in the medical records obtained upon hospitalization or medical intervention. All clinical events were reviewed by independent consultants for verification.

The outcomes of the two strategies were measured in terms of QALYs. This generic measurement weighs the length of life by the quality of life a patient experiences while in a specific health state. The utility values of the primary and secondary events recorded in this study were

derived from a systematic review based on clinical outcome data regarding the clinical effectiveness and cost-effectiveness obtained from different studies of the management of long-term oral anticoagulation therapy that compared the self-testing and self-management of oral anticoagulation treatment with clinic-based monitoring [11]. The QALY score for each study patient during the follow-up period in the trial was estimated by calculating the area under each patient's health utility curve using linear interpolation. Because the validity and reliability of these reported QALYs are untested, these estimates were allowed to vary over a wide range in the sensitivity analyses.

The trial recruited patients 30 days after their valve replacement surgery to avoid events related to the operation itself. This recruitment was conducted at the Cardiac and Thoracic Surgery Department at Ain Shams University (ASU) Teaching Hospital, one of the major tertiary hospitals used for referral nationwide. Patients were enrolled during the period from June 2013 through June 2014.

Both male and female patients in stable conditions (no other medical conditions) and with AVR and/or MVR who provided written informed consent were eligible. Patients with post-surgery complications, congenital blood disorders (to avoid excessive bleeding due to an abnormality of clotting factors in the blood), aspirin sensitivity, advanced liver and renal diseases, autoimmune diseases (to avoid complexity in the scope of the study), and/or biological bioprosthesis valves (which have a low risk of thrombosis), patients who were pregnant (who are not allowed to participate in a study of this nature), smokers, alcohol consumers, patients on any drug that interacts extensively with warfarin, and patients who expressed willingness to withdraw from the study were ineligible.

Although there is considerable disagreement regarding the calculation of an appropriate sample size for an economic evaluation, the sample size requirements can be estimated based on an important clinical outcome that is also believed to be correlated with economic outcomes [12, 13]. Based on these data, to ensure sufficient statistical power and to account for "dropouts" during the study, the target number of recruited patients was 316.

A total of 316 patients aged between 15 and 50 years were included in this study and randomly assigned based on the numbers assigned to the patients' folders to either the group treated with a combined therapy of warfarin and low-dose aspirin (75 mg) or the group treated with warfarin alone. The total follow-up period from time of randomization was 17 months, and the mean patient follow-up was 1.34 years (SD 0.25).

The clinical results of this study, which was defined as the number of primary events avoided, was our primary measure to assess the clinical effectiveness because no other study or outcome data are available regarding the number of events in patients in the Egyptian population with heart valve prostheses. The primary event was determined to derive a value for the utility of this event from the literature and to obtain the QALY score for each patient. The study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS): ISPOR Task Force report for reporting economic evaluation of interventions [14]. The study protocol was approved by the Research Ethics Committee of the ASU Teaching Hospital, Cairo, Egypt, where this study was conducted. This hospital is a tertiary hospital and is considered one of the four top-rated cardiology hospitals in Egypt (serving 2 million patients annually).

2.2 Extrapolation of the Trial Data

For each study patient, trial data were collected until a primary end point was reached, at which point data collection was terminated, resulting in protocol-driven missing data. In an economic evaluation, the resource use and QALYs after the clinical event are important for the calculation of costs and outcomes. Therefore, for this analysis, extrapolation beyond a primary end point or secondary endpoint was conducted up to 4 years post-recruitment, death, or trial end, whichever occurred first. We assumed that all patients who have suffered a particular major clinical event will be in the same health state and incur the same long-term costs. Cost of additional events was added and disutility of these events was subtracted whenever it occurred.

A 4-year time frame was chosen because the majority of trial participants were followed-up in terms of vital stats for at least 4 years after randomization. The costs incurred by patients after a primary event or secondary event, in addition to the acute secondary care costs, included physician visits, anticoagulation clinic visits, and long-term care. For event rates, survival, physician visits, and anticoagulation clinic attendance, the resource use rates for each patient in the period preceding the trial were calculated and applied to the post-event period. Long-term care costs (including the additional physician visits and INR visits) were assumed to apply if a patient had suffered a disabling event and literature-based estimates of quality of life were applied due to the lack of patient self-report data in Egypt.

2.3 Economic Analysis

Both economic and clinical analyses were conducted as intent-to-treat analyses. Clinical outcomes are expressed in terms of the avoidance of primary and secondary events and QALY gained [15]. The economic analysis was planned as a cost-utility analysis (i.e., cost per QALY).

The economic study was performed from the perspective of the Egyptian health sector. Related nonmedical resources (e.g., patient transportation to and from the clinics) and effects of treatment on workplace productivity (i.e., indirect costs) were not assessed in this study. We present the results with costs and outcomes discounted at 3.5 %, as is recommended by the Egyptian guidelines for economic analyses of health technologies for which costs and benefits accrue beyond 1 year [16].

2.4 Data Collection

Medical resource use forms from the accounting department of this tertiary hospital were used as the means of data collection on resource use. The resource use data were concentrated on three main areas: clinical events, physician visits, and anticoagulation clinic visits. Primary and secondary outcome data on clinical events were obtained from primary-care records, hospital records, and death certificates. The total number of physician visits was recorded for every patient. Data on INR tests were collected from the oral anticoagulation service provider. The investigators compared the resources used onsite with those used outside the study site by checking with potential providers of care in the patient's community to ensure that the resources used were within the norms.

The health-service resource costs were estimated using the mean hospital costs published for certain services [17]. This secondary research method provided the best available evidence for the valuation of health-service resources in terms of their unit costs. Gross costing was performed because micro costing was deemed to be overly costly and burdensome for the study [18, 19]. No capital costs were included. Given the very low costs of both warfarin and aspirin and minimal difference from warfarin alone, these drug costs were not included in the cost analysis. Local currency conversions to USD were performed using the purchasing power parity rate [10]. All of the costs are reported in USD for the year 2014.

2.5 Statistical Analysis

Statistical analyses were performed using the SPSS package, version 22 (SPSS, Inc., Chicago, IL, USA). All events were recorded until the closing date regardless of whether a patient stopped taking the study drug. The subject characteristics for both treatment groups were summarized using descriptive statistics. Means, standard deviations, standard errors, and mean differences with 95 % confidence intervals (CIs) were computed for each treatment arm. Two-sample comparisons were performed using two-sided Student's t tests for normally distributed variables and Mann-Whitney U tests for non-normally distributed data. Comparisons of proportions were conducted using Chi-square or Fisher's exact tests. Curves showing event-free survival were plotted using the Kaplan Meier method. The differences in event-free survival were plotted using the Wilcoxon test. A significance level of $P \leq 0.05$ was used.

2.6 Sensitivity Analysis

To address the uncertainty associated with the incremental cost-effectiveness ratio (ICER) and to test the stability of our results across variations in the key variables, we performed various one-way sensitivity analyses as recommended by the CHEERS: ISPOR Task Force report [13]. All key variables were varied through standard errors or reasonable ranges (Table 1). Additional analyses were conducted: comparing LOS related to events in the study population with the LOS used to calculate the mean hospital costs; extrapolating the time horizon of the analysis (lifetime horizon); using cost per event avoided as an alternative outcome instead of QALYs.

To assess how a simultaneous change in several variables affects the ICER, a probabilistic sensitivity analysis (PSA) was performed. This technique runs a large number of simulations (here, 1000) by repeatedly drawing samples from probability distributions of the input variables and thus provides a probability distribution of the output variables, i.e., incremental costs, incremental effectiveness, and ICERs [20]. One-way sensitivity analyses and PSA were performed using Microsoft Excel 2010.

3 Results

A total of 316 patients were included and screened in this study (group treated with warfarin plus aspirin, 160 patients; group treated with warfarin alone, 156). The baseline characteristics in terms of key variables were similar (non-significant) in both arms of the trial (Table 2). The baseline mean ejection fraction was higher (P value of 0.001) in the warfarin-plus-aspirin arm (59 %; SD 5.5) than in the warfarin arm (55 %; SD 6.3). Of the recruited patients, 4.4 % (14 patients; non-significant) were lost to follow-up after randomization. Patients from both groups withdrew from the study during the follow-up period based on the physician's or patient's decision (no significant difference among the groups).

Fewer primary events were found in the warfarin-plus-aspirin arm than in the warfarin arm (1.4 %/year; SE 6, versus 4.8 %/year; SE 10.9), and a significant difference was found in the event rate among the arms ($P = 0.05$). Additionally, the mean QALY score obtained for the warfarin-plus-aspirin arm was higher (difference, 0.058;

Table 1 Uncertainty ranges used in one-way sensitivity analysis of the ICER

Input parameters	Base case	SE	Distribution	Low value	High value
Major extracranial hemorrhage W + ASA event rate	0.009	0.045	Beta	−0.036	0.054
Non-fatal intracranial hemorrhage W + ASA event rate	0.009	0.045	Beta	−0.036	0.054
Major systemic embolism W + ASA event rate	0.005	0.035	Beta	−0.03	0.05
Valve thrombosis W + ASA event rate	0.009	0.045	Beta	−0.036	0.054
Physician visits W + ASA[a] event rate	3.9	0.15	Normal	3.7	4
INR visits W + ASA[a] event rate	32.7	2	Normal	30.6	34.7
Major extracranial hemorrhage W event rate	0.016	0.06	Beta	−0.045	0.077
Non-fatal intracranial hemorrhage W event rate	0.016	0.06	Beta	−0.045	0.077
Major systemic embolism W event rate	0.037	0.09	Beta	−0.05	0.12
Valve thrombosis W event rate	0.03	0.08	Beta	−0.05	0.11
Physician visits W[a] event rate	3.7	0.3	Normal	3.3	4
INR visits W[a] event rate	16.7	2.7	Normal	13.9	19.4
Major extracranial hemorrhage cost[b]	US$3030	NA	Normal	US$2424	US$3636
Non-fatal intracranial hemorrhage cost[b]	US$2500	NA	Normal	US$2000	US$3000
Major systemic embolism cost[b]	US$1363	NA	Normal	US$1090	US$1635
Valve thrombosis cost[b]	US$4545	NA	Normal	US$3636	US$5454
Physician visits cost	US$16.6	NA	Normal	US$13.28	US$19.92
INR visits cost	US$2.2	NA	Normal	US$1.76	US$2.64
# of events W	−9	NA	Normal	−7.2	−10.8
# of events W + A	−3	NA	Normal	−2.4	−3.6
Discount rate	3.5 %	NA	Normal	2 %	6 %
Major extracranial hemorrhage_W + ASA utility	0.54	NA	Beta	0.44	0.64
Non-fatal intracranial hemorrhage_W + ASA utility	0.72	NA	Beta	0.71	0.73
Major systemic embolism_W + ASA utility	0.45	NA	Beta	0.35	0.55
No events utility	0.738	NA	Beta	0.718	0.758

ICER incremental cost-effectiveness ratio, *SE* standard error, *W* warfarin, *W + ASA* warfarin plus aspirin, *INR* international normalized ratio, *NA* non-applicable

[a] Additional physician visits event rate for W, 1.3; additional physician visits event rate for W + ASA, 1.6; additional INR visits event rate for W, 7.3; additional INR visits event rate for W + ASA, 9.1

[b] One-time cost

95 % CI 0.013–0.118), but the difference did not reach a conventional level of statistical significance ($P = 0.116$; Table 3). The event-free survival curves are shown in Fig. 1, and the patients in the warfarin-plus-aspirin group presented a significantly longer duration of protection against the first event. The overall difference in effect yielded a P value of 0.046 (Wilcoxon method).

Table 4 shows a breakdown of the resource use data and mean healthcare costs per patient over 4 years. The intention-to-treat principle was maintained throughout the analysis. The warfarin-plus-aspirin arm presented lower event costs, and this difference was primarily driven by the difference in primary events. As expected, the warfarin-plus-aspirin arm presented slightly higher physician visit costs and considerably higher INR visit costs. The warfarin-plus-aspirin group had lower total costs per patient than the warfarin group (US$310 vs. US$554), and this difference between the groups was significant ($P = 0.049$).

The warfarin-plus-aspirin arm was associated with lower costs and a higher QALY score than the warfarin arm: an ICER of –US$4206 per QALY gained was found for the warfarin-plus-aspirin arm, indicating that the combined therapy (warfarin plus aspirin) is the dominant treatment option.

3.1 Sensitivity Analysis

To take into account the uncertainty around the point estimates, an incremental cost-effectiveness plane was constructed. The plane in Fig. 2 shows the 1000-iteration cost-outcome difference pairs. As shown, most difference pairs are found in the northeast and southeast quadrants, this indicates that the warfarin-plus-aspirin strategy is more effective (i.e., positive incremental QALYs scores), and there is a greater proportion in the southeast quadrant indicating the treatment is less costly.

Table 2 Baseline characteristics of the patients in both arms

Demographic data	Warfarin ($n = 156$)	Warfarin plus aspirin ($n = 160$)	P value
Mean age, years (SD)	37.5 (8.5)	38 (7.5)	0.5
Sex, male, n (%)	67 (42.9)	71 (44.3)	0.7
Mean weight, kg (SD)	79.8 (10.4)	78.4 (9.6)	0.1
Valve type, n (%):			0.36
Mitral	84 (53.8)	75 (46.8)	
Aortic	34 (21.7)	45 (28.1)	
Double valves	38 (24.3)	40 (25)	
History, n (%):			0.7
Heart valve replacement	2 (1.2)	4 (2.5)	
Arterial thromboembolism	25 (16)	20 (12.5)	
Bleeding	93 (59.6)	103 (64.3)	
Rheumatic fever	26 (16.6)	20 (12.5)	
Uncontrolled hypertension	9 (5.7)	11 (6.8)	
Heart failure	1 (0.6)	2 (1.2)	
Mean mitral valve size, mm (SD)	27.4 (2.1)	27.5 (2.3)	0.7
Mean aortic valve size, mm (SD)	21.1 (1.5)	21.2 (1.9)	0.8
Mean pre-operation pulse rate, n (SD):			
Sinus	54 (34.6)	67 (41.8)	0.3
Atrial fibrillation	15 (9.6)	11 (6.8)	
Procedures, n (%):			0.2
Coronary artery bypass graft	12 (7.6)	6 (3.7)	
Other	40 (25.6)	50 (31.2)	
Mean valve area, cm^2 (SD)	3.0 (0.5)	3.1 (0.5)	0.57
Mean valve gradient, mmHg (SD)	3.4 (2.5)	3.7 (2.0)	0.25
INR, n (%):			0.7
Within range	81 (51.9)	84 (52.5)	
Below range	42 (26.9)	47 (29.3)	
Above range	33 (21.1)	29 (18.1)	
Mean ejection fraction, % (SD)	55 (6.3)	59 (5.5)	0.001

INR international normalized ratio, *SD* standard deviation

Table 3 Mean outcomes per patient

Outcomes	Warfarin ($n = 156$) mean (SE)	Warfarin + aspirin ($n = 160$) mean (SE)	Difference in mean	P value	95 % CI for difference in mean
Annual primary event rate	4.8 % (10.9)	1.4 % (6)	−3.4 %	0.05	−7.8 to 0.1
Overall total events	12.1 % (16.5)	4.7 % (10.8)	−7.4 %	0.05	−13.6 to −1.7
QALYs	2.087 (0.18)	2.145 (0.09)	0.058	0.116	0.013 to 0.118

QALY quality-adjusted life-year, *SE* standard error, *CI* confidence interval

A one-way sensitivity analysis (Fig. 3) was conducted to determine how changes in key variables affect the results. The utility for major extracranial hemorrhage of warfarin plus aspirin was found to have the greatest effect on the results. Given the uncertainty surrounding the point estimates of the event utilities, a sensitivity analysis using published ranges [10] was conducted. This analysis revealed no effect on treatment decision, using the threshold ICER in Egypt (three times gross domestic product per capita). The base-case analysis conducted in the present study utilized the cost for mean ASU teaching hospital costs. The sensitivity analysis performed using the uncertainty ranges (Table 1) assumed from the low and high values of the hospital costs did not alter the conclusions reached. The treatment decision was not significantly affected by most other variables over plausible ranges.

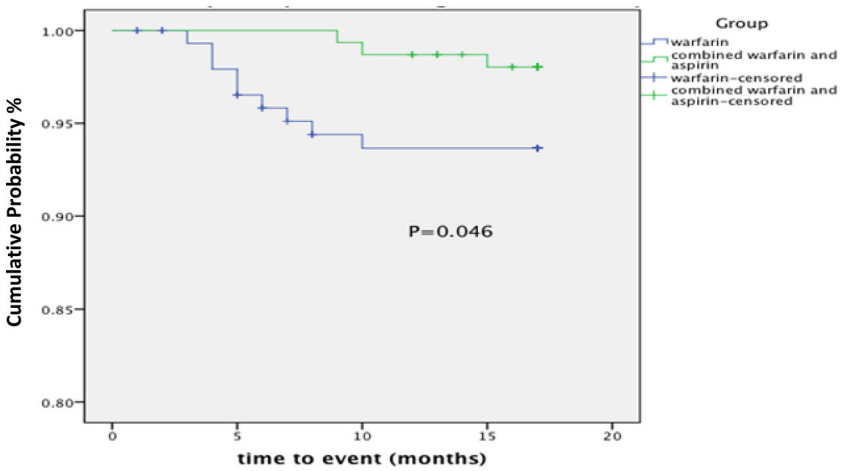

Fig. 1 Event-free survival curves for the primary end point

Table 4 Unit costs, mean use of healthcare resources, and mean total costs per patient over 4 years

Event	Warfarin ($n = 156$)		Warfarin + aspirin ($n = 160$)		Unit cost (US$)	Differences in the mean use	Differences in the mean cost
	Mean use (SE)	Mean cost	Mean use (SE)	Mean cost			
Major extracranial hemorrhage	0.016 (0.06)	48	0.009 (0.045)	29	3030	−0.007	−19
Non-fatal intracranial hemorrhage	0.016 (0.06)	40	0.009 (0.045)	24	2500	−0.007	−16
Major systemic embolism	0.037 (0.09)	50	0.005 (0.035)	7	1363	−0.032	−43
Valve thrombosis	0.03 (0.08)	138	0.009 (0.045)	42	4545	−0.021	−96
Physician visits	3.7 (0.3)	62	3.9 (0.15)	66	16.6	0.2	4
INR visits	16.7 (2.7)	38	32.7 (2.04)	75	2.2	16	37
Mean total costs	554 (660)		310 (388)				
Difference in total cost	−244						
95 % CI for difference in total cost	−483.1 to −3.8						

SE standard error, *CI* confidence interval, *INR* international normalized ratio

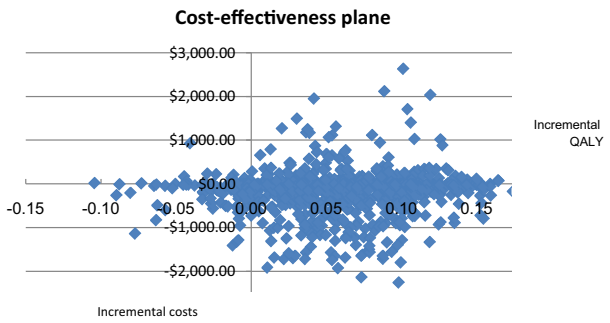

Fig. 2 Incremental cost-effectiveness plane for warfarin + aspirin versus warfarin

Additional analyses were conducted. The first analysis compared the LOS related to events in the study population with the LOS used to calculate the mean hospital costs, but did not change the treatment decision. The second analysis extrapolated the time horizon to a longer period, which resulted in a gain in QALYs and negative incremental costs for the combined therapy that seemed to be driven by the trend toward decreased disabling event rates in the patients who were treated with the combined therapy. In the other scenario, the cost per event avoided as an alternative outcome instead of QALYs, yielded an ICER of −US$40 per QALY gained for warfarin plus aspirin, indicating that the combined therapy is the dominant treatment option.

Additionally, a PSA on the ICER was conducted. All of the variables were simultaneously varied within various error distributions over 1000 iterations. The results of the PSA are also depicted in the cost-effectiveness plane scatter plot shown in Fig. 2. A cost-effectiveness acceptability curve was generated to illustrate the probability that each strategy is cost-effective at varying levels of willingness to pay (per QALY gained; Fig. 4).

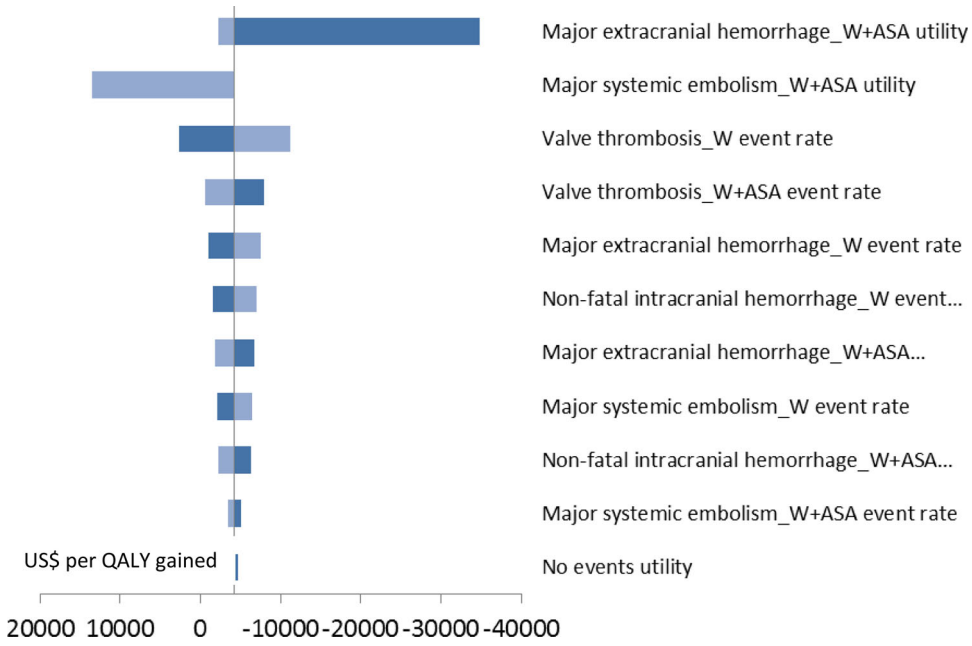

Fig. 3 Results of the one-way sensitivity analysis of the ICER. The *darker color bar* corresponds to results when lower value of parameter is used. *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *W* warfarin, *W + ASA* warfarin plus aspirin

4 Discussion

This is the first trial-based economic evaluation that utilized data from a randomized, controlled trial designed specifically to address the question of warfarin-plus-aspirin use in a younger population. The results of this trial have important implications for current treatment decisions regarding prosthetic heart valves. First, this analysis finds that the addition of aspirin to warfarin therapy for the prosthetic heart valve patient population saves healthcare resources. Second, the results of the PSA performed in this study indicate that the warfarin-plus-aspirin strategy is likely to be less costly and more effective, as depicted by the greater proportion shown in the southeast quadrant, which indicates that the treatment is more effective. Together, these findings suggest that healthcare decision makers in Egypt should consider adopting the warfarin-plus-aspirin regimen as a standard therapy for the prevention of complications due to prosthetic heart valves.

A key strength of this work is the employment of a site that is most representative of centers where the target population will be treated to avoid bias if patients who receive care at trial sites differ from patients receiving care at standard practice settings. Additionally, the variability resulting from different management strategies and testing methods was controlled because all of the patients were managed at the same anticoagulation clinic with the same anticoagulation monitor. We addressed the effects of blinding on real-world practice by subtracting the resources consumed for the purposes of maintaining blinding from the total costs. The present study is the first trial-based economic evaluation study that addresses both the economic and the clinical implications of the combined therapy in patients with mechanical heart valve prostheses. Similar cost-effectiveness analyses of the combined use of warfarin and aspirin are lacking in Egypt. This study addresses the debate that exists between physicians regarding the costs of potential complications.

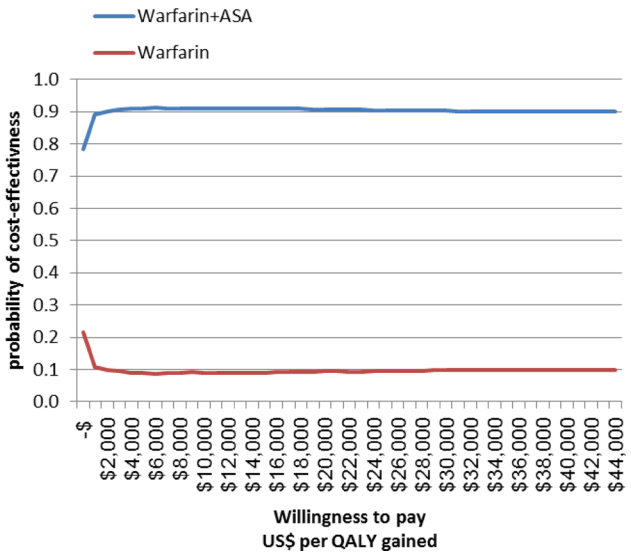

Fig. 4 Cost-effectiveness acceptability curve for warfarin + aspirin versus warfarin. *QALY* quality-adjusted life-year, *W* warfarin, *W + ASA* warfarin plus aspirin

Similar findings were obtained in other studies that assessed the clinical effectiveness and cost-effectiveness of

different models of managing long-term oral anticoagulation therapy in older age groups [10, 21]. Previous studies have demonstrated that the addition of aspirin to warfarin therapy reduces the risk of thromboembolic events but results in an increased or equivalent risk of bleeding compared with warfarin alone [10, 22–24].

This study has several limitations that are worth mentioning. First, it was not feasible to control for all confounders; these were limited to the greatest extent possible by excluding smokers, alcohol consumers, and patients taking any drug that interacts extensively with warfarin. Although we attempted to account for as many confounding factors as possible, we did not gather information on the patients' diet, compliance with anticoagulant drug therapy, and changes in health status. However, because our data were collected from stable patients, and because the INRs did not vary, we do not believe that any changes in these variables were sufficiently significant to affect anticoagulation control. Second, in this study, we derived the quality of life gains for the clinical events experienced by the mechanical heart valve patients from literature-based estimates because their valuations are lacking in Egypt. However, outcomes that matter to patients or healthcare systems are increasingly emphasized instead of surrogate end points, but this study focused on the potential for quality-of-life gains due to a reduction in clinical events. Third, the accuracy of our study would have been improved by the inclusion of information on genetic polymorphisms because polymorphisms of the vitamin K epoxide reductase complex subunit 1 gene and the CYP2C9 gene are important determinants of warfarin dosing. However, information on genetic polymorphisms was not included in many studies due to the difficulty and the questionable utility of performing genetic evaluations in clinical settings. Many clinicians believe that a genetic-based dosing scheme is unlikely to result in a practical advantage because of several reasons, including timely access to genotyping, which may result in unnecessary treatment delays and subsequent prolongation of the parenteral anticoagulation, increased costs, and inability of genetic-based models to account for environmental factors. Furthermore, dosing adjustments continue to be based on INR values that could be considered a surrogate marker of genetic information.

Other major limitations that need to be considered when assessing the relative generalizability of this study were missing data, short trial period, and consideration of only direct medical cost. An additional limitation is our assumption that the resource use rates after and before the event are similar due to lack of data. We recommend that future research studies on the same specific population address these limitations.

The results of our trial-based economic evaluation were primarily driven by differences in the primary and secondary event rates that occurred among the warfarin-plus-aspirin arm in this study. This combined therapy strategy will potentially be applicable to other settings in Egypt because there are no major differences in clinical practices between rural and urban areas; thus, the combined therapy could lead to the best protection and substantial savings in healthcare system resources.

5 Conclusions

In this time of growing demands on limited healthcare resources, assessments of the cost-effectiveness of therapies are becoming increasingly necessary in Egyptian healthcare. Overall, the results of this analysis indicate that from the perspective of the Egyptian health sector, the addition of aspirin to warfarin therapy is more effective and less costly than treatment with warfarin alone for patients with mechanical valve prostheses. This combined strategy could be adopted to prevent complications of mechanical valve prostheses. Our study adds to the body of evidence supporting the option of warfarin-plus-aspirin therapy for patients with mechanical valve prostheses. Additionally, future research should seek to establish the health-state preferences for this specific patient population using methods that are conducive to cost-effectiveness analysis, such as standard gamble and time trade-off.

Author contributions G. Elsisi collected the data, performed the analysis, and wrote the manuscript. M. Elhamamsy, R. Eldessouki, and G. Elsisi designed the study, developed the methodology, interpreted the data, and revised the manuscript. A. Taha, H. Elmansy, M. Elmazar, and B. Awad revised and edited the manuscript.

Compliance with Ethical Standards

M. El-Hamamsy, G. Elsisi, R. Eldessouki, M. Elmazar, A. Taha, B. Awad, and H. Elmansy do not have any conflicts of interest to declare. No funding was received for this study. Both male and female patients in stable condition (no other medical conditions), with aortic valve replacement and or mitral valve replacement provided written informed consent. The study protocol was approved by the Research Ethics Committee of Ain Shams University Teaching Hospital, Cairo, in which this study was conducted. The study was performed in accordance with the ethical standards of the Declaration of Helsinki.

References

1. Carapetis JR, Steer AC, Mulholland EK, et al. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005;5(11):685–94.
2. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005–11.

3. Sun JC, Davidson MJ, Lamy A, et al. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. Lancet. 2009;374(9689):565–76.
4. Piazza N, Kalesan B, van Mieghem N, et al. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. JACC Cardiovasc Interv. 2013;6(5):443–51.
5. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA guidelines for the management of patients with valvular heart disease. J Am Coll Cardiol. 2008;52(13):e1–142.
6. Mohamed H. Antithrombotic therapy in patients with prosthetic heart valves. Libyan J Med. 2009;4(1):54–6.
7. Perez-Gomez F, Salvador A, Zumalde J, et al. Effect of antithrombotic therapy in patients with mitral stenosis and atrial fibrillation: a subanalysis of NASPEAF randomized trial. Eur Heart J. 2006;27:960–7.
8. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet. 1998;351:233–41.
9. Elsisi GH, Eldessouki R, Kaló Z, et al. Cost-effectiveness of the combined use of warfarin and low-dose aspirin versus warfarin alone in Egyptian patients with aortic valve replacements: a Markov model. Value Health RI. 2014;4C:24–30.
10. IMF World Economic Outlook (WEO) data website. http://www.econstats.com/weo/V013.htm.
11. Connock M, Stevens C, Fry-Smith A, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. Health Technol Assess. 2007;11(38):7–38.
12. O'Sullivan, Thompson D, Drummond MF. Collection of health-economic data alongside clinical trials: is there a future for piggyback evaluations? Value Health. 2005;8(1):67–79.
13. Oyejide OO. Health reseach methods. Ibadan: Leniks Publishers; 1992.
14. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: a Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16:231–50.
15. Jowett S, Bryan S, Mant J, et al. Cost effectiveness of warfarin versus aspirin in patients older than 75 years with atrial fibrillation. Stroke. 2011;42:1717–21.
16. Elsisi GH, Kaló Z, Eldessouki R, et al. Recommendations for reporting pharmacoeconomic evaluations in Egypt. Value Health RI. 2013;2:319–27.
17. Ain Shams University Teaching Hospital local data.
18. Glasziou PP, Simes RJ, Hall J, et al. Design of a cost-effectiveness study within a randomized trial: the LIPID trial for secondary prevention of IHD. Control Clin Trials. 1997;18:464–76.
19. Gold MR, Siegel JE, Russell LB, et al, editors. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
20. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.
21. Larson RJ, Fisher ES. Should aspirin be continued in patients started on warfarin? A systematic review and meta-analysis. J Gen Intern Med. 2004;19:879–86.
22. Laffort P, Roudaut R, Roques X, et al. Early and long-term (one year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. J Am Coll Cardiol. 2000;35:739–46.
23. Turpie AG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med. 1993;329:524–9.
24. Meschengieser SS, Fondevila CG, Frontroth J, et al. Low-intensity oral anticoagulation plus low-dose aspirinversus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. J Thorac Cardiovasc Surg. 1997;113:910–6.