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Percutaneous left atrial appendage closure for stroke prevention in patients with atrial fibrillation: an assessment of net clinical benefit

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Aims The PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial found left atrial appendage (LAA) closure an alternative to anticoagulation in selected patients with non-valvular atrial fibrillation (AF). We aim to estimate the net clinical benefit (NCB) of percutaneous LAA closure.

Methods and results *Post hoc* analysis of outcomes among 707 adults with AF in the PROTECT-AF trial and 566 in the Continued Access (CAP) registry undergoing LAA closure with the Watchman device compared with sustained anticoagulation. Outcomes were ischaemic stroke, intracranial haemorrhage, major bleeding, pericardial effusion, and death, weighted to reflect the relative impact in terms of death and disability. Net clinical benefit was calculated as the sum of annualized rates of these outcomes after intervention minus rates on warfarin. The NCB of LAA closure during 1623 person-years follow-up in the trial was 1.73%/year (95% CI: −0.54 to 4.39%/year) and during 741 patient-years in the registry was 4.97%/year (95% CI: 3.07–7.15%/year). Among patients with a history of ischaemic stroke, the NCB was greater in the registry (8.68%/year, CI: 2.82–14.92%/year) than the trial (4.30%/year, CI −2.07 to 11.25%/year). In the registry, the NCB of LAA closure increased from 2.22%/year (CI: 0.27–6.01%/year) in patients with $CHADS_2$ scores = 1 to 6.12%/year (CI: 3.19–8.92%/year) in those with scores ≥2.

Conclusion Combining rates of thrombo-embolism, intracranial haemorrhage, major adverse events, and death allows objective comparison of the benefit and risk of device therapy vs. anticoagulation in patients with AF. The NCB of LAA closure is greatest for patients at a higher risk of stroke.

Keywords Net clinical benefit • Atrial fibrillation • Left atrial appendage • Watchman • Stroke

Introduction

Although anticoagulation is effective in reducing the risk of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF), warfarin increases the risk of intracerebral haemorrhage (ICH) even when given at the recommended dose intensity.[1,2] In an attempt to weight the relative benefit of warfarin, the net clinical benefit (NCB) of warfarin anticoagulation was assessed in 13 599 patients in the community-based Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) cohort followed over a median of 6 years. This study assigned an impact factor of 1.0 to ischaemic stroke and 1.5 to ICH, and revealed an overall benefit of warfarin.[3] However, one criticism was that the study took a neurologically focused view of NCB, and did not account for the risk of extracranial bleeding or non-stroke mortality.[4]

Embolism of thrombus from the left atrial appendage (LAA) is thought to account for most ischaemic strokes in patients with AF.[5] Warfarin remains the standard therapy to prevent thrombus

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formation, but newer Factor IIa and Xa inhibitors have at least comparable efficacy with lower rates of ICH.[6–8] Another alternative for thrombo-embolism prevention is percutaneous catheter-based LAA closure.[9,10] The previously reported results of The PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial demonstrated the efficacy of LAA closure using the Watchman filter device compared with warfarin therapy in selected patients with AF.[11,12] The procedure was associated with complications, however—most notably, pericardial effusion (PEF) with tamponade physiology, and procedure-related stroke. These complications were related to operator experience over the course of the trial.[13] Indeed, a subsequent non-randomized Continued Access PROTECT-AF registry (CAP) that involved more experienced operators demonstrated significantly fewer PEFs and no instances of procedure-related stroke.[13]

To examine the NCB of LAA closure, we examined the annualized rates of ischaemic stroke, ICH, major extracranial bleeding, PEF, and death (DE) for patients enrolled in either the randomized PROTECT AF trial or the non-randomized CAP registry. After weighting these events relative to DE, the resulting combined annualized rates on warfarin were then subtracted from the respective annualized rates after LAA closure. The results shed light on optimum selection of patients with AF for percutaneous LAA closure as an alternative to long-term anticoagulation.

Methods

Study populations

The PROTECT-AF trial cohort enrolled 707 patients with non-valvular AF at 59 sites in the USA and Europe between February 2005 and June 2008. The design of the trial and clinical characteristics of the cohort have been described.[11] In brief, consenting patients aged 18 years or older with paroxysmal, persistent, or permanent AF were eligible if they had $CHADS_2$ risk scores ≥ 1. Exclusion criteria included contraindications to warfarin, comorbidities other than AF requiring anticoagulation, detection by transoesophageal echocardiography (TEE) of LAA thrombus, patent foramen ovale with atrial septal aneurysm and right-to-left shunt, mobile aortic atheroma, and symptomatic carotid artery disease. Eligible patients underwent baseline neurological assessment, and those with a history of stroke or transient ischaemic attack (TIA) underwent CT or MR imaging at entry.

Patients were randomly assigned to the intervention or control groups in a 2:1 ratio. The intervention involved percutaneous LAA closure with the Watchman device (Atritech, Plymouth, MN, USA), a self-expanding nickel–titanium (Nitinol) frame with fixation barbs and a permeable polyester fabric cover, implanted via trans-septal catheter-based approach to seal the ostium of the LAA.[10,12] After implantation, patients were treated with warfarin for 45 days to allow endothelialization of the device, following which clopidogrel (75 mg daily) plus aspirin (81–325 mg daily) were prescribed until completion of the 6-month follow-up visit, and aspirin alone was continued thereafter. Patients in the control group received warfarin for the duration of the study [target international normalized ratio (INR) 2.5, range 2.0–3.0]. Follow-up visits occurred at 45 days after entry, 6, 9, and 12 months, and twice annually thereafter, with neurological assessments at baseline, 12 and 24 months, or whenever neurological symptoms developed during follow-up.

At the end of the trial, 566 additional patients with AF were enrolled in the non-randomized, single-arm CAP registry at academic medical centres in the USA and Europe. Percutaneous LAA closure procedures and subsequent antithrombotic management were the same, but operators were more experienced than during the trial.

Outcome assessments

In both cohorts, patients were evaluated using the NIH stroke scale (NIHSS) at baseline, 45 days, 12 and 24 months after entry and within 48 h after the onset of symptoms suggestive of stroke or TIA. The modified Rankin score (MRS) and the Barthel index (BI) were measured at 6-, 9-, and 18-month telephone follow-up contacts, at all clinic visits, and within 90 days of stroke or TIA. Patients were referred for neurological evaluation if there was an increase in the NIHSS score of ≥ 2 points, increase in the MRS ≥ 1 point or increase in BI ≥ 15 points. Ischaemic stroke was defined as the sudden onset of a focal neurological deficit in the distribution of a single brain artery with symptoms and/or signs persisting ≥ 24 h or when ≤ 24 h if accompanied by the evidence of tissue loss without haemorrhage based on CT or MR brain imaging. Diagnosis of ICH was based on the sudden onset of neurological deficit with CT or MR evidence of haemorrhage.

All DEs were investigated, and the circumstances surrounding the event were documented. Autopsy results and explantation of the device were obtained whenever possible. Mortality was categorized as cardiovascular or non-cardiovascular in aetiology. Cardiovascular DE included sudden DE and DE due to cardiac arrhythmia, MI, stroke, heart failure, and DE of uncertain aetiology when witnessed as instantaneous or near-instantaneous, occurring without warning or within 1 h of non-diagnostic symptoms, or when the cause could not be determined.

Patients underwent screening for PEF by transthoracic echocardiography (TTE) and by TEE before and within 2 days after device implantation. A TEE was repeated at 45 days, 6 months, and 12 months afterwards in the PROTECT-AF trial. In the CAP registry a TEE was repeated at 45 days and 12 months afterwards in all patients, and at 6 months at the discretion of the treating physician. We defined PEF as significant when fluid in the pericardial space resulted in haemodynamic compromise or required percutaneous or open surgical drainage. This definition includes cardiac perforation, defined as effusion measuring >1 cm by TTE causing cardiac tamponade or haemodynamic derangement requiring surgical closure. It does not include effusions requiring no intervention, because such effusions are rarely associated with mortality or residual morbidity.[14,15]

The whole blood haemoglobin content was measured at baseline and daily during the procedural hospitalization. We defined major bleeding (MB) as that requiring transfusion of ≥ 2 units of packed red blood cells or surgical intervention. All events were adjudicated by an independent Clinical Events Committee.

Net clinical benefit

We defined the NCB of percutaneous LAA closure as the sum of the differences between the annualized rates of ischaemic stroke (TE), ICH, DE, MB, and significant PEF occurring after intervention and the respective rates on warfarin, weighting each component by a factor reflecting the severity of functional impact relative to DE (unity), according to the following equation:

$$\begin{aligned}\mathrm{NCB} = {} & (\mathrm{DE}_{\mathrm{warfarin}} - \mathrm{DE}_{\mathrm{intervention}}) + \mathbf{0.6} * (\mathrm{ICH}_{\mathrm{warfarin}} - \mathrm{ICH}_{\mathrm{intervention}}) \\ & + \mathbf{0.2} * (\mathrm{TE}_{\mathrm{warfarin}} - \mathrm{TE}_{\mathrm{intervention}}) + \mathbf{0.1} * (\mathrm{MB}_{\mathrm{warfarin}} - \mathrm{MB}_{\mathrm{intervention}}) \\ & + \mathbf{0.1} * (\mathrm{PEF}_{\mathrm{warfarin}} - \mathrm{PEF}_{\mathrm{intervention}}).\end{aligned}$$

In their analysis of mortality data from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events

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(ACTIVE) trials, Connolly *et al.*[16,17] reported that the adjusted hazard ratio for DE after haemorrhagic stroke was 3.08 higher than that of ischaemic stroke. In addition, they reported that the adjusted hazard ratio for DE after major extracranial bleeding was 0.67 times lower than that of ischaemic stroke.[16] In our model, the maximum weight is ascribed to DE (1.00), while all other adverse events are given a weight as a fraction (0.00–1.00). We selected a weight of 0.20 for ischaemic stroke as our reference weight, and applied the relative weights described by Connolly *et al.* to our model in the same ratios. We also provide additional sensitivity analysis by using reference weight factors of 0.10 and 0.30 (*Table 1*). In our base case, we set the weight of a haemorrhagic stroke (0.60) to be three times the risk of an ischaemic stroke (0.20), and the weight of an MB event (0.10) or pericardial tamponade (0.10) to be roughly half the weight of an ischaemic stroke. Major bleeding requiring transfusion and PEFs requiring intervention were both assigned impacts of 0.1, reflecting the lower mortality associated with these events.[14,15] Indeed, in both PROTECT-AF and the CAP registry, there were no instances of mortality associated with PEFs. Patients managed with warfarin in the control group of the PROTECT-AF trial served as the comparator against which the NCB of LAA closure was assessed for patients undergoing intervention in both the randomized trial and subsequent CAP registry.

Statistical analysis

The incidence of thrombo-embolism, ICH, DE, MB, and PEF was calculated as the number of events per 100 person-years of follow-up. Person-years were calculated from the date of randomization to the date of last known follow-up or DE. The NCB was calculated using outcome events from the PROTECT-AF cohort and CAP registry. Risk factors used as control variables included age, sex, prior ischaemic stroke, hypertension, diabetes, and heart failure. Statistical significance was accepted at the 95% confidence level (CI) (two-sided $P \leq 0.05$) without adjustment for multiple comparisons. To obtain the 95% CI surrounding the NCB, we used a bootstrap sample of 1000 replications. The analysis was stratified by the $CHADS_2$ score,[18] ATRIA bleeding risk score,[19] and risk factors associated with stroke. Analysis was performed using the STATA software, version 9.2 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

Table 2 lists the baseline characteristics of patients enrolled in the PROTECT-AF trial and CAP registry. The mean age was 72.7 years in the PROTECT-AF control group, 71.7 years in the intervention group, and 74.0 years in the CAP registry. The mean $CHADS_2$ score was 2.3 in the PROTECT-AF control group, 2.2 in the intervention group, and 2.4 in the CAP registry. Patients enrolled in the registry were more likely to have a history of ischaemic stroke or TIA (30.6%) than those in the control (20.1%) or intervention (17.7%) groups of the trial. Patients in the registry had a lower incidence of heart failure (18.9%) than those in the control (27%) or intervention (26.8%) groups of the trial.

Follow-up of patients in the PROTECT-AF trial accumulated 1623 person-years of observation (mean ± SD = 28 ± 13 months per patient). During this period, 27 thrombo-embolic events occurred, 8 among 244 patients in the control group (1.39%/year; 95% CI: 1.25–1.55%/year), and 19 among 463 patients in the intervention group (1.80%/year; 95% CI: 1.68–1.94%/year). Nine ICH events developed, 7 among 244 patients in the control group (1.22%/year; 95% CI: 1.08–1.37%/year), and 2 among 463 patients in the intervention group (0.19%/year; 95% CI: 0.15–0.23%/year). Among patients undergoing intervention, 4.1% (19/463) developed PEF requiring intervention (1.81%/year; 95% CI: 1.69–1.94%/year), as opposed to none in the control group. Major bleeding requiring transfusion occurred in 25 patients altogether, 12 in the control group (2.09%/year; 95% CI: 1.92–2.28%/year), and 13 in the intervention group (1.24%/year; 95% CI: 1.14–1.34%/year). Death from all-causes occurred in 60 patients: 10.6% (26/244) in the control group (4.54%/year; CI 4.27–4.81%/year), and 7.34% (34/463) in the intervention group (3.24%/year; 95% CI: 3.08–3.41%/year).

The NCB of LAA closure in the trial cohort was 1.74%/year (95% CI: −0.54 to 4.39%/year) in favour of LAA closure; however, the CI crossed zero (consistent with no benefit or possible harm). The net benefit was greatest in patients with a history of ischaemic stroke (4.30%/year; 95% CI: −2.07 to 11.25%/year). The benefit increased from 0.70%/year (95% CI: −1.99 to 3.93%/year) in those with $CHADS_2$ scores = 1 to 2.00%/year (95% CI: −1.15 to 5.56%/year) in those with $CHADS_2$ scores ≥2. The NCB of intervention was higher in those patients in whom the device was used as secondary prevention—that is, patients who had already sustained a thrombo-embolic event (*Table 3*, *Figure 1*). The NCB of intervention increased from 0.96%/year (95% CI: −1.37 to 3.61%/year) in patients with ATRIA bleeding risk scores <4 to 2.78%/year (95% CI: −2.85

Table 1 Net clinical benefit of LAA closure over warfarin by impact weights applied

Impact weight					Net clinical benefit, PROTECT-AF[a]	95% CI	Net clinical benefit, CAP	95% CI
DE (A)	TE (B)	ICH (C)	MB (D)	PEF (E)				
1.00	0.10	0.30	0.05	0.05	1.52	−0.54 to 3.81	4.75	3.07 to 5.51
1.00	0.20	0.60	0.10	0.10	1.73	−0.54 to 4.39	4.97	3.07 to 7.15
1.00	0.30	0.90	0.15	0.15	1.96	−0.67 to 4.79	5.19	3.02 to 7.59

[a]$NCB = \mathbf{A}*(DE_{warfarin} - DE_{intervention}) + \mathbf{B}*(ICH_{warfarin} - ICH_{intervention}) + \mathbf{C}*(TE_{warfarin} - TE_{intervention}) + \mathbf{D}*(MB_{warfarin} - MB_{intervention}) + \mathbf{E}*(PEF_{warfarin} - PEF_{intervention})$, where NCB, net clinical benefit; DE death; ICH intracerebral haemorrhage; TE, thrombo-embolic events; MB, major bleeding, and PEF, haemodynamically significant pericardial effusion requiring intervention.

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Table 2 Baseline characteristics and risk factors in the PROTECT-AF and CAP registry baseline characteristics and risk factors

	PROTECT-AF control group ($n = 244$)	PROTECT-AF intervention group ($n = 463$)	*P*-value[a]	CAP registry ($n = 566$)	*P*-value[a]
Characteristics					
Age in years (SD; range)	72.7 (9.2; 41–95)	71.7 (8.8; 46–95)	0.179[b]	74.0 (8.3; 44–94)	0.045[b]
Males (%)	171 (70.1)	326 (70.4)	0.931[c]	371 (65.5)	0.223[c]
Risk factors					
$CHADS_2$ score (%)			0.058[d]		0.161[d]
1	66 (27.0)	157 (33.9)		133 (23.5)	
2	88 (36.1)	158 (34.1)		199 (35.2)	
3	51 (20.9)	88 (19.0)		120 (21.2)	
4	24 (9.8)	37 (8.0)		79 (13.9)	
5	10 (4.1)	19 (4.1)		31 (5.5)	
6	5 (2.0)	4 (0.9)		4 (0.7)	
Heart failure (%)	66 (27.0)	124 (26.8)	1.000[c]	107 (18.9)	0.012[c]
History of hypertension (%)	220 (90.2)	413 (89.2)	0.796[c]	500 (88.3)	0.542[c]
Age ≥75 years (%)	115 (47.1)	190 (41.0)	0.129[c]	293 (51.8)	0.251[c]
Diabetes mellitus (%)	72 (29.5)	113 (24.4)	0.150[c]	140 (24.7)	0.164[c]
Prior stroke or TIA (%)	49 (20.1)	82 (17.7)	0.476[c]	173 (30.6)	0.002[c]

[a]The *P*-values were calculated by comparing PROTECT-AF intervention group and CAP registry group, respectively, to the PROTECT-AF control group.
[b]The *P*-value was calculated by the *t*-test.
[c]The *P*-value was calculated by Fisher's exact test.
[d]The *P*-value was calculated by the Wilcoxon rand-sum test.

to 9.06%/year) in those with bleeding risk scores ≥4. Male patients and those with a history of heart failure or diabetes were more likely to benefit from intervention (*Table 3*).

While warfarin treatment is associated with a relatively linear temporal distribution of clinical events, the procedural nature of LAA closure results in a bimodal distribution of events following intervention—a cluster of events occurring in the periprocedural period, followed by a linear distribution thereafter (*Figures 2* and *3*).[13] To understand the impact of this pattern, the NCB was calculated as a function of time following randomization. As shown in *Figure 4*, the benefit of LAA closure increased over time, becoming positive between 6 and 9 months following intervention for patients in the randomized cohort.

We performed a separate analysis of the NCB using outcomes from the CAP registry to account for the reduction in procedural complications associated with greater operator experience. The registry accumulated 741 person-years of follow-up, with mean of 16 ± 7 months per patient, during which 10 thrombo-embolic events occurred (1.35%/year; 95% CI: 1.26–1.45%/year) and there was one ICH (0.13%/year; 95% CI: 0.11–0.17%/year). Among the 566 patients enrolled, there were 30 DEs (4.04%/year; 95% CI: 3.89–4.22%/year) and 1.41% (8/566) experienced PEF requiring intervention (1.08%/year; 95% CI: 0.99–1.17%/year), compared with 4.1% in the intervention group of the PROTECT-AF trial. Major bleeding occurred at an annualized rate of 3.24% (95% CI: 3.09–3.39%/year).

The NCB associated with LAA closure in the registry was 4.97%/year (95% CI: 3.07–7.15%/year) and was greatest among patients with a history of ischaemic stroke—that is, when used as secondary prevention (8.68%/year; 95% CI: 2.82–14.92%/year; *Figure 1*). The benefit increased from 2.22%/year (95% CI: 0.27–6.01%/year) in those with $CHADS_2$ scores = 1 to 6.12%/year (95% CI: 3.19–8.92%) with a score ≥2. When viewed from the standpoint of predictors of bleeding, the NCB increased from 3.71%/year (95% CI: 1.87–6.07%/year) in patients with ATRIA scores <4 to 7.98%/year (95% CI: 3.91–13.93%/year) when the score was ≥4. Male patients enrolled in the registry, those ≥75 years old, and those with diabetes mellitus were more likely to benefit from the intervention (*Table 3*). From a temporal perspective, when compared with the PROTECT-AF cohort, the NCB more consistently favoured intervention in the registry cohort from the time of earliest follow-up at 3 months (*Figure 4*).

We performed additional sensitivity analyses to assess the impact of PEF on the NCB for both cohorts (*Figure 5*). In the randomized trial, which occurred earlier in the development of the technology and operator experience, a weight of >1.1 (compared with DE =1) was required for PEFs to result in an NCB assessment favouring warfarin. In the registry, which benefited from more experienced operators, the weight assigned to pericardial complications would have to increase beyond 4.7 for warfarin therapy to compare favourably with LAA closure.

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Table 3 Annual net clinical benefit by risk factor in the PROTECT-AF cohort and CAP registry

Risk factor	*n*	Net clinical benefit, PROTECT-AF[a]	95% Confidence interval	*n*	Net clinical benefit, CAP	95% Confidence interval
All patients	707	1.73	−0.54 to 4.39	810	4.97	3.07–7.15
Age ≥75 years	305	1.18	−3.16 to 5.89	408	6.92	3.50–10.84
Age <75 years	402	1.68	−0.83 to 4.41	402	3.31	1.12–5.72
Male	497	2.73	−0.03 to 6.00	542	5.43	2.90–8.44
Female	210	−0.70	−4.62 to 3.92	268	3.87	1.39–7.37
Prior stroke or TIA[b]	131	4.30	−2.07 to 11.25	222	8.68	2.82–14.92
No prior stroke or TIA	576	1.20	−0.96 to 3.77	588	4.32	2.36–6.79
History of hypertension	633	1.18	−1.16 to 3.52	720	4.57	2.64–6.82
No history of hypertension	74	7.53	−0.22 to 18.19	90	9.43	1.97–20.48
Heart failure	190	3.64	−0.97 to 9.24	173	7.29	3.60–12.22
No heart failure	517	1.04	−1.63 to 3.83	637	4.07	2.30–7.12
Diabetes mellitus	185	2.19	−2.57 to 8.04	212	6.84	2.98–11.52
Non-diabetic	522	1.45	−0.92 to 4.25	598	4.18	2.17–6.79
$CHADS_2$ score = 5–6[b]	38	4.53	−9.66 to 21.34	50	11.12	1.75–27.33
$CHADS_2$ score = 3–4	200	2.07	−2.74 to 7.60	274	6.72	3.06–12.47
$CHADS_2$ score = 2	246	1.37	−2.14 to 6.02	287	4.89	1.75–8.82
$CHADS_2$ score = 1	223	0.70	−1.99 to 3.93	199	2.22	0.27–6.01
ATRIA score ≥4	180	2.78	−2.85 to 9.06	249	7.98	3.91–13.93
ATRIA score <4	527	0.96	−1.37 to 3.61	561	3.71	1.87–6.07

[a]$NCB = (DE_{warfarin} - DE_{intervention}) + \mathbf{0.6}*(ICH_{warfarin} - ICH_{intervention}) + \mathbf{0.2}*(TE_{warfarin} - TE_{intervention}) + \mathbf{0.1}*(MB_{warfarin} - MB_{intervention}) + \mathbf{0.1}*(PEF_{warfarin} - PEF_{intervention})$, where NCB, net clinical benefit; DE, death; ICH, intracerebral haemorrhage; TE, thrombo-embolic events; MB, major bleeding, and PEF, haemodynamically significant pericardial effusion requiring intervention.

[b]TIA, transient ischaemic attack. $CHADS_2$ refers to the risk of stroke defined by assigning one point for a clinical history of heart failure or impaired left ventricular systolic function (ejection fraction <35%), hypertension, age ≥75 years and diabetes mellitus, and 2 points for a history of stroke or TIA. ATRIA refers to the bleeding risk score developed by Fang *et al.*,[16] where 1 point is assigned for hypertension or prior haemorrhage, 2 points for age ≥75 years, and 3 points for severe renal disease or anaemia.[19]

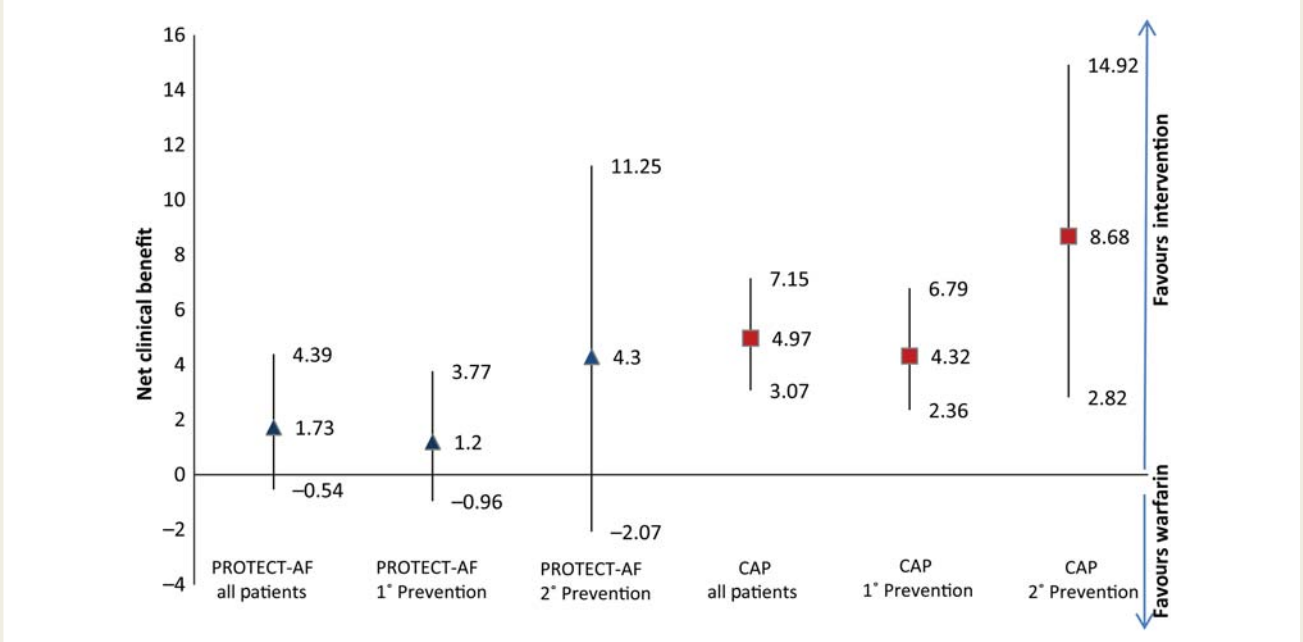

Figure 1 Net clinical benefit by primary vs. secondary stroke prevention.

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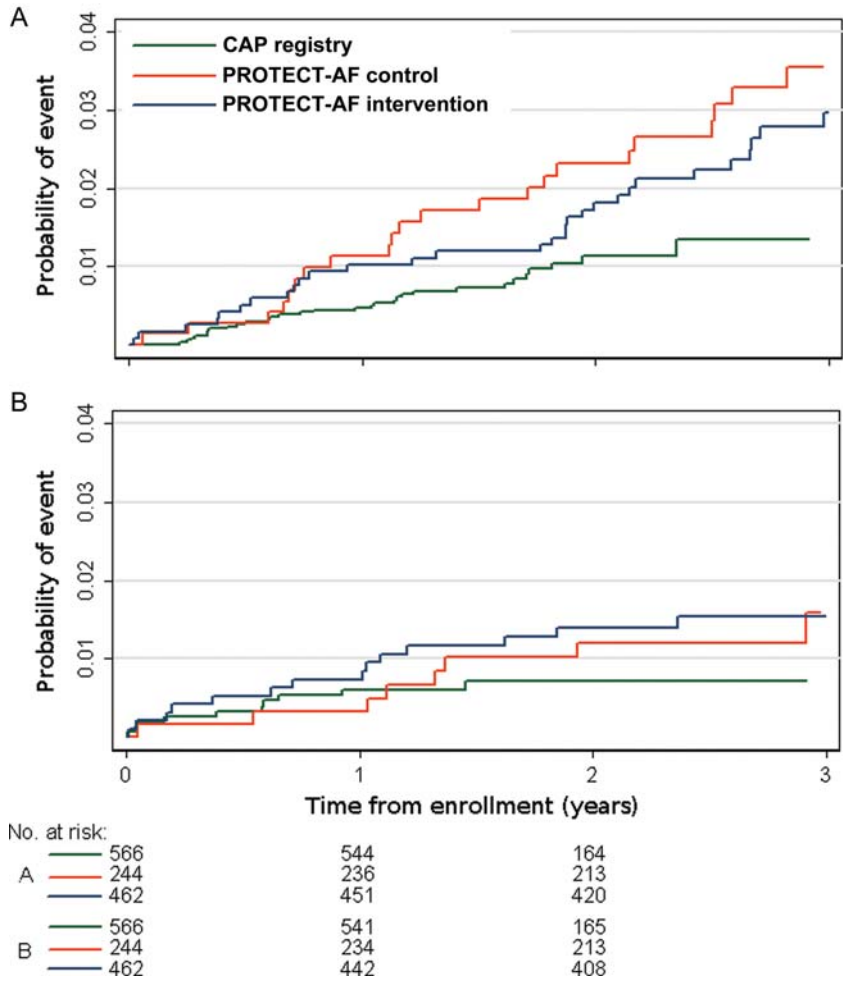

Figure 2 Kaplan–Meier failure curves for (*A*) death and (*B*) ischaemic stroke by study group, adjusted by the $CHADS_2$ score.

Discussion

The PROTECT-AF trial demonstrated that percutaneous closure of the LAA using the Watchman device is a viable approach for the prevention of stroke in patients with AF, offering an alternative to long-term anticoagulant therapy for high-risk patients. This technology is still under investigation the USA, but has gained regulatory approval in other parts of the world, including Europe and parts of Asia. Like most interventional cardiovascular procedures, catheter-based occlusion of the LAA is associated with a higher initial risk resulting from complications of device deployment; but once LAA closure is achieved successfully, this strategy accumulates the benefit over time by avoiding the continuing risk of bleeding associated with sustained systemic anticoagulant therapy. The disadvantages associated with LAA closure that are not inherent to pharmacological therapies include the need for hospitalization and specific procedure-related risks—most notably PEF and procedure-related embolic events including ischaemic stroke. In contrast, warfarin therapy is associated with the risk of bleeding, including ICH, need for regular INR monitoring, and the risk of thrombo-embolism when the intensity of anticoagulation falls below the therapeutic range. Device-related complications usually occur during or shortly after the procedure, while adverse events during pharmacological therapy develop continuously over time, making direct comparisons of the relative risks of these treatments inherently difficult.

The definition of the NCB employed in this analysis was designed to balance adverse events associated with each treatment against the efficacy for stroke prevention. We selected clinically MB events, haemodynamically significant PEF and DE to represent the risks of these therapies based on their incidence in the PROTECT-AF trial. Analysis of the PROTECT-AF randomized trial cohort found the NCB of closure greatest for patients at highest risk for stroke—most notably those with higher $CHADS_2$ scores, and those in whom LAA closure was employed as secondary prevention. Because of the bimodal distribution of events in the intervention group—early procedure-related strokes and PEFs and later events related to intrinsic cardiovascular disease—the cumulative benefit was assessed as a function of time. Largely driven by the procedure-related stroke events, the NCB

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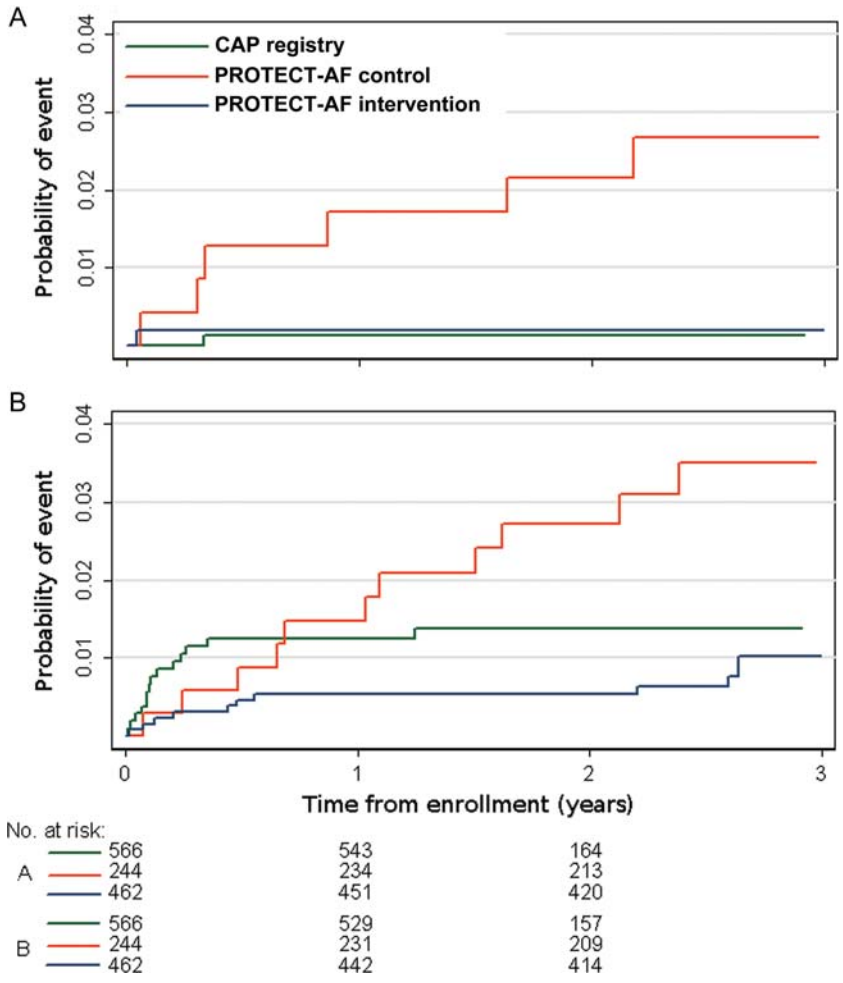

Figure 3 Kaplan–Meier failure curves for (*A*) intracranial haemorrhage and (*B*) major bleeding by study group, adjusted by the $CHADS_2$ score.

initially favoured anticoagulation, but after 6 to 9 months had elapsed following the procedure the NCB crosses over in favour of the device-based intervention, driven mainly by reductions in ICH and DE in patients undergoing LAA closure.

Operator experience is an important factor to consider in assessing the safety and efficacy of any intervention. Once operators gained experience over the course of PROTECT-AF, the incidence of procedure-related events was considerably lower in the non-randomized CAP registry that followed. When this non-randomized registry cohort was compared with the control arm of the PROTECT-AF trial cohort, the NCB more clearly favoured intervention. In the PROTECT-AF trial cohort, the 95% CI cross zero, suggesting the possibility of no benefit or possible harm. However, in the CAP registry it is notable that when various risk factors were examined, the lower bounds of the 95% CI were largely also above zero, that is, in favour of intervention. The NCB was again higher for patients at greatest risk of stroke (those with higher $CHADS_2$ scores or prior thrombo-embolism. Given the reduction in periprocedural events, the intervention was associated with earlier net benefit.

Limitations

There are several possible ways to calculate the NCB of a new treatment against the standard of care, and no perfect method has been developed. Accordingly, our analysis has the inherent limitation of the relative weighting of adversity we assigned to the various potential morbid events and complications that can befall patients with AF during long-term anticoagulation or with deployment of a percutaneous LAA closure device. To mitigate this, the weighting was based on the mortality observed with various clinical events in other large studies such as ACTIVE A. While no such data were available for PEFs, (i) it is important to recognize that there were no instances of mortality associated with PEFs in either the PROTECT-AF or CAP registry cohorts, and (ii) even when various degrees of weighting were assigned to PEFs, the NCB failed to favour the intervention only after the weight was increased to over 1.1 and 4.7 for the PROTECT-AF and CAP registry cohorts, respectively.

Secondly, all patients underwent TEE prior to randomization to exclude intracardiac thrombus or other contraindications to device

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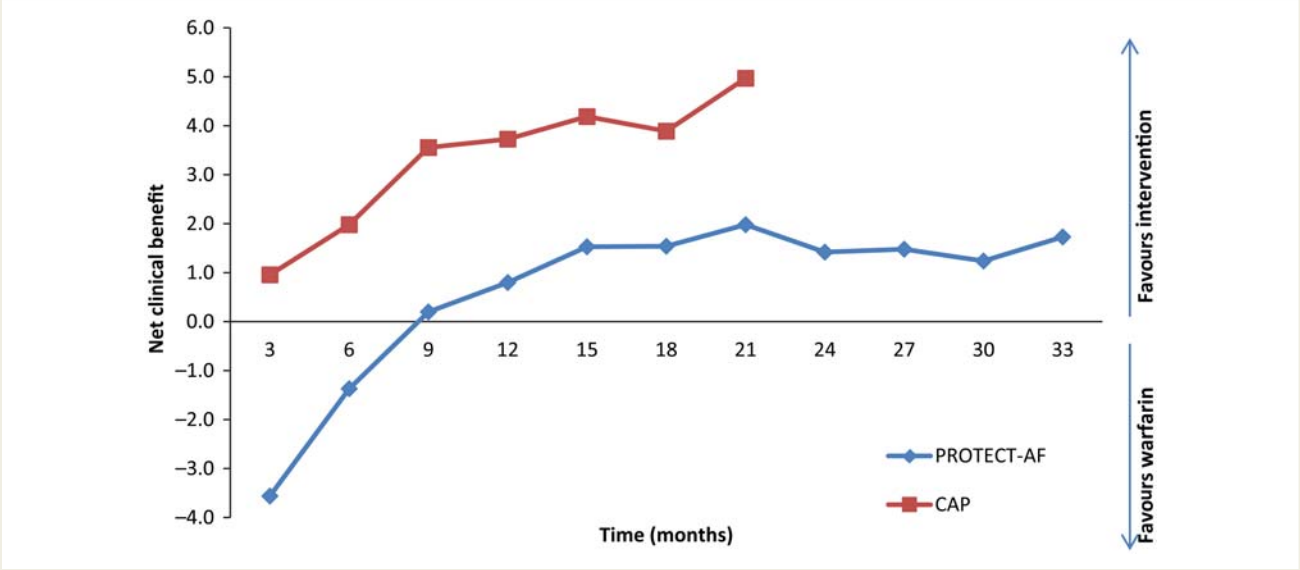

Figure 4 Net clinical benefits as a function of time in the PROTECT-AF and CAP Cohorts

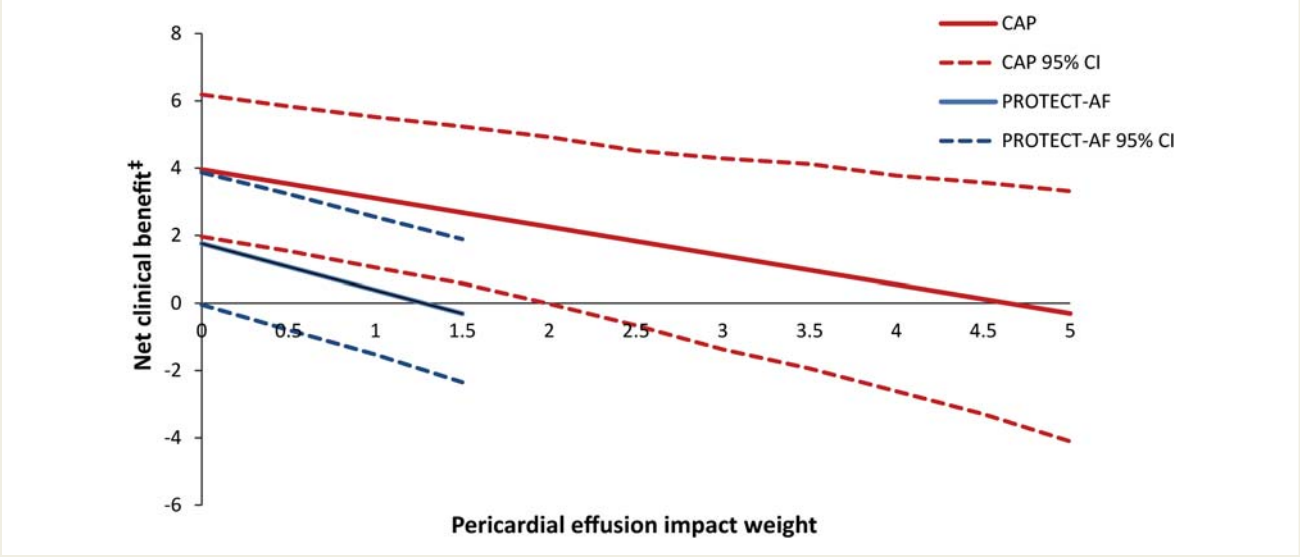

Figure 5 Net clinical benefit of left atrial appendage closure over warfarin in anticoagulation as a function of pericardial effusion impact weight. ‡Net clinical benefit = $(DE_{warfarin} - DE_{intervention}) + \mathbf{0.6} * (ICH_{warfarin} - ICH_{intervention}) + \mathbf{0.2} * (TE_{warfarin} - TE_{intervention}) + \mathbf{0.1} * (MB_{warfarin} - MB_{intervention}) + \mathbf{X} * (PEF_{warfarin} - PEF_{intervention})$, where $\mathbf{X}$ = pericardial effusion impact weight.

deployment. This might have selected lower risk patients for inclusion, but it is difficult to predict the direction in which this could skew the NCB calculation. Thirdly, since all patients enrolled in the CAP registry underwent LAA closure, estimation of the NCB was based on comparison with the control group of the randomized trial, overlooking differences in patient selection criteria or outcomes. Compared with the trial cohort, patients included in the registry had a higher mean $CHADS_2$ score (2.4 vs. 2.2), and more often had a history of stroke or TIA (30.6 vs. 17.7%), both features associated with higher risk. Fourthly, the assessment of the NCB assumes that all ischaemic strokes have a similar clinical impact on patients, yet stroke mechanisms and severity may differ according to the type of treatment received. As previously reported, strokes in patients undergoing LAA closure in the PROTECT-AF trial resulted in less functional disability than that occurring in the anticoagulation arm.[13] Fifthly, novel oral anticoagulants (inhibitors of factors IIa or Xa) appear to have NCB superior to warfarin for prevention of ischaemic and haemorrhagic events in

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patients with AF, making warfarin a suboptimal comparator to inform treatment decisions in many patients with AF. Sixthly, competitive LAA closure devices such as the Amplatzer Cardiac Plug or next generation devices such as the Gen-4 WATCHMAN are currently under investigation, and, if shown to have a lower risk of peri-procedural stroke and pericardial tamponade, may further enhance the NCB.[20–22]

Future studies must address these new agents, technological advances in device design that reduce the need for intensive peri-procedural antithrombotic therapy, and the improvement in performance characteristics that typically occur as the 'learning curve' reduces complication rates and enhances procedural success rates associated with LAA closure. Finally, the duration of follow-up was limited, and one cannot rule out the possibility that observations of the NCB during the first 2 to 3 years of treatment may not be sustained, as AF represents a marker of a population at risk of ischaemic events that have multiple mechanisms and respond favourably to anticoagulation over time.

In conclusion, the NCB of percutaneous LAA closure in patients with non-valvular AF is greatest for those at highest risk of stroke. An assessment that considers the combined risk of thromboembolism, ICH, DE, and other clinically important adverse events may better inform the selection of patients for device-based therapy over long-term anticoagulation and improve clinical outcomes.

Conflict of interest: V.Y.R. has received consulting fees from Atritech and Boston Scientific, Inc. J.L.H. received consulting fees from the following pharmaceutical manufacturers for advisory activities involving the development of new anticoagulant drugs or embolism-prevention devices: Astellas Pharma, US, Atricure/Boston Biomedical Associates, AstraZeneca, Bayer AG HealthCare, Biotronik, Boehringer Ingelheim, Bristol Meyers-Squibb, Daiichi Sankyo, Johnson & Johnson, Pfizer, Inc., and Sanofi-Aventis. The remaining authors report no conflicts of interest.

References

1. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL; ACC/AHA/ESC. 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;**8**:651–745.
2. Hart RG, Halperin JL. Do current guidelines result in overuse of warfarin anticoagulation in patients with atrial fibrillation. *Ann Intern Med* 2009;**151**:355–356.
3. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 2009;**151**:297–305.
4. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunso J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011;**106**:739–749.
5. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;**61**:755–759.
6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–11351.
7. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
9. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, Omran H, Bartorelli AL, Della Bella P, Di Mario C, Pappone C, Casale PN, Moses JW, Poppas A, Williams DO, Meier B, Skanes A, Teirstein PS, Lesh MD, Nakai T, Bayard Y, Billinger K, Trepels T, Krumsdorf U, Sievert H. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. *J Am Coll Cardiol* 2005;**46**:9–14.
10. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, Mishkel G, Almany S, Holmes DR. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2007;**49**:1490–1495.
11. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–542.
12. Fountain RB, Holmes DR, Chandrasekaran K, Packer D, Asirvatham S, Van Tassel R, Turi Z. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. *Am Heart J* 2006;**151**:956–961.
13. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation* 2011;**123**:417–424.
14. Tsang TS, Barnes ME, Hayes SN, Freeman WK, Dearani JA, Butler SL, Seward JB. Clinical and echocardiographic characteristics of significant pericardial effusions following cardiothoracic surgery and outcomes of echo-guided pericardiocentesis for management: Mayo Clinic experience, 1979–1998. *Chest* 1999;**116**:322–331.
15. Tsang TS, Enriquez-Sarano M, Freeman WK, Barnes ME, Sinak LJ, Gersh BJ, Bailey KR, Seward JB. Consecutive 1127 therapeutic echocardiographically guided pericardiocenteses: clinical profile, practice patterns, and outcomes spanning 21 years. *Mayo Clin Proc* 2002;**77**:429–436.
16. Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J, de Caterina R, Hohnloser S, Hart RG. Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable. *Ann Intern Med* 2011;**155**:579–586.
17. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**:1903–1912.
18. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–2870.
19. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A New Risk Scheme to Predict Warfarin-Associated Hemorrhage The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011;**58**:395–401.
20. Landmesser U, Holmes DR Jr. Left atrial appendage closure: a percutaneous transcatheter approach for stroke prevention in atrial fibrillation. *Eur Heart J* 2012;**33**:698–704.
21. Park JW, Bethencourt A, Sievert H, Santoro G, Meier B, Walsh K, Lopez-Minquez JR, Meerkin D, Valdes M, Ormerod O, Leithauser B. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv* 2011;**77**:700–706.
22. Lam YY, Yip GW, Yu CM, Chan WW, Cheng BC, Yan BP, Clugston R, Yong G, Gattorna T, Paul V. Left atrial appendage closure with Amplatzer cardiac plug for stroke prevention in atrial fibrillation: Initial Asia-Pacific experience. *Catheter Cardiovasc Interv* 2012;**79**:794–800.

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