Occurrence of Atrial Fibrillation During Dobutamine Stress Echocardiography

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Dobutamine stress echocardiography (DSE) is a widely used examination for assessment of coronary ischemia, but several complications have been reported. The aim of this study was to assess the incidence of atrial fibrillation (AF) during DSE, and a systematic review and meta-analysis were also performed to determine an accurate estimate of the AF incidence. Over a 16-year period, we reviewed all patients referred for DSE. We systematically analyzed all ECG performed during DSE to detect AF during the examination. DSE was completely performed in 4,818 patients (mean age: 62.1 ± 11.7 years). AF was observed in 40 patients (31 men, mean age: 79.7 ± 8.9 years). Incidence of AF during DSE was 0.83%. Regarding the meta-analysis, the combined AF incidence was 0.86%. In our study, patients with AF occurrence had more frequent previous history of paroxysmal AF (p = 0.02) were also older (p < 0.0001) and incidence of AF during DSE increased with age: 0% below 60 years, 0.45% in patients 60 to 69 years, 1.3% in patients 70 to 79 years, and 4% in patients >80 years (p < 0.0001). In multivariate analysis, the factors significantly associated with an increased risk of AF were age (adjusted odds ratio (aOR) = 2.4, 95% confidence interval: 1.5 to 3.3, p = 0.003) and previous history of paroxysmal AF (aOR = 1.5, 95% confidence interval: 1.1 to 1.9; p = 0.04). In conclusion, AF is uncommon during DSE, and elderly patients and patients with previous history of paroxysmal AF are at risk of AF during DSE. **(Am J Cardiol 2019;123:1277−1282)**

Dobutamine stress echocardiography (DSE) is routinely performed for the assessment of coronary ischemia, with an excellent diagnostic and prognostic value. Despite its wide use, several complications or side effects of DSE have been reported: myocardial infarction, supraventricular or ventricular arrhythmias, hypotension, coronary spasm, and death.[1,2] Thus, atrial fibrillation (AF) may occur during DSE, but studies for the incidence of this specific side effect of DSE remain rare.[3−30] The aim of this study was to assess the incidence of AF during DSE and to pool it with the AF incidence during DSE of all other published studies, in order to determine an accurate estimate with an aggregated incidence.

Methods

Over a 16-year period (from November 2001 to October 2017), we reviewed all consecutive patients (n = 4,917) referred for DSE. Entry criteria included age >18 years and all patients who underwent DSE. Patients presenting with permanent or persistent AF were not included in this study. All DSE were performed by a medical doctor. We distinguished patients presenting with normal DSE (no significant symptoms, no ECG modifications nor wall motion abnormalities during examination) from patients presenting with positive DSE, according to guidelines. All patients had an ECG monitoring during DSE and we systematically analyzed all ECGs performed during the echocardiographic examination, thus identifying occurrence of AF (>5 seconds). All echocardiographic examinations were performed using a Siemens/Sequoia Acuson C512 system (Acuson, Mountain View, CA) or a Vivid 7 or 9 system (GE Medical Systems, Horten, Norway), equipped with multifrequency transducers and capable of low energy (0.2 to 0.3 mechanical index). In the case of suboptimal acoustic windows, left ventricular cavity opacification was performed by peripheral venous injection of Sonovue contrast agent (Bracco Altana, Inc., Milan, Italy). Dobutamine was administered intravenously in an incremental regimen of 10, 20, 30, and 40 μg/kg/min every 3 minutes for each dose (from 2001 to 2004) and every 2 minutes after the first period. Atropine (0.25 to 1 mg) was administered at the beginning of 20, 30, and 40 μg/kg/min of dobutamine (in case of noncontraindication), and DSE was stopped when the target heart rate (85% of the predicted maximal heart rate [220- age {years}]) was achieved. Without contraindication, intravenous β blockers were performed at the end of DSE. DSE was interpreted according to guidelines.

Continuous variables were compared using Student's test. Categorical data are compared using the chi-square test, Fisher's exact test, or Wilcoxon test as appropriate. We performed a multivariate logistic regression analysis to identify sets of factors that together are significantly associated with the occurrence of AF. All the tests were 2-sided and the results were considered significant at p < 0.05. Statistical

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See page 1281 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.01.022

analysis was performed with STATA 12.0 (Stata-Corp, College Station, TX). To further determine an accurate estimate of the AF incidence during DSE, we performed a meta-analysis. A previous literature review was published in 2010, but the combined incidence of AF during DSE was not calculated.[1] Moreover, this review was not exhaustive and since 2010 other studies have been published. Our meta-analysis complies with the preferred reporting items of PRISMA for systematic reviews and meta-analyses. A comprehensive search of several electronic databases (between 1948 and August 26, 2018) was conducted in EMBASE between 1988 and August 26, 2018; Ovid MEDLINE in-process and other nonindexed citations and Ovid MEDLINE between 1948 and August 26, 2018; and EBM Reviews-Cochrane Central Register of Controlled Trials and EBM Reviews−Cochrane Database of Systematic Reviews between 2005 and August 26, 2018. In addition, we searched the reference lists of relevant studies and reviews for additional published and unpublished data and used the web search engine "Google" for abstracts, conference proceedings, and unpublished studies. We used a combination of keywords related to the type of exposure ("DSE") and to the type of outcome ("AF"). The studies involved adults and could be of any design and any language. We excluded animal studies, ex vivo and toxicological studies, duplicates, summaries, commentaries, editorials, case reports, studies that did not evaluate AF incidence during DSE, and studies without original data. Two independent reviewers (NM and HM) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then screened to determine the eligibility of the study for the review and meta-analysis. Disagreements regarding eligibility were resolved by consensus. Data extraction using a standardized form included a full description of the study characteristics. Incidences were reported in percentage with 95% confidence interval (CI) and the combined incidence was estimated using a random-effects model. This model was chosen because of anticipated significant heterogeneity between studies in terms of population and methods. The random-effects model is the most conservative approach in this setting because it incorporates within and between-study heterogeneity in the CI. Statistical heterogeneity across the studies was calculated by the I^2 statistics to quantify inconsistencies between studies. I^2 values <25%, 25% to 50%, 50% to 75%, and >75%, respectively represent low, moderate, high, and very high inconsistency. To assess the potential for publication bias, we added the Egger's regression test p value for funnel symmetry, a p value <0.05 is an argument for a potential publication bias. All analyses were performed with Comprehensive Meta-analysis software, version 2.0 (Biostat, Englewood, New Jersey, USA).

Results

Among 4,917 patients referred for DSE in our institution, 4,818 patients (3,592 [76%] men) underwent complete DSE (Figure 1). Mean age was 62.1 ± 11.7 years. DSE was considered as positive in 1,535 patients and negative in 3,283 patients. AF occurred in 40 patients (31 men, mean age: 79.7 ± 8.9 years). Incidence of AF during DSE was 0.83% (95% CI: 0.57 to 1.09) and was similar whatever the result of DSE (0.85% in case of positive DSE vs 0.82% in case of negative DSE, p = 0.93). AF occurred with 40γ/kg/min of dobutamine in 29 patients (72.5%) versus with 30γ/kg/min of dobutamine in 6 patients (15%), with 20γ/kg/min of dobutamine in 2 patients (5%) and in early recovery in 3 patients (7.5%). The use of atropine was similar in the 2 groups of patients (Table 1). Several patient characteristics were univariately associated with the occurrence of AF (Table 1). AF during DSE was significantly more frequent in patients with previous history of paroxysmal AF (p = 0.02). Patients with AF occurrence were also significantly older (p < 0.0001) and incidence of AF during DSE increased with age: 0% below 60 years, 0.45% in patients 60 to 69 years, 1.3% in patients 70 to 79 years, and 4% in patients >80 years (p < 0.0001). In multivariate analysis, the factors significantly associated with an increased risk of AF during DSE were age (adjusted odds ratio (aOR) = 2.4, 95% CI: 1.5 to 3.3, p = 0.003) and previous history of paroxysmal AF (aOR = 1.5, 95% CI: 1.1 to 1.9; p = 0.04).

Dobutamine infusion was immediately discontinued in case of AF. Duration of AF was less than 1 hour in most of patients (67.5%) with spontaneous termination of AF (Table 2). For the 13 patients with duration of AF higher than 1 hour and after anticoagulation, pharmacological cardioversion (amiodarone or flecainide) was systematically attempted and only 7.5% had persistent AF. For those patients, an electrical cardioversion was performed at distance and all patients had a recovery of sinus rhythm.

Regarding the meta-analysis, the search strategy on the mentioned electronic databases, identified 199 citations to which we added 3 citations from reference lists of relevant studies and reviews. After screening titles and abstracts, 35 citations were considered potentially eligible and the full-text article was retrieved. Of those, 7 citations were excluded, resulting in 28 selected studies to which we added our present study (Figure 2).[3−30] Thus, we calculated a combined incidence of AF during DSE from a total of 29 studies. Inter-rater agreement for study selection was very high between the 2 reviewers. The number of DSE performed per study ranged between 63 and 11,806, the number of AF incident cases ranged between 1 and 122. AF incidence during DSE ranged from 0.29% to 2% and this incidence was investigated in several sites on every continent from 1990 to 2017. The combined incidence of AF during DSE was 0.86% (95% CI: 0.70 to 1.02), the statistical heterogeneity across the studies was high (I^2 = 71.5%) but expected and there was no statistical argument for any publication bias (Egger's regression test p = 0.15; Figure 3).

Discussion

The main results of the present study were: (1) AF during DSE is uncommon (our study incidence was 0.83% and of the same magnitude order as the combined incidence of the meta-analysis); (2) age and previous history of paroxysmal AF are predictive factors of AF occurrence; (3) most of AFs are paroxysmal, and cardioversion is rarely performed.

DSE is a routine test performed for the diagnosis of coronary artery disease because of its accuracy. Its indications have increased notably these last years, leading to more

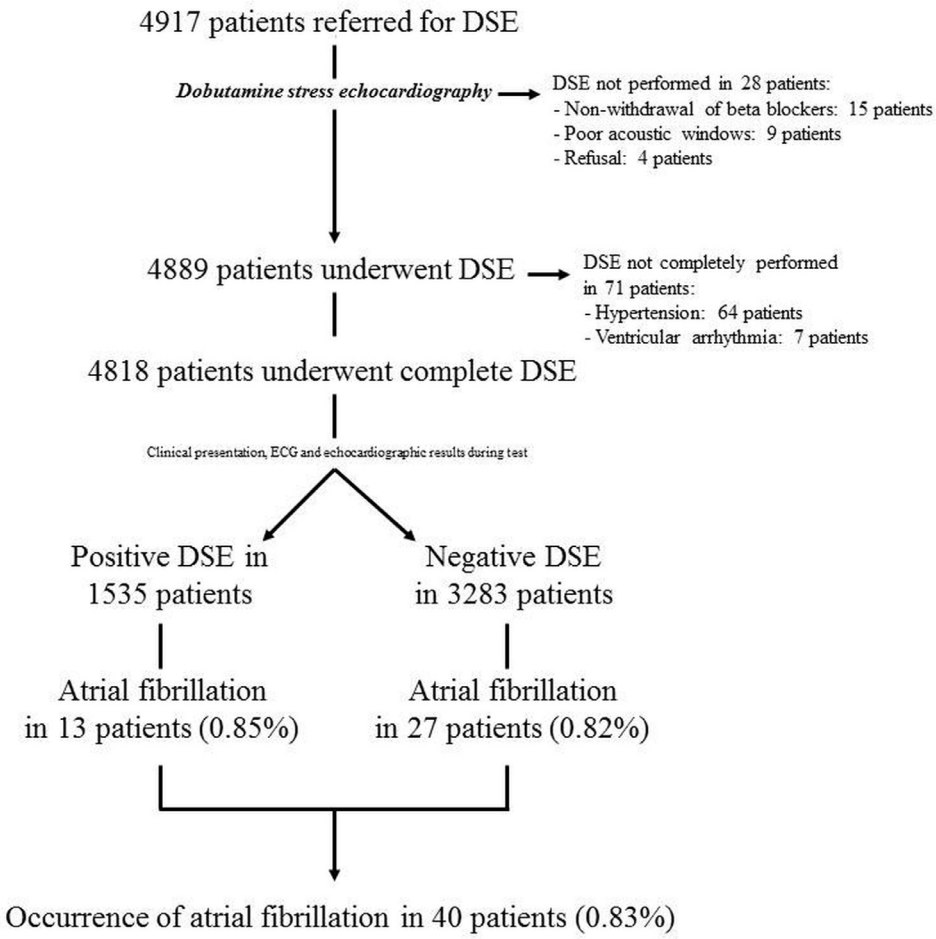

Figure 1. Flowchart of patients in the study. DSE = dobutamine stress echocardiography.

Table 1
Characteristics of patients with complete DSE (n = 4,818)

Variable	AF occurrence during DSE: No (n = 4,778)	AF occurrence during DSE: Yes (n = 40)	p Value
Age (y)	62.0 ± 11.6	79.7 ± 8.9	<0.0001
Men	3,588 (75%)	31 (78%)	0.73
Previous history of paroxysmal AF	573 (1%)	10 (25%)	0.02
Cardiovascular risk factors			
Smoker	1,615 (34%)	13 (32.5%)	0.86
Hypertension	2,435 (51%)	30 (75%)	0.17
Diabetes mellitus	514 (11%)	5 (13%)	0.72
Dyslipidemia*	1,720 (36%)	15 (38%)	0.84
Echocardiographic measurements			
Left ventricular enddiastolic diameter (mm)	51 ± 6	49 ± 7	0.64
Left ventricular ejection fraction (%)	60 ± 7	61 ± 5	0.92
Left atrial volume (ml/m^2)	32 ± 4	35 ± 7	0.41
Dobutamine stress echocardiography			
Mean dosing of dobutamine (γ/kg/min)	37 ± 3	38 ± 2	0.73
Mean duration of examination (min)	12 ± 2	11 ± 3	0.86
Use of atropine during examination	4252 (89%)	35 (88%)	0.96
Use of intravenous betablockers at the end of examination	4526 (95%)	39 (98%)	0.72

AF = atrial fibrillation; DSE = dobutamine stress echocardiography.
* Defined as high low-density lipoprotein cholesterol ≥4.14 mmol/L or patients treated with statin.

Table 2
Characteristics and outcome of DSE in 40 patients with atrial fibrillation

Heart rate according to dobutamine dose	
At baseline	67 ± 12
At 10γ/kg/min	70 ± 13
At 20γ/kg/min	77 ± 17
At 30γ/kg/min	109 ± 21
At 40γ/kg/min	147 ± 27
Systolic blood pressure according to dobutamine dose	
At baseline	149 ± 18
At 10γ/kg/min	158 ± 17
At 20γ/kg/min	159 ± 25
At 30γ/kg/min	167 ± 31
At 40γ/kg/min	170 ± 26
Diastolic blood pressure according to dobutamine dose	
At baseline	75 ± 11
At 10γ/kg/min	80 ± 10
At 20γ/kg/min	76 ± 11
At 30γ/kg/min	80 ± 14
At 40γ/kg/min	78 ± 13
Ischemia documented during DSE	13 (32.5%)
Inferior or lateral wall ischemia	9 (69%)
Septoapical or anterior wall ischemia	4 (31%)
Duration of AF	
<1 h	27 (67.5%)
<24 h	10 (25%)
Persistent (>7 d, <1 mo)	3 (7.5%)

AF = atrial fibrillation; DSE = dobutamine stress echocardiography.

DSE tests and consequently more side effects. Several complications or side effects of DSE may occur.[1] The most frequent complications are hypertension, hypotension, and induced arrhythmias. However, other less frequent complications may occur, such as myocardial infarction, coronary artery spasm, and death. Occurrence of AF is a potential side effect of DSE. Dobutamine acts directly through β-adrenergic receptor activation, leading to increase the risk of AF through enhancement of intracellular 3'-5'-cyclic adenosine monophosphate. In the present study, we found an incidence of 0.83% and very close to the aggregated incidence of AF in our meta-analysis, confirming that AF during DSE remains uncommon. The heterogeneity between the studies was very high but expected because of the different methods used, the analyzed populations also were different in terms of age, gender, history of AF, and high blood pressure. There was no statistical argument for a publication bias and therefore the estimate by the aggregated incidence must be pretty close to the real incidence.

We found that the main factor associated with AF occurrence during DSE is age. The incidence of AF significantly increased with age (0% in patients <60 years vs 4% in patients ≥80 years). Previous history of paroxysmal AF is also a predictive factor of AF during DSE. Physicians should be aware of these interactions between AF and elderly patients, and previous history of AF should discuss the utility of this specific examination and could eventually propose another ischemic test with less risk of AF.

The occurrence of AF during DSE is usually associated to a prompt and fast recovery of sinus rhythm in most of patients (<1 hour), with discontinuation of dobutamine infusion and intravenous β blockers. For the remaining patients with AF >1 hour (32.5%), an attempt to restore sinus rhythm with antiarrhythmic agents was performed and finally only 7.5% of our patients had AF >1 day. These remaining patients had persistent AF and we performed electrical cardioversion, allowing to restore sinus rhythm. Thus, at distance, with adequate and conventional management, no patient had persistent AF secondary to DSE.

The limits of our study are that only 40 patients presented with AF during 4,818 complete DSE. However, this population was in sinus rhythm and no patient was

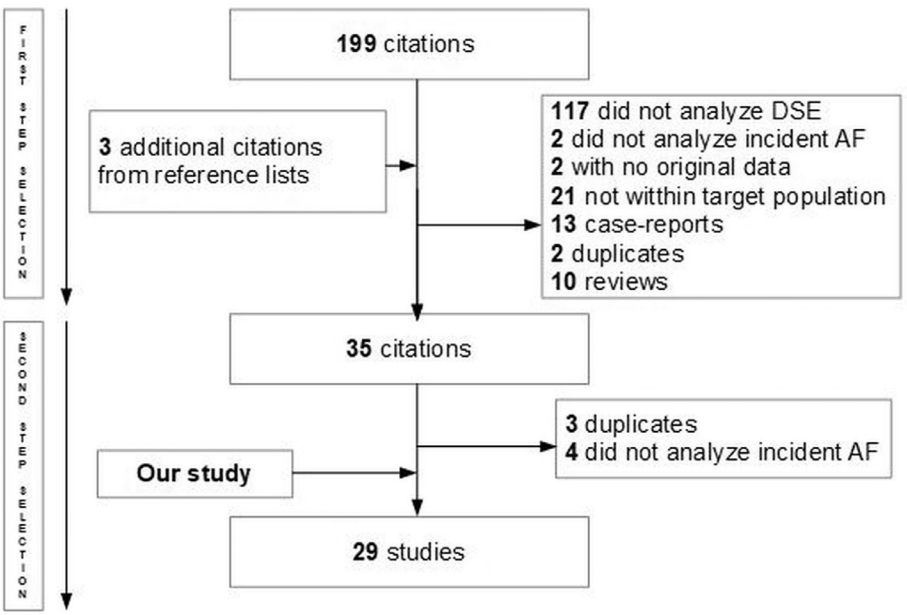

Figure 2. Search strategy and study selection flowchart for the meta-analysis. AF = atrial fibrillation; DSE = dobutamine stress echocardiography.

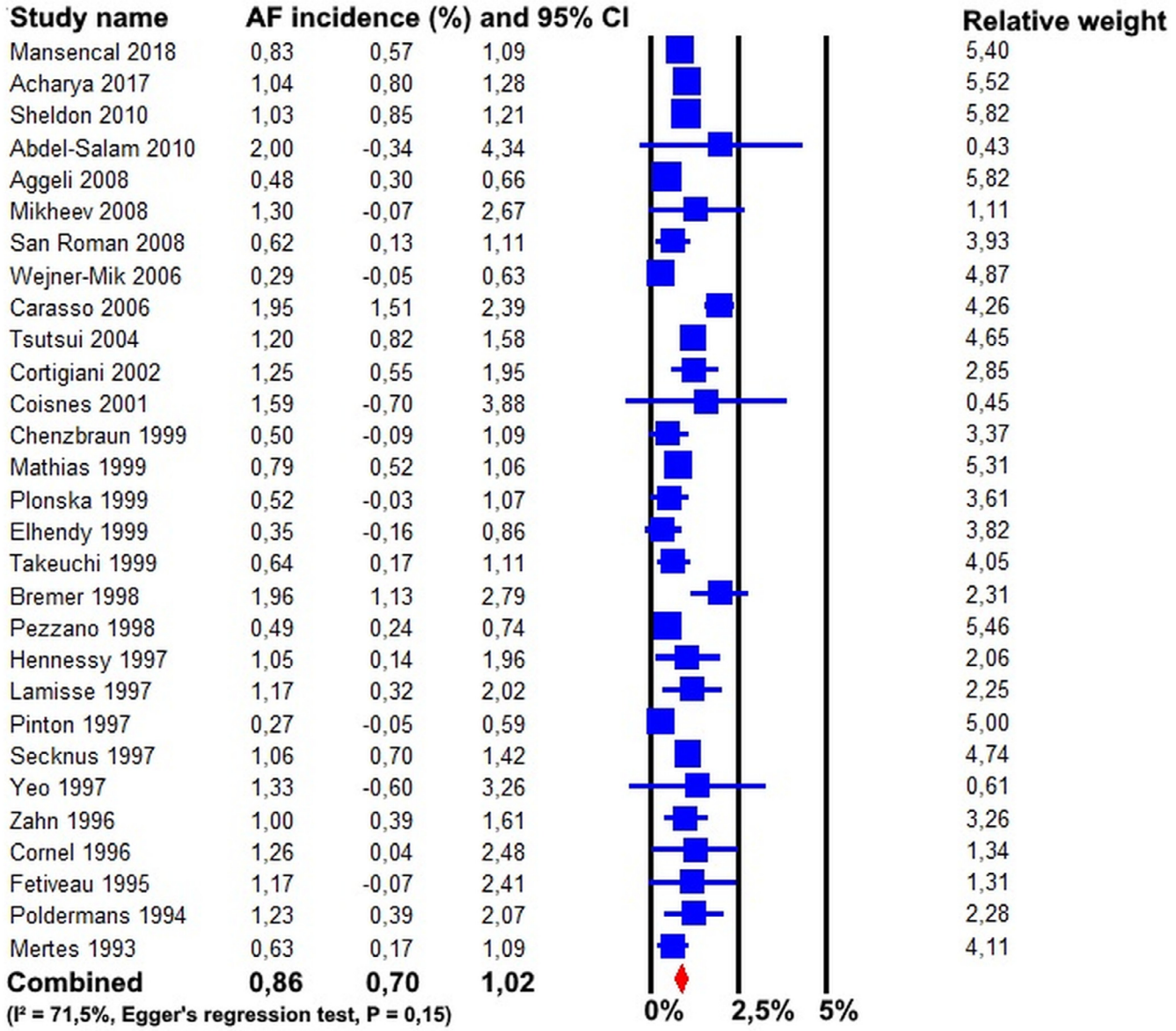

Figure 3. Incidence of atrial fibrillation during dobutamine stress echocardiography – meta-analysis forest plot. AF = atrial fibrillation; CI = confidence interval.

in AF at the beginning of DSE. Thus, we were able to clearly identify AF occurrence during DSE. This side effect of high level of dobutamine infusion remains uncommon and we demonstrate that elderly patients and patients with previous history of paroxysmal AF are at risk of AF during DSE.

Disclosures

The authors declare no conflict of interest.

Authors' Contribution

Each author has contributed significantly to the submitted manuscript.

Conception and design: NM, HM, OD.

Analysis and interpretation of data: NM, HM, MHM, SL, CS, OD.

Drafting of the manuscript: NM, HM.

Revising the manuscript critically for important intellectual content: NM, HM, MHM, SL, CS, OD.

Final approval of the manuscript submitted: NM, HM, MHM, SL, CS, OD.

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