

# Urgent surgery compared with fibrinolytic therapy for the treatment of left-sided prosthetic heart valve thrombosis: a systematic review and meta-analysis of observational studies

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## Aims

Left-sided prosthetic valve thrombosis (PVT) occurs frequently in developing countries and causes major morbidity and mortality. Fibrinolytic therapy (FT) is most commonly used as treatment, but increases the risk of stroke and bleeding. Urgent surgery may be more efficacious and cause fewer complications. Our aim was to compare the efficacy and safety of urgent surgery and FT for the treatment of left-sided PVT.

## Methods and results

We searched EMBASE and MEDLINE for articles which included at least five patients each treated with surgery and FT. The primary outcome was complete restoration of valve function. Other outcomes were in-hospital death, thrombo-embolism (stroke, transient ischaemic attack, or non-CNS systemic embolism), major bleeding, and recurrence of PVT on follow-up. We calculated odds ratios (ORs) for each outcome and pooled them using a random effects model. We included seven eligible studies with 690 episodes of PVT, 446 treated with surgery, and 244 with FT. There was no significant difference in the occurrence of the primary outcome (86.5 vs. 69.7%, OR 2.53, 95% CI 0.94–6.78,  $P = 0.066$ ,  $I^2 = 74\%$ ) or death (13.5 vs. 9%, OR 1.95, 95% CI 0.63–5.98,  $P = 0.244$ ,  $I^2 = 59\%$ ) between the two treatments. However, compared with FT, urgent surgery was associated with significant reductions in thrombo-embolism (1.6 vs. 16%, OR 0.10, 95% CI 0.04–0.24,  $P < 0.001$ ,  $I^2 = 0\%$ ), major bleeding (1.4 vs. 5%; OR 0.27, 95% CI 0.08–0.98,  $P = 0.046$ ,  $I^2 = 0\%$ ), and recurrent PVT (7.1 vs. 25.4%; OR 0.25, 95% CI 0.08–0.74,  $P = 0.013$ ,  $I^2 = 59\%$ ).

## Conclusion

Urgent surgery was not superior to FT at restoring valve function, but substantially reduced the occurrence of thrombo-embolic events, major bleeding, and recurrent PVT. In experienced centres, urgent surgery should probably be preferred over FT for treating left-sided PVT, pending the results of randomized controlled trials.

## Keywords

Fibrinolysis • Thrombolysis • Heart valve surgery • Prosthetic heart valve thrombosis

## Introduction

Left-sided prosthetic valve thrombosis (PVT) is a potentially devastating complication that occurs in patients with mechanical heart valves who are poorly anticoagulated. Though rare in the developed world, it occurs frequently in developing countries. In a retrospective analysis from a large tertiary care hospital in India,

left-sided PVT occurred in 6.1% of patients within 6 months of valve replacement.<sup>1</sup> More recently, using data from a randomized controlled trial, we estimated that ~10% of patients with mechanical heart valves have an episode of valve thrombosis per year.<sup>2</sup> Patients with PVT have a high risk of death and stroke during the index hospital admission.<sup>3</sup> Moreover, despite successful treatment with fibrinolytic therapy (FT), up to a third of patients may

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develop PVT in the future, thereby multiplying the risk of death and stroke.<sup>4,5</sup>

Because of the paucity of prospectively collected data and the absence of randomized controlled trials, the optimal treatment of left-sided PVT is unclear. Guidelines differ in their recommendations regarding the choice of treatment for PVT (Table 1).<sup>6–9</sup> For example, although the Society for Heart Valve Disease (SHVD) recommends FT for all patients,<sup>6</sup> the European Society of Cardiology (ESC) recommends FT only if the risk of surgery is prohibitive or in the event that it is not available and the patient cannot be transferred.<sup>8</sup> The SHVD recommends surgery only if FT is contraindicated, whereas the ESC advocates surgery in all ‘critically ill’ patients. Practice is therefore dictated by local availability of resources and physician preferences rather than considerations of benefit and harm. Presumably because of the limited availability and high initial cost of surgery, FT has become the first-line treatment in much of the developing world.<sup>4,5,10–12</sup> Though it is acknowledged that surgery may be more successful, despite a possible increase in the risk of death, and that FT may be less efficacious while causing more strokes and bleeding, the magnitude of these risk–benefit trade-offs is not known. We therefore undertook a systematic review and meta-analysis of the available literature comparing emergency surgery with FT for left-sided PVT, in an attempt to quantify and compare the risks and benefits of these interventions.

# Methods

## Study eligibility

We included studies comparing surgery and FT for left-sided PVT as initial therapy, which reported data on successful restoration of valve function and complications with each of the interventions. We defined success as objectively documented complete restoration of valve function in the presence or absence of complications. We also

collected information on the following outcomes: in-hospital death, stroke or transient ischaemic attack (TIA), non-CNS systemic embolism, major bleeding, and recurrence of PVT. We included only those studies which enrolled at least 5 patients each in the surgery and fibrinolytic arm (i.e. a total of at least 10 patients). We excluded studies involving fewer patients as these likely represent opportunistic case reports and may be subject to positive publication bias. We also excluded studies describing thrombosis of tissue valves or right-sided valves. In the event that such patients were part of a study, we abstracted data only for mechanical valves where possible.

## Search strategy

We searched EMBASE (1980 to 2012, January, week 4) and Ovid MEDLINE (1946 to 2012, January, week 3) using the Ovid SP search engine (Ovid Technologies, Inc., 2000–2012). We used the following search terms alone and in combination: prosthetic heart valve, mechanical heart valve, thrombosis, prosthetic heart valve thrombosis, prosthetic valve thrombosis, surgery, valve replacement, thrombectomy, fibrinoly\*, thromboly\*, streptokinase, urokinase, tissue plasminogen activator, tenecteplase, and heparin. To improve the sensitivity of our search, we used the multiple posting (.mp) suffix with each term. We ran the searches separately for FT and surgery. This was to ensure that we did not miss articles which while predominantly reporting results with either of the modalities also provided information on a smaller number of patients treated with the other modality. We hand-searched the reference lists of retrieved articles, reviews, guideline documents, and case reports for relevant articles. We did not apply any language restrictions. Our search strategy is detailed in the Supplementary material available online.

## Eligibility assessment

Two authors (N.B.S. and J.J.) independently screened the titles and abstracts of the citations retrieved by the two searches. We included an article if either of the reviewers felt that it merited full-text review. Full-text versions of the selected articles were again reviewed independently by the two authors for eligibility. Any disagreements were resolved by a third person (G.K.).

**Table 1** Differences between practice guidelines for the treatment of left-sided prosthetic valve thrombosis

Guideline	Surgery	FT	Intensification of anticoagulation
Society for Heart Valve Disease, 2005 <sup>6</sup>	Only if FT contraindicated or has failed	For all patients (class I recommendation)	May be considered in patients with thrombus <5 mm in length on TEE
European Society of Cardiology, 2012 <sup>8</sup>	All critically ill patients without serious comorbidity (class I, C), large (>10 mm) non-obstructive thrombus with embolism (class IIa, C), persistent thrombus despite optimal anticoagulation	Critically ill patients with serious comorbidity, or impaired cardiac function before developing valve thrombosis, or if surgery is unavailable	Intravenous UFH ± aspirin if inadequately anticoagulated
American College of Cardiology, 2008 (Update) <sup>7</sup>	For all patients in NYHA class III, IV or those with large clot burden (class IIa, C)	NYHA class I, II patients with low clot burden (class IIb, C); all others if they are at high risk for surgery or if surgery is unavailable	Intravenous UFH in patients who are class I, II with low clot burden (class IIb, C)
American College of Chest Physicians, 2012 <sup>9</sup>	All patients with thrombus area ≥0.8 cm <sup>2</sup> on TEE (grade 2C)	All patients with thrombus area <0.8 cm <sup>2</sup> on TEE; all others if they are at high risk for surgery (grade 2C)	For very small non-obstructive thrombi, intravenous UFH monitored by serial echocardiography (grade 2C)

FT, fibrinolytic therapy; TEE, transoesophageal echocardiography; UFH, unfractionated heparin.

## Data abstraction

We abstracted the following data from all the eligible studies: the number of patients treated with either modality, their average age, the position of the thrombosed valve, valve type, functional class at presentation, presence of atrial fibrillation, duration of symptoms before diagnosis of PVT, time from valve replacement, adequacy of anticoagulation at presentation, and a history of stroke in the past.

## Validity assessment

The main parameters on which we assessed study validity were, the design of the study (prospective or retrospective), the sampling method used (a selected population, or all patients treated during a defined period), and whether baseline characteristics of patients receiving surgery and FT were described separately. We determined if outcomes were measured using objective criteria, and were consistently assessed in patients undergoing either treatment. If effect estimates for outcomes were provided, we checked whether any adjustments to these estimates were made for baseline differences. For prospective studies, we also determined the method of outcome assessment (review of patient records or by direct patient assessment) and evaluated whether data collection and outcome adjudication were blinded, whether all outcomes were reported, and whether any patients were lost to follow-up.

Data abstraction and validity assessment were done independently by two of the authors (N.B.S. and J.J.) and any differences were resolved by a third (G.K.).

## Statistical analysis

The primary outcome for our analysis was the occurrence of complete success (i.e. complete restoration of valve function) in patients undergoing either intervention. Other outcomes that we considered were in-hospital death, stroke, TIA or non-CNS systemic embolism, major bleeding, and recurrence of PVT. We accepted the definitions used by study authors for our analyses. For each study, we compared the efficacy and safety of surgery with FT by deriving odds ratios (ORs) for each of these outcomes. We pooled the ORs across studies using the DerSimonian and Laird random effects model.<sup>13</sup> We assessed between-study heterogeneity, using the  $I^2$  statistic. An  $I^2$  value  $>25\%$  was considered to represent significant heterogeneity. To evaluate the consistency of results, we also derived pooled estimates from a fixed effects model. The primary *a priori* hypothesis to explain heterogeneity was the varying baseline risk of study populations across the included studies (reflected principally by functional class at presentation). Other baseline characteristics invoked to explain between-study differences were position of the thrombosed valve, the duration of symptoms at the time of presentation, time from valve replacement, varying centre experience, fibrinolytic agent used, and differences in the definition of outcomes. Analyses were performed using Stata 11 (College Station, TX, USA).

## Results

Our initial search identified 1025 references. From these, we selected 53 articles for a detailed review and assessment of eligibility. Seven studies fulfilled our eligibility criteria and are included in this systematic review.<sup>14–20</sup> The reasons for excluding the remaining 46 studies are detailed in Figure 1. Studies reporting on a single modality of treatment (either fibrinolysis or surgery alone) constituted the majority (26/46) of exclusions. Two groups of investigators presented the results of patients treated over various time

periods at their centres in multiple publications. Of these, we included only the reports which were most recent and therefore provided the most complete data from these centres.

## Characteristics of included studies

We abstracted data for a total of 690 episodes of valve thrombosis in 598 patients from the seven studies. Two large studies<sup>17,18</sup> contributed nearly three-fourths of the 690 episodes. Several of the studies included a small number of patients with tricuspid valve or bioprosthetic valve thrombosis.<sup>14,16–20</sup> There were 25 such instances (15 tricuspid valves and 10 bioprosthetic valves), constituting  $<0.4\%$  of the analysed population. Where possible, we have reported baseline characteristics after excluding the data of these patients.

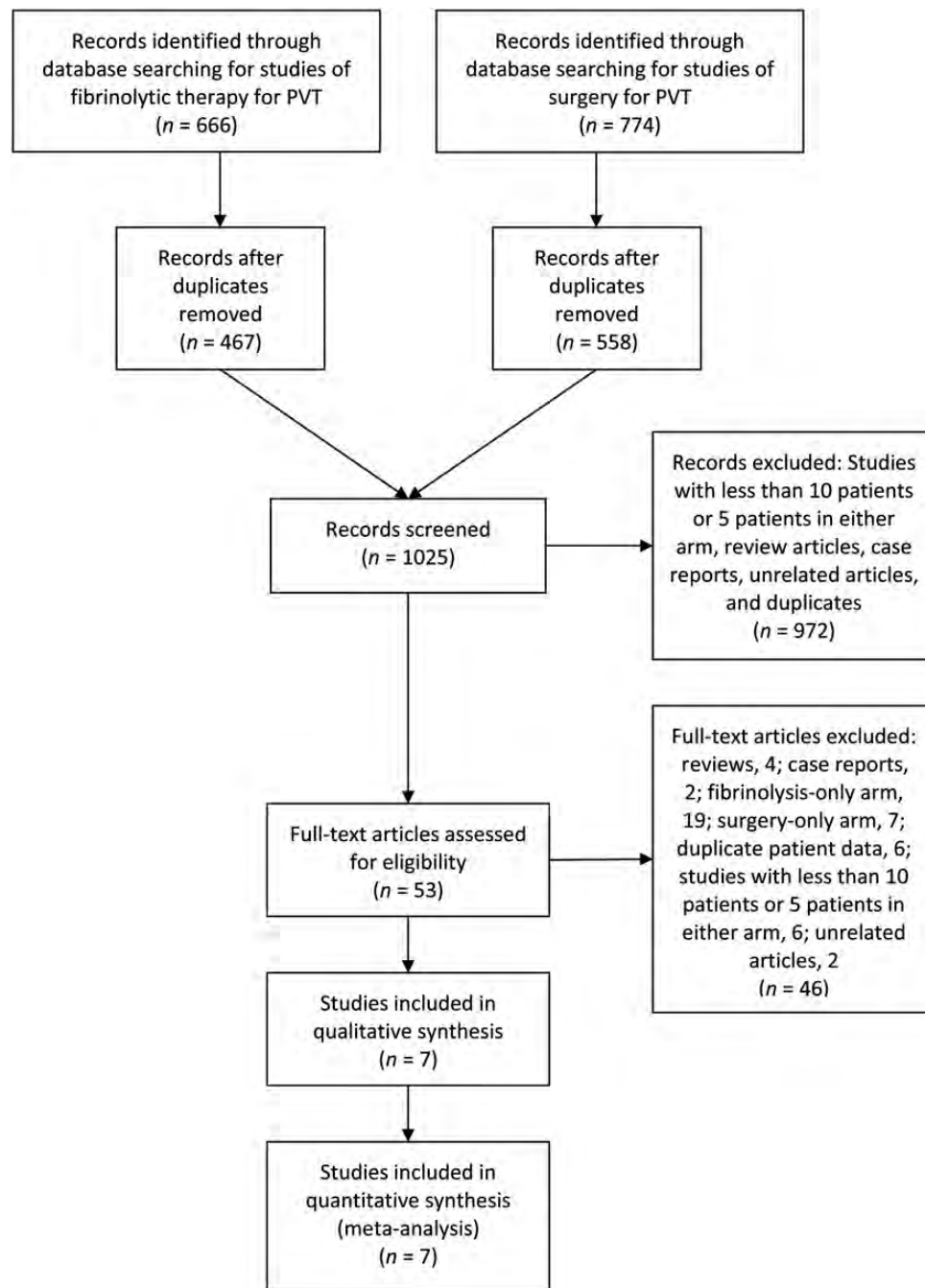
All the included studies were retrospective but reported on accumulated data of all patients treated at study centres, over periods of time ranging from 8 to 24 years. All were single-centre studies except for the one by Renzulli *et al.*<sup>17</sup> The mean age of patients ranged between 52 and 63 years. There was a preponderance of females (range 60–82%). The mitral position was the most common site for thrombosis and the majority of affected valves were bileaflet. The mean duration of symptoms before presentation was reported in only one study and was 2.8 weeks. Severe functional impairment was common, with the majority of patients presenting in NYHA class III or IV (Table 2).

## Methodological quality of included studies

All the included studies were retrospective and data were collected from patient records. However, they included all patients of PVT treated over a defined period of time at a given centre or group of centres. The decision to perform surgery or administer FT was guided by local practices and was at the discretion of treating doctors. In six of the seven studies, complete success was objectively determined with the use of a combination of clinical assessment, transthoracic or transoesophageal echocardiography (TEE), and cinefluoroscopy. However, definitions of the primary and secondary outcomes were not standardized or pre-specified in six of the seven studies, and it is also unclear if they were consistently assessed in both treatment arms for four of the seven included studies. None of the studies explicitly reported baseline characteristics of patients receiving either treatment separately, though we were able to retrieve these data from the published reports for four studies. No study provided effect estimates for any of the efficacy or safety outcomes (see Supplementary material online, Table S4).

## Surgery and fibrinolytic therapy

Data regarding details of surgery were available for a total of 397 operated patients. The majority (328, 82.6%) underwent valve replacement. The remaining patients were treated with thrombectomy and/or removal of pannus. Streptokinase was the most commonly used fibrinolytic agent (used in 44%), followed by t-PA in 38% of cases. Eighteen per cent of patients received urokinase (see Supplementary material online, Table S5). Most studies used the standard recommended doses of each agent,<sup>15,19</sup> with some adopting minor variations in duration of infusion without any significant change in dose.<sup>14,17,20</sup> One study<sup>18</sup> used locally



**Figure 1** Search results and study selection.

developed protocols, and details of fibrinolytic dosage were not reported for one study.<sup>16</sup> Details of FT are provided in Supplementary material online, Table S5.

## Outcomes

Overall, 446 episodes of PVT were treated with surgery and 244 were treated with fibrinolytic agents. Of the patients who received emergency surgery, 64 (9%) had received a trial of FT. However, we were unable to isolate the outcomes in these patients, from

the overall outcomes reported in the publications, and have therefore analysed them in the groups they were assigned to by the authors of these studies.

## Complete success

Urgent surgery resulted in complete success in 86.5% (386/446) of episodes and FT in 69.7% (170/244) (OR 2.53, 95% CI 0.94–6.78,  $P = 0.066$ ). There was substantial between-study heterogeneity for this outcome ( $I^2 = 74\%$ ) (Figure 2). The pooled results from the

**Table 2** Characteristics of patients in the included studies<sup>a</sup>

Study	Study period (duration, years)	Number of patients (episodes)	Patient age (mean, years)	Females, n (%)	Atrial fibrillation, n (%)	Bileaflet valves, n (%)	Mitral valve thrombosis, n (%)	NYHA class III or IV at presentation, n (%)	Duration of symptoms (mean, weeks)	Time from valve replacement (mean, years)
Azpitar et al. <sup>14</sup>	1991–1998 (8)	33 (33) <sup>b</sup>	55	33 (70.0)	39 (83.0)	17 (37.8)	23 (69.7)	35 (83.0)	NA	8.0
Lengyel and Vandro <sup>15</sup>	1993–2000 (8)	57 (63)	54	40 (70.1)	NA	47 (75.8)	60 (95.2)	44 (69.8)	NA	4.4
Durleman et al. <sup>16</sup>	1981–2001 (11)	38 (38)	58	32 (81.6)	16 (41.0)	28 (72.0)	31 (81.6)	34 (87.0)	NA	3.3
Renzulli et al. <sup>17</sup>	1979–2002 (24)	206 (239)	63	149 (62.3)	NA	47 (21.2)	179 (80.6)	170 (74.9)	NA	8.4
Roudaut et al. <sup>18</sup>	1978–2001 (24)	210 (263)	58	168 (63.9)	NA	161 (61.2)	170 (64.6)	175 (66.5)	NA	5.9
Ermis et al. <sup>19</sup>	2001–2008 (8)	29 (29)	52.2	20 (60.6)	19 (57.6)	20 (60.6)	24 (72.7)	26 (78.8)	2.8	5.4
Keuleers et al. <sup>20</sup>	1988–2008 (21)	25 (25)	61.6	25 (81)	17 (68.0)	NA	17 (68.0)	21 (84.0)	NA	11.3

NA, not available.

<sup>a</sup>As stated in the text, where possible, we have reported baseline characteristics after excluding the data of the 25 patients with bioprosthetic and right-sided valves.<sup>b</sup>Total number of patients included in the study was 47; we have excluded 12 patients with non-obstructive PVT and 2 with obstructive PVT treated with heparin.

two largest studies<sup>17,18</sup> which contributed nearly 73% of the patients showed a statistically significant 20% absolute increase in complete success with surgery (88 vs. 68%; OR 4.32, 95% CI 2.54–7.35,  $P < 0.0001$ ,  $I^2 = 0\%$ ). The pooled OR for the seven studies obtained by the fixed effects method also indicated a statistically significant effect in favour of surgery (2.81, 95% CI 1.85–4.26,  $P = 0.001$ ).

### Adverse outcomes

Among the 446 episodes treated with surgery, there were 60 deaths (13.5%) compared with 22 deaths (9%) among the 244 treated with fibrinolysis (OR 1.95, 95% CI 0.63–5.98,  $P = 0.244$ ). There was moderate between-study heterogeneity for this outcome ( $I^2 = 58.7\%$ ). The pooled OR derived from a fixed effects model was similar (1.67, 95% CI 0.98–2.85,  $P = 0.060$ ) (Figure 3A).

Major bleeding occurred significantly less frequently among patients treated surgically compared with those receiving FT (1.4 vs. 5%; OR 0.27, 95% CI 0.08–0.98,  $P = 0.046$ ). The reduction was consistent across studies ( $I^2 = 0\%$ ) (Figure 3B). Likewise, stroke, TIA, or non-CNS systemic embolism occurred significantly less frequently among patients treated with surgery (7/446, 1.6%) compared with those receiving fibrinolysis (39/244, 16%), with an OR of 0.10 (95% CI 0.04–0.24,  $P < 0.001$ ), without any heterogeneity ( $I^2 = 0\%$ ) (Figure 3C). Valve thrombosis recurred less frequently among surgically treated patients (7.1 vs. 25.4%; OR 0.25, 95% CI 0.08–0.74,  $P = 0.013$ ). There was less consistency between studies for this outcome ( $I^2 = 58.5\%$ ) (Figure 3D). The effect estimates for all the adverse outcomes were consistent with those obtained from a fixed-effects model (data not shown).

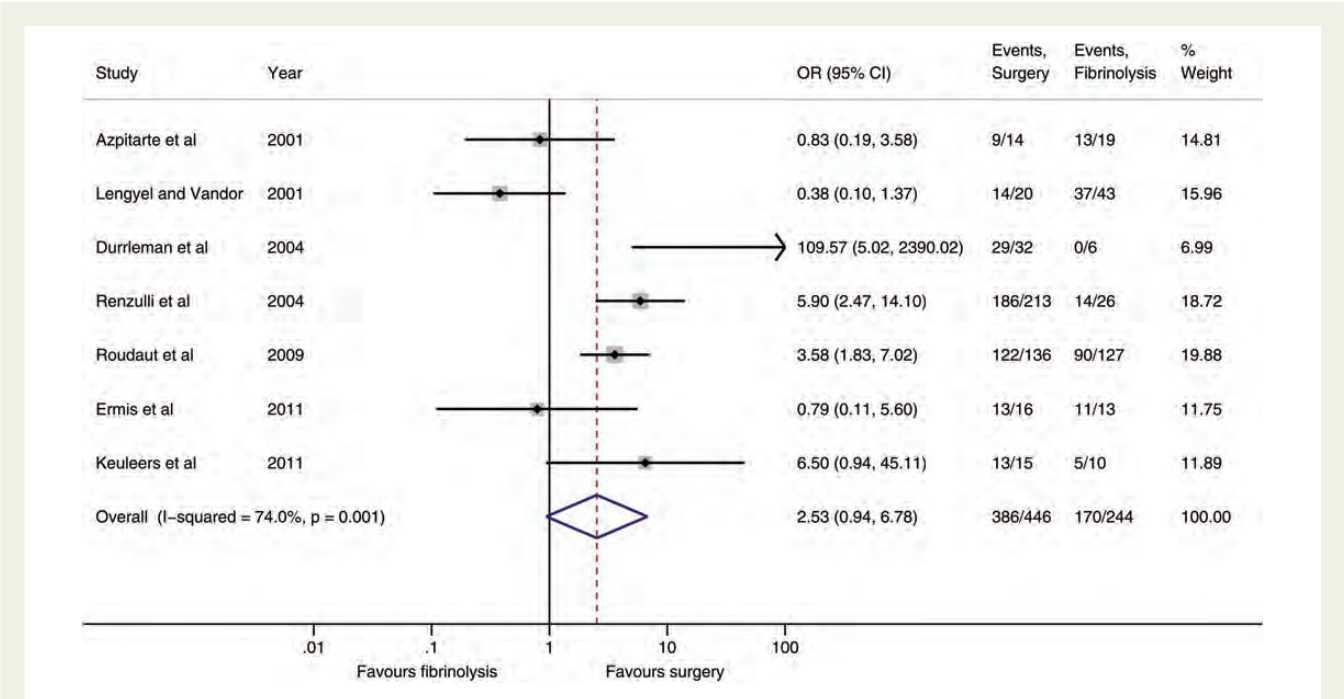
### Differences in outcomes between studies

The two studies<sup>17,18</sup> reporting on the largest number of patients undergoing surgery (a surrogate for surgical expertise) showed significantly better outcomes with surgery. Four of the studies<sup>15,18–20</sup> allowed us to evaluate patient characteristics at baseline separately for the two treatment groups (Table 3). The time from valve implantation was significantly longer for patients treated with surgery compared with those who were treated with FT (7.7 vs. 4.2 years,  $P < 0.001$ ) in one of the large studies favouring surgery.<sup>18</sup> There was no significant difference in this parameter in the other studies. Patients in poor functional class (NYHA class III or IV) were treated more often with surgery in two of the studies<sup>15,20</sup> and more often with fibrinolysis in the other two,<sup>18,19</sup> although these differences were not statistically significant. Moreover, there was no correlation between the proportion of patients in poor baseline functional class treated with either modality, and outcomes with that modality. The effect estimate in favour of surgery did not differ from the overall estimate in the studies in which most<sup>14</sup> or all patients<sup>17,20</sup> received t-PA (a more efficacious fibrinolytic agent). The position of the thrombosed valve did not correlate with success with either treatment.

## DISCUSSION

We did not find any published prospective studies comparing urgent surgery with FT for the treatment of left-sided PVT.





**Figure 2** Comparison of complete success between urgent surgery and fibrinolytic therapy.

Meta-analysis of the existing retrospective studies suggests that emergency surgery may result in a 2.5-fold increase in the odds of a successful outcome when compared with FT, but may also cause a two-fold increase in the odds of death. However, the confidence intervals around these effect estimates were wide, and included a null effect. There was also significant between-study heterogeneity for these outcomes. Surgery, however, was associated with large, consistent, and statistically significant reductions in the occurrence of major bleeding, stroke, TIA or non-CNS systemic embolism, and recurrent PVT. Fibrinolytic therapy was considerably less successful (69.7% complete success) than previously reported.<sup>3,21</sup>

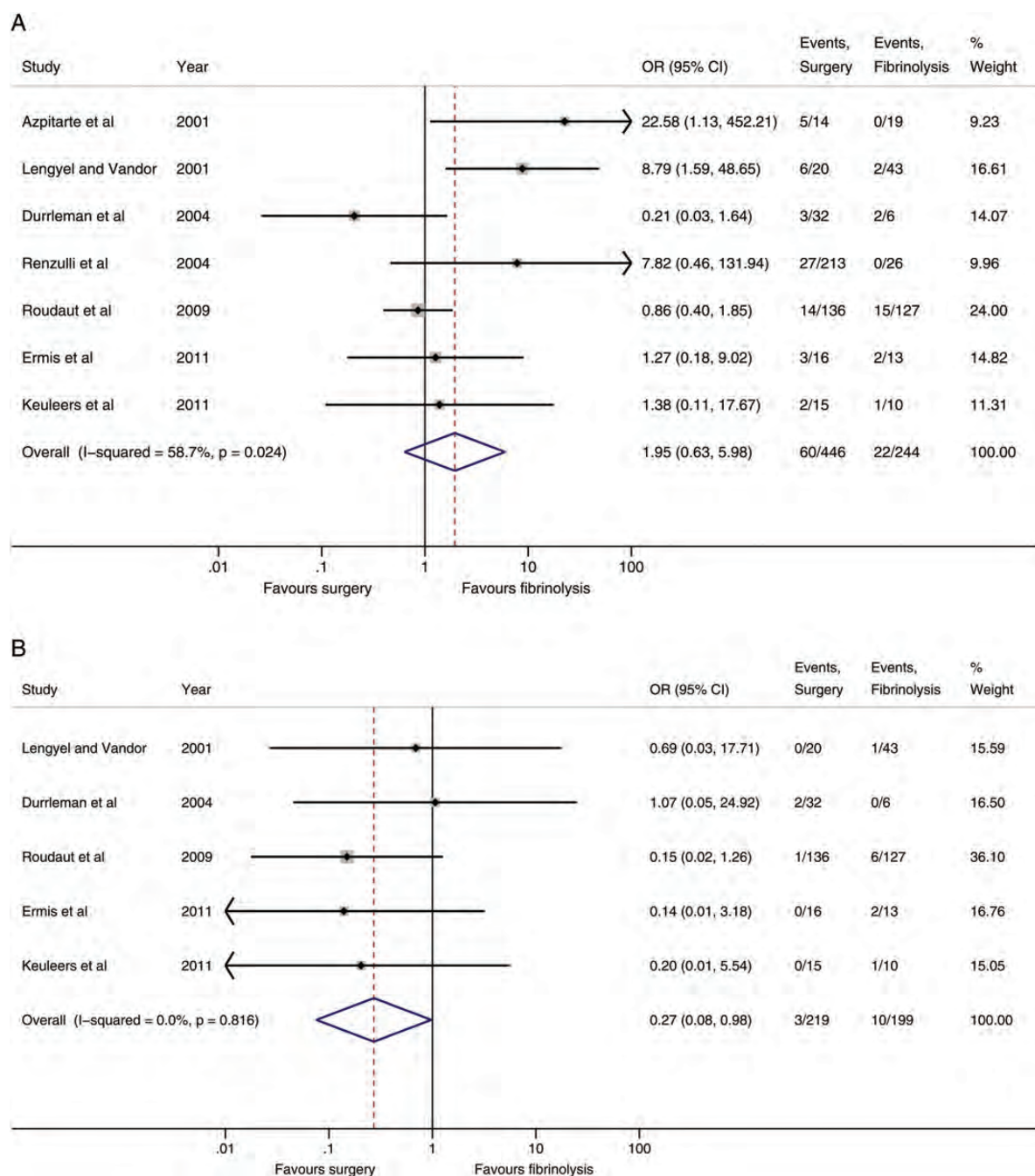
**Fibrinolytic therapy for left-sided prosthetic valve thrombosis**

Fibrinolytic therapy is believed to be successful over 80% of the time and has been recommended by several authorities as the first-line treatment for left-sided PVT.<sup>6</sup> In this review, we found a lower success rate (i.e. 70%). This difference highlights the two major problems with the available data on the efficacy of FT for the treatment of PVT. First, most of the reports of FT are case reports or small case series, which may be subject to positive publication bias with potential overestimation of success rates. For example, Lengyel *et al.*<sup>3</sup> reported the results of a review of over 200 studies of FT for left-sided PVT. The vast majority of the studies in this review were presumably case reports or small case series, as the five largest studies in this analysis included between 8 and 63 patients. The overall success with FT in this review was 82%.<sup>3</sup> A more recently conducted systematic review attempted to minimize this small study effect by excluding reports with less than

three cases. This review of 32 studies (904 patients) suggested that FT was marginally less successful (76%).<sup>21</sup> The only large study with prospective data collection suggested that success rates may be even lower (~60%).<sup>2</sup>

The second important problem with the available literature is that there is inconsistency in the use of definitions of success in published reports. Arguably the most meaningful definition of success is the restoration of valve function without the occurrence of major complications. Although several investigators have applied this definition, others have not distinguished between mere ‘haemodynamic success’ and ‘clinical success’. Studies show a 7–10% reduction in the proportion of patients with successful outcomes, when the absence of complications is included in the definition. In one study, the rate of haemodynamic success was 81.5% and dropped to 72.7% when patients who suffered complications were excluded.<sup>5</sup> Likewise, in the report by Balasundaram *et al.*,<sup>4</sup> the proportions of episodes with haemodynamic success and clinical success were 68 and 61.3%, respectively. These results are consistent with the results of FT in our systematic review, though only one of the included reports<sup>18</sup> applied clinical definitions of success.

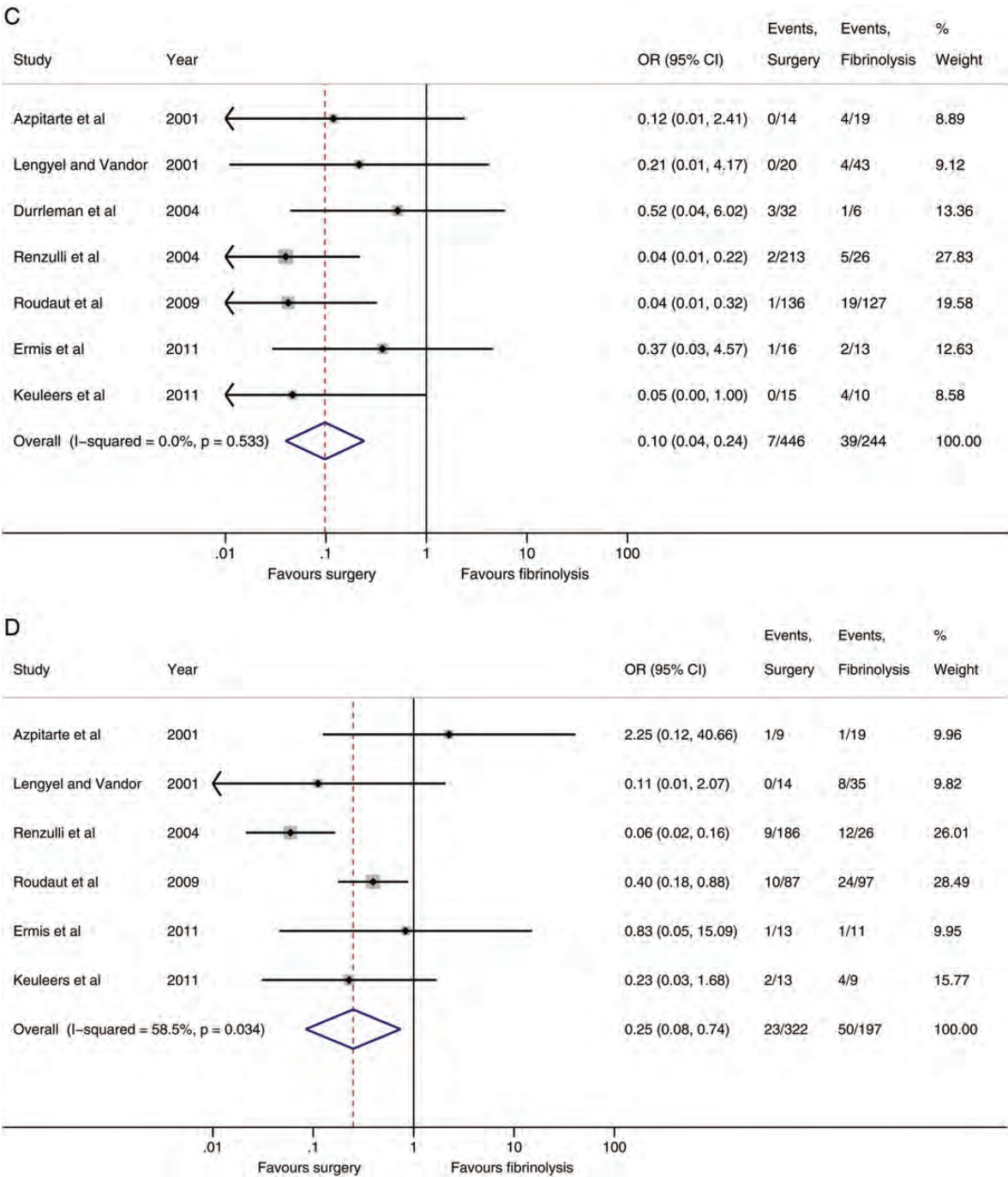
We found a 3-fold increase in the incidence of major bleeding and a 10-fold increase in the incidence of thrombo-embolism with FT when compared with surgery. Mortality was lower at 9% but not significantly different from that with surgery. The proportions of patients suffering adverse events in our review are broadly consistent with those from the two earlier reviews of FT. The review by Lengyel *et al.*<sup>3</sup> reported that 5% of patients had major bleeding, 5–10% had stroke (12% had any thrombo-embolic event), and 6% died. Similarly, the proportion of patients with major bleeding in the review by Reyes-Cerezo *et al.*<sup>21</sup> was



**Figure 3** Comparison of adverse events and recurrent valve thrombosis between urgent surgery and fibrinolytic therapy. (A) Death. (B) Major bleeding. (C) Stroke, transient ischaemic attack, or non-CNS systemic embolism. (D) Recurrent prosthetic valve thrombosis.

5%, overall thrombo-embolism 14% (8% TIA or stroke), and cardiovascular mortality 10%. Initial treatment with FT was also associated with a three-fold increase in the likelihood of recurrent PVT compared with surgery. The proportion of patients with recurrence in the earlier reviews was 11 and 18%, respectively.<sup>3,21</sup> Recurrent PVT may be associated with a poorer response<sup>4</sup> and all the attendant risk attributable to the condition and its subsequent treatment.

Some investigators advocate the use of TEE to quantify thrombus burden to reduce the risk of thrombo-embolism due to FT,<sup>22</sup> and some current guidelines recommend performance of TEE for guiding treatment decisions.<sup>7,9</sup> Although the use of TEE was reported in several of the included studies, its influence on outcomes was reported only in the study by Roudaut *et al.*<sup>18</sup> A landmark analysis of their data suggested that the routine use of TEE did not change the efficacy or safety of FT.<sup>18</sup>



**Figure 3** Continued.

**Urgent surgery for left-sided prosthetic valve thrombosis**

Surgery almost invariably restores valve function in all patients with PVT, but the major concern has been the high risk of death associated with the procedure. The rate of success with urgent surgery was 86.5% in our review, with practically all the failures attributable to death. The distinction between haemodynamic and clinical

success may be less relevant for surgery as the proportion of non-fatal adverse event rates with surgery is small. Although the mortality rate with surgery is high, it varies considerably with patient characteristics at baseline, the most important of which is the functional class at presentation. For example, in the study by Roudaut et al.,<sup>18</sup> 10 of the 14 deaths reported in the surgery group occurred in patients who presented in NYHA class IV. However, patients in



**Table 3** Characteristics of patients treated with surgery or fibrinolytic therapy in the included studies<sup>a</sup>

Study	Study period (duration, years)	Study group	Number of patients (episodes)	Patient age (mean, years)	Females, n (%)	Atrial fibrillation, n (%)	Bileaflet valves, n (%)	Mitral valve thrombosis, n (%)	NYHA class III or IV at presentation, n (%)	Duration of symptoms (mean, weeks)	Time from valve replacement (mean, years)
Lengyel and Vandro <sup>15</sup>	1993–2000 (8)	Surgery	20 (20)	53	15 (75.0)	NA	15 (79.0)	19 (95.0)	16 (80.0)	NA	4.6
		FT	37 (43)	55	25 (58.1)	NA	32 (74.5)	41 (95.3)	28 (65.1)	1.98	4.1
Roudaut et al. <sup>18</sup>	1978–2001 (24)	Surgery	136 (136)	59	86 (63.2)	NA	82 (60.3)	91 (67.9)	85 (62.5)	NA	7.7
		FT	110 (127)	57	82 (64.6)	NA	79 (62.2)	79 (63.2)	90 (70.8)	NA	4.2
Ermis et al. <sup>19</sup>	2001–2008 (8)	Surgery	16 (16)	53.0	12 (66.7)	12 (66.7)	10 (55.6)	13 (81.3)	13 (72.2)	4.1	6.2
		FT	13 (13)	51.3	8 (53.3)	7 (46.7)	10 (76.9)	11 (84.6)	13 (86.7)	1.4	5.5
Keuleers et al. <sup>20</sup>	1988–2008 (21)	Surgery	15 (15)	59.2	NA	11 (73.3)	NA	9 (60.0)	13 (86.7)	NA	11.6
		FT	10 (10)	63.9	NA	6 (60.0)	NA	8 (80.0)	8 (80.0)	NA	11.0

FT, fibrinolytic therapy; NA, not available.

<sup>a</sup>Some patients underwent an initial trial of FT before undergoing surgery; we were unable to isolate the characteristics of these patients from the overall characteristics reported in the publications and have assigned them to the groups they were allocated to by the authors of the respective studies in their analyses.

poor functional class fare poorly irrespective of the treatment given. We have previously shown that only a quarter of patients in NYHA class III/IV have a complete clinical response with FT, with a quarter suffering a major complication (death, major bleeding, or stroke).<sup>2</sup> Therefore, poor outcomes in the minority of patients in NYHA class IV should not dictate against performing urgent surgery, as it is likely to benefit the large majority of patients with left-sided PVT. Finally, notwithstanding the observational nature of the data, the magnitude and consistency of the reductions in major adverse events with surgery observed in this review suggest a true beneficial effect.

## Study limitations

There are several caveats to the interpretation of the results of this review, primarily arising out of the observational design and retrospective data collection in the included studies. Since the decision to treat patients using either modality was at the discretion of treating doctors, selection bias was inevitable. This may have resulted in systematic differences in variables which could have influenced outcomes with either treatment modality. Although we were unable to demonstrate interactions between the observed differences in some key variables and outcomes with treatment, the existence of such interactions cannot be ruled out. However, the reduction in adverse events with surgery was large and consistent across studies and is likely to represent a true effect. It must be emphasized that the data included in this review are from centres with expertise in surgery and FT for left-sided PVT. Therefore, the conclusions cannot be extrapolated to smaller, less experienced centres.

In all the included studies, outcomes were objectively measured but definitions were not pre-specified and may not have been consistently applied in an unbiased manner to both treatment groups. Some of the studies included data for patients with tricuspid and tissue valves where the risk–benefit trade-offs between surgery and FT may be different from patients with left-sided mechanical valve thrombosis. But the number of such patients was small and is unlikely to have influenced the final effect estimates. Finally, some patients were initially treated with FT and subsequently underwent surgery due to persistent valve dysfunction, but were analysed as part of the surgery arm. Again, the number of such patients was small, and moreover, this may only have reduced the effect in favour of surgery seen in this meta-analysis.

## Implications for clinical practice

The results of this systematic review should give pause to the current widespread and indiscriminate use of FT as the treatment of choice for left-sided PVT in developing countries. Both treatments must be systematically compared, preferably in randomized trials, to obtain more reliable estimates of the risk–benefit trade-offs. Urgent surgery will have higher initial costs, and a formal economic evaluation will be required to quantify the additional costs involved and the return on this additional investment. The limited availability of centres with surgical expertise in developing countries will also pose challenges to providing surgery as the initial treatment. Nonetheless, determination of relative efficacy must precede considerations of effective provision of services. We have recently designed a randomized trial which will test the

efficacy, safety, and cost-effectiveness of urgent surgery compared with FT for the treatment of symptomatic patients with left-sided PVT (clinicaltrials.gov registration number NCT01641549), which we hope will provide definitive answers to these questions.

## Conclusion

This systematic review suggests that in experienced centres, urgent surgery is safer and also perhaps more efficacious when compared with FT for the treatment of left-sided PVT. However, because of the observational nature of the data, these results need to be confirmed in an adequately powered randomized controlled trial. Till the results from such studies are available, surgery should probably be considered the preferred treatment for left-sided PVT.

## Authors' contributions

G.K.: conception, design, data collection, analysis, interpretation, writing the first draft, critical revision of the manuscript for important intellectual content, overall study supervision; N.B.S.: data collection, interpretation, critical revision of the manuscript for important intellectual content; J.J.: data collection, interpretation, critical revision of the manuscript for important intellectual content; N.D.: design, data analysis, interpretation, critical revision of the manuscript for important intellectual content; V.K.B.: data interpretation, critical revision of the manuscript for important intellectual content; B.A.: data interpretation, critical revision of the manuscript for important intellectual content. The final version of the manuscript was approved by all the authors.

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## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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