RECURRENT RISK OF ADVERSE EVENTS IN MEDICALLY TREATED PATIENTS WITH PATENT FORAMEN OVALE: A REVIEW OF THE LITERATURE

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SUMMARY – Patent foramen ovale is associated with stroke. However, the rate of recurrent events in medically treated patients with patent foramen ovale remains undefined. Estimates differ by the studies. In order to provide a more accurate estimate of the recurrent adverse event rates in medically treated patients with patent foramen ovale, we reviewed the literature and analyzed the results from a total of 1,108 patients combining 12 studies. We found the annual rate of stroke or death to be 3.12% (95% CI, 2.32–4.11%). This estimate will provide a valuable guideline for any future study to compare the efficacy of other modalities such as percutaneous device closure of patent foramen ovale with medical treatment.

Key words: Cerebrovascular accident, etiology; Cerebrovascular disorders, complications; Heart septal defects; Prognosis; Risk factors

Introduction

Patent foramen ovale (PFO) has been associated with stroke, especially with stroke of undefined etiology or ‘cryptogenic’ stroke. Up to 40% of strokes are deemed cryptogenic, and given the annual rate of 750,000 patients in the United States experiencing ischemic stroke, the number of cryptogenic stroke patients in this country reaches over 250,000. Now there are a variety of methods to potentially reduce the rate of recurrent events in cryptogenic stroke patients with PFO, which include surgery and percutaneous closure.

The interest in closing PFO remains very high as a potential therapeutic modality. As such, in designing a trial to prevent recurrent events, it becomes critical, to have the best available data on the recurrent event rates in medically treated cryptogenic stroke patients with PFO. Except for a publication from 2001, there has been no systematic literature review to assess the recurrent event rates in patients with ischemic stroke and PFO. As such, we thought to assess this issue by pooling the data available in the literature on medically treated cryptogenic stroke patients with PFO.

Material and Methods

Recurrent event rates were estimated from all published studies that are included in MedLine as well as abstracts known to the authors to be presented at national meetings since 1990. The number of subjects, medical treatment modality, and follow-up time were obtained for each publication. There were 12 publications that were considered appropriate and one not appropriate for inclusion in this analysis. Summaries of these 12 studies are shown below. Inclusion criteria were as follows:

1) patients with presumed paradoxical embolic events without obvious cause, including patients with cryptogenic stroke, transient ischemic attacks (TIA), or other arterial embolic events;
2) documented PFO documented on echocardiography, either transthoracic (TTE) or transesophageal (TEE) echocardiography;
3) original manuscript is available in English.

For the purpose of creating a summary table, all-cause mortality was included. Thus, when discrepancies in the

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numbers exist in some of the cells compared with the published manuscript, this is due to the difference in the criteria used for end-points. Table 1 includes author names and year, number, type and mean age of study patients, mean follow-up in months, and treatment modality used. In terms of end-points, stroke, any-cause death, TIA, stroke or death, stroke or TIA, and stroke, death or TIA are included. In this study, we assessed the events in medically treated patients irrespective of the type of therapy. We did not have adequate information to determine the efficacy of each therapy.

Studies included in the analysis

1) Schneck MI, DiSavino EM, Leurgans S. Recurrence rates in patent foramen ovale (PFO) and cryptogenic stroke or transient ischemia (TIA). Circulation 2002;106:I154. (Abstract)12

Forty-four patients with cryptogenic stroke and PFO, 14 of whom aged ≥55, were followed up for 45 to 14 months. Eleven patients also had atrial septal aneurysm (ASA) and recurrent events (4 strokes and 7 TIA) each. At initial event, 21 patients received antiocoagulants, 20 antiplatelet agents, and three no therapy. Log-rank tests showed significant differences in recurrence between the patients initially prescribed antiocoagulants and those administered antiplatelet agents (5% vs. 35%; \( \chi^2 = 5.55; \text{df} = 1; \text{p} = 0.019 \)). Time to recurrence did not differ according to age (p = 0.29) or presence of ASA (p = 0.37). Information on the time of events is offered.


A total of 179 patients with presumed paradoxic cerebral embolism and PFO underwent transvenous occlusion with an Angel Wings device (n = 8), Amplatzer occluder (n = 108), or a PFO-Star device (n = 62). The patients were followed up for a mean of 12.7 months. A series of 111 patients with presumed paradoxic embolism and PFO treated with aspirin (n = 90) or phenprocoumon (n = 21) were followed up for 31 ± 11 months. The mean annual rate of embolic event recurrence was 1.1% in patients treated with an occluder system as compared with 4.1% in medically treated patients (p < 0.05). No information on the time of events is offered.


PICSS was a 42-center study that evaluated transesophageal echocardiographic (TEE) findings in patients randomly assigned to warfarin or aspirin in the Warfarin-Aspirin Recurrent Stroke Study (WARSS). In this study, 630 stroke patients were enrolled, 312 (49.5%) of them randomized to warfarin and 318 (50.5%) to aspirin. Of these, 265 patients experienced cryptogenic stroke and 365 had known stroke subtypes. End-points were recurrent ischemic stroke or death. PFO was present in 203 (33.8%) patients. There was no significant difference in the time to primary end-points between the patients with and those without PFO in the overall population (p = 0.84; hazard ratio 0.96; 95% CI 0.62-1.48; 2-year event rate 14.8% vs. 15.4%) or in the cryptogenic subset (p = 0.65; hazard ratio 1.17; 95% CI 0.60-2.37; 2-year event rate 14.3% vs. 12.7%). There was no significant difference among those with no, small or large PFO (p = 0.41 for small PFO and p = 0.16 for large PFO; 2-year event rates for no, small, and large PFO were 15.4%, 18.5% and 9.5%, respectively). There was no significant difference between patients with isolated PFO and those with PFO in association with ASA (p = 0.84; 2-year event rate 14.5% vs. 15.9%). In patients with PFO there was no significant difference in the time to primary end-points between those treated with warfarin and those on aspirin (p = 0.49; hazard ratio 1.29; 95% CI 0.63-2.64; 2-year event rate 16.5% vs. 13.2%). Ninety-eight cryptogenic stroke patients with PFO were treated with warfarin (n = 56) or aspirin (n = 42), and followed up for 24 ± 1 months. Amongst the warfarin treated patients there were 2 strokes, 2 deaths and 3 TIA. In the aspirin treated group there were 8 strokes, 2 deaths and 5 TIA. Information on the time of events is available.


A total of 318 patients (mean age 50.7 ± 13.5 years) with cryptogenic stroke or TIA and PFO were followed up for 29 ± 23 months. Of these, 159 patients received medical treatment (79 oral anticoagulation and 80 platelet inhibitors) and constituted study population. The remaining 159 patients underwent endovascular or surgical closure of PFO and were not considered study population. The event leading to the diagnosis of PFO was a TIA in 38 (23.9%), an ischemic stroke in 119 (74.8%), and amaurosis fugax in two (1.3%) patients. Forty-four (27.7%) patients had sus-
tained multiple cerebrovascular ischemic events before the diagnosis of PFO. Twenty-one (13.4%) patients had recurrent cerebrovascular events (7 strokes and 14 TIs). The mean annual rate of recurrent stroke was 1.8%, and of recurrent stroke or TIA 5.5%. When the patients with PFO and multiple cerebrovascular events sustained before the diagnosis of PFO were analyzed in separate, the mean annual rate of recurrent cerebral ischemia was 3.6% for recurrent stroke, and 9.9% for recurrent stroke and TIA. These rates were significantly higher than those recorded in patients with first ever stroke or TIA (p=0.02). Information on the time of events is available.


A series of 581 patients (age range 18 to 55 years) with cryptogenic stroke sustained within the preceding 3 months received aspirin (300 mg per day) for secondary prevention. After 4-year (38±10 months) follow-up, the risk of recurrent stroke was 2.3% (95% CI 0.3-4.3%) in patients with PFO alone (n=216), 15.2% (95% CI 1.8-28.6%) in patients with both PFO and ASA (n=51), and 4.2% (95% CI 1.8-6.6%) in patients with neither PFO nor ASA (n=304). There were no recurrences among the patients with ASA alone (n=10). The presence of both cardiac abnormalities was a significant predictor of an increased risk of recurrent stroke (hazard ratio for comparison with the absence of these abnormalities, 4.17; 95% CI 1.47-11.84), whereas isolated PFO, either small or large, was not. Information on the time of events is available.


Seventy-four patients (mean age 53±14 years) with acute ischemic stroke or TIA within 1 week of admission, and with PFO identified by contrast TE were followed up for a median of 31 (range 4 to 58) months. Thirteen PFO subjects without the history of embolism were designated as a control group. In comparison with control subjects, PFO patients with acute stroke or TIA more frequently presented with a right-to-left shunt at rest and a higher membrane mobility (p<0.05). Eight patients experienced recurrent cerebrovascular events (5 strokes and 3 TIs), and two died from neoplasms. Of note, the patients enrolled in the study had sustained cryptogenic stroke or TIA and differentiation according to entry finding was not possible. Information on the time of events is available.

7) Cajec B, Mainura R, Johnson DH. Prevention of recurrent cerebral ischemic events in patients with patent foramen ovale and cryptogenic strokes or transient ischemic attacks. Can J Cardiol 1999;15:57-64.18

The study included a series of 90 consecutive patients aged <60 who underwent TE following a cryptogenic stroke or TIA, 52 with and 38 without PFO. During a mean follow-up of 46 months, 19 recurrent cerebral ischemic events (7 strokes and 12 TIs) were recorded in 14 patients with PFO, and 8 recurrent events (5 strokes and 3 TIs) in six patients without PFO. The recurrence rate was 12% and 5% per patient year in the PFO and control group, respectively, for a crude recurrence rate ratio of 2.39 (95% CI 1.01-6.32; p<0.03). The risk attributable to PFO in recurrent neurologic events was 7% per patient year. In the Cox regression model, the predictors of recurrent neurologic events were the presence of PFO (hazard ratio 5.27; 95% CI 1.58-7.6; p<0.007), history of migraine (hazard ratio 4.54; 95% CI 1.11-18.52; p<0.035), hypertension requiring therapy (hazard ratio 3.5; 95% CI 1.33-9.01; p<0.01), and antiplatelet or no therapy instead of warfarin therapy (hazard ratio 2.88; 95% CI 1.11-8.7; p<0.04). Fourteen patients underwent surgical closure of PFO, with no neurologic recurrences during a mean follow-up of 43 months (crude incidence rate difference 12% per patient year; 95% CI 6.6-17.9; p<0.02). Information on the time of events is offered.


A series of 140 consecutive patients (mean age 44±14 years, ≤60 years) with acute stroke and PFO were followed up for 36 months. The initial event was stroke in 118 (84%) and TIA in 22 (16%) patients. Pulmonary embolism, Valvula’s maneuver at onset, and coagulation abnormalities were rare, however, one-fourth of the patients had interatrial septal aneurysm (ISA) coexisting with PFO. An alternative cause of stroke, mostly cardiac, was present in only 22 (16%) patients. The stroke or death rate was 2.4% per year (stroke n=8, death n=5, TIA n=8), but only eight (1.9% per year) patients had a recurrent infarct. This low rate of recurrence contrasted the initial stroke severity. Multivariate analysis showed that interatrial communica-
tion, a history of recent migraine, posterior cerebral artery territory infarct, and a coexisting cause of stroke were associated with recurrence, whereas ISA and treatment modality (coagulant or antiaggregant therapy, surgical closure of PFO) were not. The presenting stroke was often severe but recurrence was uncommon. The authors conclude that the demonstration of factors associated with a higher risk of recurrence in patient subgroups is critical for the long-term management of these patients. The total number of patients also includes those undergoing surgery (n=11), therefore the patient type at entry is not clearly discernible as to either cryptogenic stroke or TIA. No information on the timing of events is offered.


The aim of this retrospective study was to assess the absolute risk of recurrent cerebrovascular events in 132 patients aged <60 with PFO, ASA (diagnosed by TE) or both, and an otherwise unexplained stroke or TIA. During a mean follow-up of 22.16 months, 6 patients sustained recurrent stroke (n=2) or TIA (n=4). No systemic embolism was observed. The actuarial risk of recurrent stroke was 2.3% (95% CI 0.6-8.2%), whereas the risk of stroke or TIA was 6.7% (95% CI 3.1-14.2%). The mean annual rate of recurrence was 1.2% and 3.4%, respectively. In patients with both PFO and ASA, the actuarial risk of first recurrent stroke was 9.0% (95% CI 2.4-28.5%) at 2 years, with a mean annual rate of recurrence of 4.4%. As a group, the patients with PFO, ASA or both, and an otherwise unexplained stroke or TIA appear to have a low risk of recurrent stroke whatever the prophylactic antithrombotic therapy used. The association of ASA and PFO may be an indicator of a higher risk of recurrent stroke. In our Table 1, patients with ASA alone (n=25) are not included. The number of cryptogenic stroke and TIA is not given because ASA has been included in the number. One patient that died from a ‘neoplasm’ has been excluded from the ‘death’ category. Information on the time of events is available.


The study included 78 patients with PFO detected by contrast TE. 21 patients with an otherwise unexplained arterial ischemic event and clinical evidence implying paradoxical embolism (group I); 30 patients with an unexplained ischemic event but no clinical evidence for paradoxical embolism (group II); and 27 patients without ischemic event (group III). On contrast TE, group I patients showed a more severe right-to-left shunt (mean ± SD, 52±16% of the left atrial area filled with contrast medium) and wider PFO opening (7.1±3.6 mm separation between the septum primum and septum secundum) than group II (35±15% and 4.4±32 mm, respectively; p<0.001) or group III (23±12% and 3.0±2.0 mm, respectively; p<0.001) patients. The incidence of ASA was similar in the three groups. Severe contrast shunting (250% of the left atrial area filled with contrast medium) and wide PFO opening (≥5 mm separation) showed high sensitivity (71% and 86%, respectively) and specificity (86% and 96%, respectively) for identification of group I patients. Forty-four of 51 patients (groups I and II) treated with aspirin (n=17) or warfarin (n=24) were followed-up for 59±12 months. There was 1 recurrent stroke and 1 TIA in the aspirin group, and 1 TIA in the warfarin group. Three patients underwent surgery for PFO closure as a treatment modality. It is not clear whether these patients were included in the follow-up number, however, the implication is that they were not. The time to events is not available in this report.


During a 60-month period, PFO was identified on TE by color Doppler or saline contrast study in 74 patients. According to final clinical situation, patients were divided into 3 groups: group 1, infarct with PFO a likely cause (n=16); group 2, infarct with PFO an unlikely cause (n=23); and group 3, no infarct (n=35). TEs were reviewed to assess PFO characteristics and associated cardioembolic sources without the knowledge of clinical details or group assignment. Follow-up data were obtained by telephone or written correspondence in 15 of 16 group 1 patients. ASA was more common in group 1 (38%) as compared with group 2 (10%) and group 3 (8%) (p=0.02). Contrast right-to-left shunting occurred in 88% of group 1 (p=0.06) and 86% of group 2 (p=0.07) patients as compared with 60% of group 3 patients. The prevention of recurrence in subjects with presumed PFO-related brain infarcts varied. Aspirin was usually chosen after initial brain ischemia. Warfarin and PFO closure were usually reserved for subjects with symptoms of brain ischemia while taking aspirin. No recurrent infarcts occurred in 15 patients during a mean follow-up period of 28 months. Two of these
15 patients underwent surgical PFO closure, thus the number in Table 1 is 13. Information on the time of events is available.


Thirty-eight patients, mean age 55 (range 20-80) years, met the criteria for ASA by TE (base width ≥1.5 cm and excursion ≥1.5 cm). Twenty-five of these 38 patients presented with cerebral ischemic events. None of these patients had a history of significant carotid artery disease, hypertension or valvular disease, and none had intracardiac thrombus. Nine of 25 patients received anticoagulation with warfarin (4/9 patients had right-to-left shunt) and 8/25 were on antiplatelet agents (6/8 of these had right-to-left shunt). These 17 active intervention patients had a mean follow-up of 12 months. Four of 17 patients had recurrent ischemic events (three of them with right-to-left shunt). All four patients were on antiplatelet agents. None of the patients on anticoagulant therapy sustained a recurrent event. Thus, four ASA/PFO patients on warfarin and six ASA/PFO patients on aspirin were followed-up. Three events (presumably stroke or TIA) occurred in the aspirin group. Information on the time of events is available.

A study not included in the analysis

Although providing information on the prognosis, the study listed below was not included in the analysis because we felt the methodology used had not been rigorous.


The study included 34 patients with PFO identified on saline contrast TE. Eighteen procedures were performed to evaluate the potential cardiac source of embolus, 4 to rule out valvular vegetation, 3 to evaluate native mitral valve disease, and 1 to rule out aortic dissection. The patients were divided into two groups according to the maximal number of microbubbles in the left heart in any single frame after intravenous saline contrast injection: group 1 (n=16, prior stroke or TIA n=8) with a ‘large’ degree of shunt (≥20 microbubbles); and group 2 (n=18, prior stroke or TIA n=10) with a ‘small’ degree of shunt (≥3 microbubbles). Patients were followed-up for a mean of 21 months for subsequent systemic embolic events including TIA and stroke. Subsequent ischemic neurologic events were recorded in five (31%) patients with large shunts and none of the patients with small shunts. Therapy was not randomized, and no statistical adjustment for a variety of risk factors was done.

The Analysis

The results from individual studies were pooled to estimate event rates per 100 patient years of follow-up. The total number of events was calculated by summing up the events from all studies. Event calculations that utilized deaths were confined to the 4 studies that provided detailed mortality information. The total time at risk for each study was calculated as the product of the mean follow-up and the number of subjects, and summed across studies to determine the total time at risk. In some studies, follow-up times were provided for groups with PFO, whereas in others only an overall mean follow-up time was available for patients with and without PFO. In one study, median instead of mean follow-up was stated. Event rates were calculated from the ratio of the total number of events to the total time at risk and expressed per 100 patient years, along with 95% confidence intervals, assuming that the observed events followed Poisson distribution. The homogeneity of event rates across studies for stroke and TIA was assessed by Cochran’s Q test for all studies with more than 15 patients. No significant lack of homogeneity was detected for stroke (Q=7.83, p=0.55) or TIA (Q=8.93, p=0.44). The homogeneity of event rates for deaths was not tested because the number of occurrences was small and limited to a few studies.

Results

A total of 1,108 subjects were considered in the analysis (Table 1). Inclusion criteria were cryptogenic stroke and TIA. In some cases, ‘paradoxical embolism’ included peripheral embolism. The mean age of the subjects was 45 years and mean follow-up 34 months. The total number of deaths (any cause) was 15, strokes 62 and TIA 69. The annual rate of stroke was 2.01% (95% CI 1.54-2.58%), and of stroke or death 3.12% (95% CI 2.32-4.11%).

Discussion and Conclusions

PFO has been associated with cryptogenic stroke1-2. However, there is paucity of data regarding the recurrent event rates in cryptogenic stroke patients with PFO. We
Table 1. Summary of studies included in analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Patient type</th>
<th>Mean age</th>
<th>Follow-up (mo)</th>
<th>Tx type</th>
<th>Stroke (%)</th>
<th>Death (%)</th>
<th>TIA (%)</th>
<th>S/D (%)</th>
<th>S/T (%)</th>
<th>S/D/T (%)</th>
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<tbody>
<tr>
<td>1 Schenck, Circ 2002</td>
<td>44</td>
<td>Cryptogenic stroke or TIA</td>
<td>–</td>
<td>45</td>
<td>w 21, a 20, n 3</td>
<td>4</td>
<td>–</td>
<td>7</td>
<td>–</td>
<td>11</td>
<td>–</td>
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<td>2 Hofmann, Circ 2002</td>
<td>111</td>
<td>Paradoxic embolism</td>
<td>–</td>
<td>32</td>
<td>phen 21, a 90</td>
<td>6</td>
<td>–</td>
<td>3</td>
<td>–</td>
<td>9</td>
<td>–</td>
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<td>3 Homma, Circ 2002</td>
<td>98</td>
<td>Cryptogenic stroke</td>
<td>55</td>
<td>22</td>
<td>w 42, a 56</td>
<td>10</td>
<td>4</td>
<td>8</td>
<td>14</td>
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<td>Cryptogenic stroke 119, TIA 38</td>
<td>51</td>
<td>29</td>
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<td>–</td>
<td>14</td>
<td>–</td>
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<td>267</td>
<td>Cryptogenic stroke</td>
<td>40</td>
<td>38</td>
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<td>6 De Castro, Stroke 2000</td>
<td>74</td>
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<td>53</td>
<td>31</td>
<td>w, a, n</td>
<td>5</td>
<td>5</td>
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<td>46</td>
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<td>44</td>
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<td>w 37, a 92</td>
<td>8</td>
<td>5</td>
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<td>13</td>
<td>16</td>
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<td>9 Mas, AHJ 1995</td>
<td>107</td>
<td>Cryptogenic stroke, TIA</td>
<td>39</td>
<td>22</td>
<td>w, a, n</td>
<td>2</td>
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<td>–</td>
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<td>10 Hausmann, JACC 1995</td>
<td>44</td>
<td>Cryptogenic stroke, TIA, perip. emb.</td>
<td>46</td>
<td>59</td>
<td>w 24, a 17, s 3</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>3</td>
<td>–</td>
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<tr>
<td>11 Hanna, Stroke 1994</td>
<td>13</td>
<td>Cryptogenic stroke</td>
<td>43</td>
<td>27</td>
<td>w 7, a 6</td>
<td>0</td>
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<tr>
<td>12 Sharma, ASE 1991</td>
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<td>Cryptogenic stroke</td>
<td>55</td>
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<td>w, a</td>
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<td>45</td>
<td>34</td>
<td></td>
<td>62</td>
<td>15</td>
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Events/100 pt/ys: 2.01 0.94 2.23 3.12 4.32 4.86
95% CI: 1.54-1.70-2.23-3.59-3.78-3.78-2.58 1.55 2.76 4.11 5.05 5.94

S = stroke, D = death, T(TIA) = transient ischemic attack, - = unknown, w = warfarin, a = aspirin, n = no therapy
have found 12 studies that include data on the follow-up of medically treated patients with PFO. None of the studies except for PICCSS was randomized according to therapy, thus the information on the efficacy of the medical therapy modality is not reported. We combined 12 studies to see whether we could come up with the best estimate of recurrent event rates in medically treated patients with PFO.

The study population included a total of 1,108 patients, mean age 45 years, followed-up for a mean of 34 months. We note that the recurrent event rate for stroke or death was 3.12%. Individual studies included in the analysis demonstrated variable rates of recurrent events. This was probably due to the age difference in the subjects involved in particular studies. Our series is the largest one constructed to estimate the event rates in patients with PFO. It is clear that the recurrent stroke or death rate is considerably lower than that generally reported for stroke patients. However, it is important to note that the mean age of the patients considered in our analysis was quite different. The patients typically enrolled in PFO studies are significantly younger than the general stroke population.

In spite of the efforts presented, limitations remain. Inclusion criteria were different in various studies. Also, ‘cryptogenic’ stroke may not be diagnosed with the same standard. Similarly, the definition of TIA is often vague for both initial inclusion and follow-up. Age difference may also play an important role in the event rates. The mean age of the patients involved in the analysis was 45 years, i.e. considerably younger than for stroke patients in general. The method and rigor of follow-up also determined event rates in each of the studies, and it is unlikely that uniform criteria were used in different studies. Additionally, the length of follow-up was variable, and the events recorded in the studies were not assessed by the time of occurrence in relation to the initial event. Thus, the events related to the presence of PFO may have occurred more frequently at a certain time point after the initial event. Longer follow-up in some of the studies may have provided different results. In our analysis, comparison of medical therapy modalities such as warfarin, aspirin, or clopidogrel was not performed because patients were not randomized to particular therapies in any of the studies except for PICSS. Nevertheless, given the limitations, the recurrent event rate reported in this review represents the most up-to-date information and should prove useful in planning the trials aimed at demonstrating the efficacy of various therapeutic modalities.

References


Sažetak

RIZIK NEŽELJENIH DOGADAJA KOD BOLESNIKA S OTVORENIM FORAMEN OVALE LIJEČENIH LIJEKOVIMA: PREGLED LITERATURE

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Otvoreni foramen ovale (OFO) udružen je s moždanim udarom. Međutim, učestalost rekurentnih neželjenih događaja u bolesnika liječenih lijekovima s otvorenim foramen ovale nije poznata, a procjene iz različitih studija se razlikuju. Stoga smo obavili pregled literature i analizirali rezultate za ukupno 1.108 bolesnika iz 12 studija, kako bismo dobili točniju procjenu učestalosti neželjenih događaja u bolesnika s otvorenim foramen ovale liječenih lijekovima. Utvrdili smo godišnju stopu moždanog udara ili smrti od 3,12% (95% CI, 2,32-4,11%). Ova će procjena poslužiti kao vrijedna smjernica za buduću ispitivanja u kojima će se uspoređivati učinkovitost drugih načina liječenja, primjerice, zatvaranje otvorenog foramen ovale pomoću perkutanog uređaja uz medicinsko liječenje.

Ključne riječi: Moždeni udar, etiologija; Cerebrovaskularni poremećaji, kompleksne; Atrijski septumski defekt, Prognoza; Rizivi činitelji