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Drug-induced gingival overgrowth in cardiovascular patients

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Abstract

Drug-induced gingival overgrowth (DIGO) is a pathological growth of gingival tissue, primarily associated with calcium channel blockers and immunosuppressants. Consequently, it is mainly seen in cardiovascular and transplanted patients. Nifedipine remains the main calcium channel blocker related to the development of this unpleasant side-effect. As for immunosuppressants, cyclosporin is the leading causative agent, whereas other drugs from this drug-group, including tacrolimus, have better safety profiles. Accumulated collagen with inflammatory infiltrates is the histological hallmark of this condition. Several factors are involved in the pathogenesis and can increase the risk, such as male gender, younger age, pre-existing periodontal inflammation, and concomitant use of other DIGO-inducing medications. Patients with DIGO may experience severe discomfort, trouble with speech and mastication, pain, and teeth loss, aside from cosmetic implications. Furthermore, these patients also have an increased risk for cardiovascular diseases. The interdisciplinary approach and cooperation with dental care experts are necessary for patient management. Treatment includes discontinuing the drug and switching to one with a better profile, improving oral hygiene, and surgical removal of enlarged tissue. Recognizing the potential of commonly used medications to cause DIGO and its effect on patients' health is necessary for early detection and adequate management of this complication.

Key Words: Drug-induced gingival overgrowth; Calcium channel blocker; Nifedipine;

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Core Tip: Drug-induced gingival overgrowth is a side-effect of the drugs such as calcium channel blockers and immunosuppressants, commonly used in cardiovascular and transplanted patients. The condition is multifactorial and mainly depends on the potential of the used drug to cause gingival changes and the state of oral hygiene. Patients who develop drug-induced gingival overgrowth may experience severe discomfort and pain in addition to troubles with mastication, speech, and maintaining oral hygiene. Since it significantly reduces the quality of life, preventive and curative measures should be implemented as part of a care plan for patients at risk.

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INTRODUCTION

Drug-induced gingival overgrowth (DIGO) is a pathological growth of the gingiva characterized by the accumulation of connective tissue that primarily affects the anterior regions of the maxilla and mandibula^[1-3]. The first large DIGO case series was described in 1939, showing DIGO in 68 out of 119 patients treated by antiepileptic drug phenytoin^[4].

Since then, various medications showed to be associated with this side-effect^[5]. Although more than 20 different drugs are now known to cause DIGO, it most frequently results from calcium channel blockers (CCBs) and immunosuppressants^[6,7]. Antiepileptic drugs (*e.g.*, phenytoin, valproic acid, phenobarbital, vigabatrin) are recognized as a prominent group of medications causing DIGO, although in recent years, cases of DIGO resulting from these drugs were less frequently reported^[8].

Cardiovascular and transplanted patients are at particular risk due to the extensive use of CCBs alone or in combination with immunosuppressants^[9,10]. Significant variability among patients medicated with the same drugs is observed^[1], indicating the importance of additional risk factors involved in the pathogenesis. Genetic factors, male gender, bacterial plaque, and gingival inflammation are associated with increased DIGO risk^[11]. Aside from the cosmetic effect, which is the most apparent feature, patients who develop DIGO experience difficulty maintaining oral hygiene, pronunciation, and mastication. Simultaneously, the extensive disease can cause pain and loss of the teeth. As a result, quality of life is reduced significantly^[12,13]. Since this side-effect is not rare in a group of cardiovascular patients, oral health needs to be emphasized and included as part of a care plan for patients treated with the drugs mentioned above.

CLINICAL FEATURES AND PATHOGENESIS

DIGO usually starts as painless enlargement of interdental papillae and progresses towards facial and lingual margins, covering the teeth crowns. Fully developed, it forms generalized changes throughout the mouth, affecting the anterior gingiva the most^[5], although it can also occur as a localized lesion^[14]. A possible explanation for the predominance of lesions in anterior regions could be higher exposure of anterior gingiva to the irritation resulting from plaque^[15]. DIGO initially appears as pink, lobulated, and thickened gingival tissue without concomitant inflammation, with no tendency to bleed^[5,16]. In its course it becomes inflamed with red or bluish-red discolorations and frequent bleeding^[5]. As it progresses, it spreads both vertically and horizontally and affects mastication and speech^[14].

In advanced forms, enlarged gingiva may even interfere with the occlusion^[5]. Patients with DIGO have problems maintaining oral hygiene, which leads to susceptibility to infections and periodontal disease and may result in the loss of the teeth^[14]. A weakened immune system predisposes to more severe periodontal disease and puts patients on immunosuppressants at additional risk^[17]. Furthermore, periodontitis may potentially carry a risk for cardiovascular diseases, including myocardial infarction, peripheral artery disease, stroke, and heart failure. In theory, possible mechanisms behind this association could be dissemination of oral pathogens into the bloodstream and invasion of cardiovascular organs and tissues to induce inflammatory response on a local and systemic level^[18]. Additionally, periodontitis is associated with endothelial dysfunction, an important factor in atherosclerosis development^[18,19]. Aside from the functional impairment and cardiovascular risk, gingival changes also represent a significant esthetic problem for the patients^[14].

Etiopathology of DIGO is multifactorial and not fully understood^[2,20]. Genetic factors (cytochrome P450, HLA, and MDR1 gene polymorphisms) influence the interindividual difference in gingival response to DIGO-inducing drugs and could have a role in identifying patients at risk^[2,21,22]. The main histological finding in DIGO is the accumulation of collagen in the gingiva's extracellular matrix, along with the infiltration of inflammatory cells^[1]. Most of the DIGO-inducing drugs act as inhibitors of calcium ion influx^[23]. An inhibited influx of cations into fibroblasts causes a decrease in cation-dependent folic acid uptake. Folic acid is necessary for the proper function of matrix metalloproteinases, which activate collagenase. With no collagenase, there is no collagen breakdown, and it accumulates in connective tissue^[1]. Furthermore, studies demonstrated a drug-induced increase in glycosaminoglycans^[1] and collagen^[24] production along with the proliferation of gingival fibroblasts^[25]. These changes are mainly mediated by inflammatory cytokines that are a part of an inflammatory response to drugs^[23]. Inflammatory infiltrates found in the gingiva mainly consist of plasma cells^[26]. Periodontal status is a significant predictor of DIGO, as bacterial plaque induces inflammation. A significant correlation was found between bacterial plaque and a higher risk for DIGO in patients treated with CCBs or cyclosporin^[1,15,27]. In gingival tissue of patients with CCBs-associated DIGO, higher expression of androgen receptors accompanied with higher levels of type I collagen were detected, implying androgens' role in its pathogenesis^[28].

DIGO-INDUCING DRUGS

The first CCB-DIGO cases date from the early 80-ties, primarily associated with nifedipine^[29] and later with the use of other CCBs such as verapamil, diltiazem, amlodipine, and felodipine^[30]. Early studies demonstrated the highest prevalence in patients on nifedipine (6.3%), which remains to date the leading cause of DIGO in this drug group. Other CCBs, such as amlodipine (1.7%) and diltiazem (2.2%), have a lower potential to cause DIGO^[31]. The various prevalence of DIGO among different CCBs may be a consequence of pharmacokinetic characteristics, as nifedipine is more lipophilic, so it passes through cell membranes more quickly and has a half-life which allows it to reach peak levels in the plasma needed for the initiation of gingival changes^[31]. However, the prevalence of DIGO caused by CCBs varies in various studies, as for CCBs in general, it ranges between 10%-20%^[32]. It amounts from 15% to 85%^[33,34], for nifedipine, meaning that there are additional influencing factors. Male gender, drug dosage, smoking, periodontal status, previous myocardial infarction, and concomitant use of diuretics or antiepileptic drugs increase the risk of developing DIGO in CCBs users^[12,31,35]. However, drug dosage depends mostly on pharmacokinetics and pharmacodynamics and is thought to be an unreliable predictor^[36]. The majority of cases develop in the first six months of therapy, with the greatest occurrence in the first month, whereas the incidence decreases with long-term use^[12]. On the other hand, the study of Hatahira *et al*^[13] detected a median time to onset of 262 d, so long-term monitoring is still needed for patients who will develop the changes later. DIGO occurs less often using other antihypertensive drugs, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and beta-blockers^[3,37]. Therefore, in patients at risk for developing DIGO or those who already did, switching to CCBs with better safety profiles or other antihypertensive drugs is a treatment option.

Cyclosporin and tacrolimus, from the group of calcineurin inhibitors, are the leading cause of DIGO among immunosuppressive drugs^[38]. Cyclosporin was the primary immunosuppressive drug in heart-transplant patients since 1980^[39]. Many

heart transplant recipients (8.3%-67%) develop gingival enlargement, most of whom are treated with cyclosporin^[40]. The role of cyclosporin as an inducing drug in DIGO development is well known and recognized^[41]. Gingival changes in patients treated with cyclosporine show symmetry between mandibula and maxilla and within the jaw, while incisors and canines are affected the most^[15]. According to the research of Hatahira *et al*^[13], 70% of gingival overgrowth is attributed to cyclosporin. On the other hand, tacrolimus is another immunosuppressant often used as an alternative to cyclosporin in primary or rescue therapy^[27]. It is 100 times more potent and tends to cause some side-effects common to other immunosuppressants^[27,42]. However, it less often causes gingival overgrowth, and changes are less severe than those caused by cyclosporin^[27]. The prevalence of DIGO among tacrolimus treated patients is around 14%^[27,43]. DIGO can be detected as soon as 1-3 mo after immunosuppressive therapy initiation, and the plateau phase is reached at 9-12 mo^[44]. However, gingival changes resulting from tacrolimus use appear later compared to cyclosporin, as in various studies, no changes were observed before 90 d of treatment^[38,45]. Interestingly, immunosuppressants differ from other DIGO-inducing drugs since high inflammation levels and low fibrosis mostly mediate the changes^[46]. Some of the predisposing factors among cyclosporin users are male gender, gingivitis, bacterial plaque, and higher cyclosporine concentrations^[15,22]. Furthermore, younger patients are more frequently affected by DIGO^[15], and high rates have been reported among the group of pediatric heart-transplant patients treated with cyclosporin^[39,47,48]. Younger age was also a risk factor for more severe changes in patients on tacrolimus^[27]. Different therapeutic patterns and higher potential of fibroblasts to proliferate and produce collagen in a group of younger patients could be a possible explanation^[15,49]. Additionally, a higher risk for DIGO in tacrolimus users was observed in patients with the worse periodontal state, those previously medicated with cyclosporin^[27], and a with longer duration of tacrolimus therapy^[50]. The occurrence and severity of changes also depend on the concomitant use of other medications. Simultaneous use of cyclosporin and CCBs doubles the risk for DIGO, compared to using cyclosporin alone (51.9% *vs* 25%)^[22]. Furthermore, the use of CCBs in tacrolimus-treated patients results in higher severity of gingival changes^[27]. These findings indicate the synergistic effect of CCBs and calcineurin inhibitors. On the contrary, azathioprine has a protective effect in patients on cyclosporin or tacrolimus and lowers the risk for DIGO^[27,51]. Although tacrolimus provides a better safety profile regarding DIGO and could be a treatment option in patients with cyclosporin-induced gingival overgrowth, it is important to point out that in some cases, changes persist even after the switching of therapy, especially with concomitant use of CCBs^[27].

TREATMENT OPTIONS

Management of DIGO can be conservative or surgical, with the aim to provide a satisfactory cosmetic outcome and minimize discomfort and pain^[1]. Non-surgical methods are the treatment of choice, including proper oral hygiene and mechanical removal of dental plaque, together with the mandatory exclusion of the offending drug^[14]. Periodontal treatment reduces inflammation and prevents the need for surgical treatment in cyclosporin-treated patients^[52]. A rigorous oral hygiene regime has been recommended for patients with DIGO resulting from CCBs use^[32]. Since a worse periodontal state has been associated with a higher risk for DIGO^[15,27], preventive measures targeting oral health could be valuable. Reduction of drug dose or switching to that of a lower potential for side-effects should always be considered, if possible. In that case, complete improvement can be expected in 1-8 wk^[53] (Figure 1).

Stopping the use of CCBs or switching to non-CCB antihypertensives provides satisfactory results, but it is not always possible, as some patients may have problems controlling their hypertension^[54]. In an attempt to treat gingival overgrowth caused by cyclosporin, replacing this medication with tacrolimus or everolimus remains an option^[55,56] (Figure 2).

Flutamide, an androgen receptor antagonist, inhibits gingival cells' response to nifedipine and could be used to prevent or treat nifedipine associated DIGO^[28]. Non-surgical methods are often not sufficient if the drug cannot be withdrawn for other reasons^[54]. Persistent DIGO requires surgical treatment, which could either involve gingivectomy or periodontal flap^[57]. The use of carbon dioxide lasers is a solid choice that provides adequate postoperative hemostasis^[23]. Recurrence of DIGO after surgical treatment was reported in about 40% of the patients still treated with the offending drug^[58]. In conclusion, the prognosis of DIGO is good, as it can be successfully

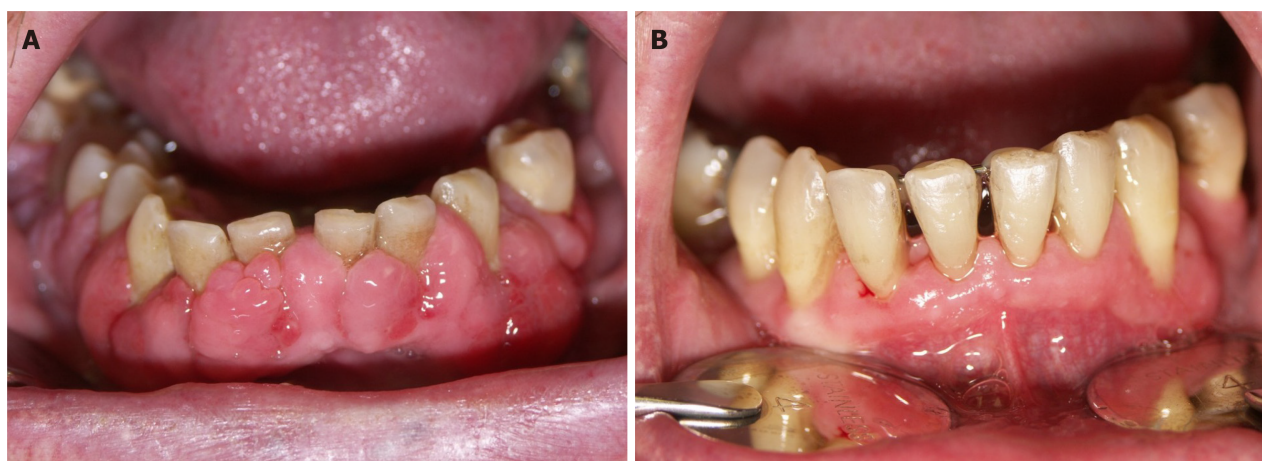


Figure 1 A complete response of a severe drug-induced gingival overgrowth case following seven weeks after amlodipine removal and six consecutive tooth scaling and cleaning treatments. A: Amlodipine induced gingival overgrowth successfully treated by vigorous weekly plaque control; B: Calculus removal during seven weeks following the drug withdrawal and substitution by angiotensin-converting enzyme inhibitor (courtesy of Prof. Vlaho Brailo).



Figure 2 An improvement in a heart transplant patient, whose medication included both cyclosporin and amlodipine, four weeks following professional teeth cleaning and switching to tacrolimus and alternative antihypertensive drug. A and B: Gingival overgrowth in a heart transplant patient receiving both cyclosporin and amlodipine; C and D: An improvement is observed following conservative periodontal treatment and four weeks of switching to tacrolimus and angiotensin-converting enzyme inhibitor.

managed and resolved with discontinuation of the inducing drugs^[1].

CONCLUSION

Since CCBs and immunosuppressants are widely used medications in patients with hypertension or after heart transplantation^[9,10], health professionals should be aware of gingival overgrowth as an unpleasant side-effect that can result from the use of these drugs^[23,55]. Although it might not be life-threatening, it poses a significant problem for the patients, not only because of the cosmetic effect but also due to the impairment of speech, eating, and maintaining oral hygiene^[12,13]. Furthermore, infections resulting from the lack of proper oral hygiene could enhance the risk for cardiovascular diseases^[59]. Recognizing the importance of DIGO and its effect on the patients' health is crucial for providing better health outcomes and satisfactory quality of life. If possible, treatment of choice should be changing of a drug and conservative periodontal treatment, whereas surgical treatment is reasonable only in resistant cases. Since it is multifactorial and reoccurs if the drug must be continued, efforts need to be made to find each patient's optimal treatment. An interdisciplinary approach and cooperation of medical and dental professionals are necessary to reach this goal.

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Challenges in managing ST elevation myocardial infarction during the COVID-19 pandemic

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) may contribute to delayed presentations of acute myocardial infarction. Delayed presentation with late reperfusion is often associated with an increased risk of mechanical complications and adverse outcomes. Inherent delays are possible as every patient who is acutely sick is being considered a potential case or a carrier of COVID-19. Also, standardized personal protective equipment precautions are established for all members of the team, regardless of pending COVID-19 testing which might further add to delays.

AIM

To compare performance measures and clinical outcomes of all patients who presented to our facility with ST elevation myocardial infarction (STEMI) during the COVID-19 pandemic to same time cohort from 2019.

METHODS

All patients who presented to our facility with STEMI during the pandemic were compared to a matched cohort during the same time period in 2019. STEMI with unknown time of symptom onset and inpatient STEMI patients were excluded. Primary outcome was major adverse cardiac events (MACE) in-hospital and up to

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14 d after STEMI, including death, myocardial infarction, cardiac arrest, or stroke. Significant differences among groups for continuous variables were tested through ANOVA, using SYSTAT, version 13. Chi-square tests of association were used to compare patient characteristics among groups using SYSTAT. Relative risk scores and associated tests for significance were calculated for discrete variables using MedCalc (MedCalc Software, Ostend, Belgium).

RESULTS

There was a significantly longer time interval from symptom onset to first medical contact (FMC) in the COVID-19 group ($P < 0.02$). Time to first electrocardiogram, door-to-balloon time, and FMC to balloon time were not significantly affected. The right coronary artery was the most common culprit for STEMI in both the cohorts. Over 60% of patients had one or more obstructive ($> 50\%$) lesion(s) remote from the culprit site. In-hospital and 14 d MACE were more prevalent in the COVID-19 group ($P < 0.01$ and $P < 0.001$).

CONCLUSION

This single academic center study in the United States suggests that there is a delay in patients with STEMI seeking medical attention during the COVID-19 pandemic which could be translating into worse clinical outcomes.

Key Words: COVID-19; ST elevation myocardial infarction; First medical contact to balloon; Major adverse cardiac events; Cardiac arrest; Death

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has affected every aspect of healthcare and has created multiple challenges in treatment of time sensitive conditions like ST elevation myocardial infarction (STEMI). We aimed to assess the behavior of presentation and outcomes of all the STEMI admissions at our facility between March 16, 2020 and August 31, 2020. We found a significantly delay from symptom onset to first medical contact in the COVID-19 group which likely resulted in significantly higher in-hospital major adverse cardiac events (MACE) and MACE at 14 d in this cohort.

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INTRODUCTION

The pandemic caused by the coronavirus disease 2019 (COVID-19) has caused a complete global shutdown and greatly affected every aspect of life, especially in the healthcare field. This has created multiple challenges in treatment of time sensitive and potentially lethal conditions like acute ST elevation myocardial infarction (STEMI). The consensus from the American College of Cardiology for management of STEMI recommends maintaining the standard of care with primary percutaneous coronary intervention, as long as there is adequate supply of resources, personal protective equipment availability, and cardiac catheterization staff. In absence of these resources, fibrinolysis should be first line treatment. Patients who are felt to be high risk for COVID-19 are recommended to be evaluated with additional cardiac studies, COVID-19 testing, and may require respiratory support, all of which may delay door-to-balloon times^[1].

Over 85% of the hospitals in the United States are considered community hospitals, yet the majority of studies are represented by university hospital systems^[2]. In April 2020, Bowling Green, Kentucky was named one of the top ten COVID-19 hotspots in the United States^[3]. Medical Center Health is a community hospital system in Bowling

Green, Kentucky with six hospitals covering ten counties in south central Kentucky, serving a population of more than 300000, and treating over 100 STEMI patients *per* year.

Given the limited observational studies guiding management of critical patients with STEMI during this pandemic, our study reports a United States community hospital's experience of management and outcomes of adult patients presenting with STEMI. One report from Hong Kong found large delays in patients seeking medical help and delays in evaluating patients with STEMI after hospital arrival but was limited by small sample size^[4]. Extensive literature review revealed no such reports from United States hospitals as of yet.

MATERIALS AND METHODS

We compared performance measures and outcomes of all patients who presented to our facility with STEMI between March 16, 2020 (when Kentucky began incorporating emergency infection protocols, mandating stay-at-home orders, and halting all elective procedures) and August 31, 2020. This study period was compared to a matched cohort during the same time period in 2019. Every patient in the 2020 group was considered a possible COVID-19 carrier, although none of our patients tested positive for COVID-19. STEMI with unknown time of symptom onset and inpatient STEMI patients were excluded. Primary outcome was major adverse cardiac events (MACE) in-hospital and up to 14 d after STEMI, including death, myocardial infarction, cardiac arrest, or stroke.

Significant differences among groups for continuous variables were tested through ANOVA, using SYSTAT, version 13. Chi-square tests of association were used to compare patient characteristics among groups using SYSTAT. Relative risk scores and associated tests for significance were calculated for discrete variables using MedCalc (MedCalc Software, Ostend, Belgium).

RESULTS

A total of 52 patients from 2019 and 48 patients from 2020 were included. Baseline demographics and comorbidities are presented in [Table 1](#). Age, gender, comorbidities, Killip score, and ejection fraction were well matched between the two groups. There was a significantly longer time interval from symptom onset to first medical contact (FMC) in the COVID-19 group ($P < 0.02$). Time to first electrocardiogram (ECG), door-to-balloon time, and FMC to balloon time were not significantly affected. The location of myocardial infarction and the state of culprit and non-culprit artery at the time of cardiac catheterization is detailed in [Table 1](#). The right coronary artery was the most common culprit for STEMI in both the cohorts. Over 60% of patients had one or more obstructive ($> 50\%$) lesion(s) remote from the culprit site. In-hospital and 14 d MACE were more prevalent in the COVID-19 group ($P < 0.01$ and $P < 0.001$).

DISCUSSION

Our study describes a United States acute care teaching hospital's experience in STEMI care utilizing emergency COVID-19 infection protocol. Contrary to reports out of major cities citing a decrease in STEMI patients, we noted a stable number of total STEMI cases compared with years prior^[5]. The time interval from symptom onset to FMC was significantly longer in the COVID-19 group, which was likely due to the general fear of contracting COVID-19 in the healthcare setting. Triage (time to first ECG) and performance measures (door-to-balloon time and FMC to balloon time) were not significantly different. We suspect that this was due to the long-standing efficient systems in place to triage and treat STEMI patients, as well as lower overall cardiac catheterization case volume allowing readily available personnel and staff for a faster throughput, despite the additional infection control protocol in triaging patients during this pandemic. MACE in-hospital and at 14 d was significantly higher in the COVID-19 group. In the 2019 group, in-hospital MACE was composed of 25% cardiac arrests (2 out of 8 patients), in contrast to the COVID-19 group, where in-hospital MACE was composed of 89% cardiac arrests (16 out of 18 patients). More cardiac arrests in the COVID-19 era could be due to late presentation to a medical facility,

Table 1 Characteristics and outcomes of patients presenting with ST elevation myocardial infarction during March-August 2019 (2019 Match Group) and March-August 2020 (coronavirus disease group)

	2019 Match		2020 COVID		P value
Patient characteristics					
Age (yr), mean ± SE	n = 52	60.23 ± 1.77	n = 48	62.73 ± 1.80	0.45
Females, n (%)	n = 52	43 (82.7)	n = 48	33 (68.8)	0.10
Comorbidities, mean ± SE	n = 47	2.67 ± 0.22	n = 44	2.74 ± 0.22	0.83
Hypertension, n (%)	n = 52	36 (69.2)	n = 48	35 (72.9)	
Hyperlipidemia, n (%)	n = 52	30 (57.7)	n = 48	28 (58.3)	
Diabetes, n (%)	n = 52	14 (26.9)	n = 48	18 (37.5)	
Coronary artery disease, n (%)	n = 52	21 (40.4)	n = 48	15 (31.3)	
Obesity, n (%)	n = 52	15 (28.8)	n = 48	19 (39.6)	
Smoking, n (%)	n = 47	20 (42.6)	n = 44	19 (43.2)	
Killip score (mean ± SE), n (%)	n = 52	1.10 ± 0.08	n = 48	1.27 ± 0.13	0.25
0		1 (1.9)		1 (2.1)	
1		49 (94.2)		42 (87.5)	
2		0 (0.0)		0 (0.00)	
3		0 (0.0)		1 (2.1)	
4		2 (3.9)		4 (8.3)	
Initial troponin level (ng/mL), mean ± SE	n = 43	2.22 ± 0.98	n = 45	2.38 ± 1.52	0.88
Peak troponin level (ng/mL), mean ± SE	n = 47	47.75 ± 7.07	n = 42	74.31 ± 14.25	0.20
Ejection fraction < 40, relative risk				1.99	
n (%)	n = 52	5 (9.6)	n = 47	9 (19.1)	0.17
Location and vessel involvement					
Location	n = 51		n = 48		
Anterior/anteroseptal, n (%)		11 (21.6)		16 (33.3)	
Anterolateral, n (%)		2 (3.9)		3 (6.2)	
Inferior/inferoposterior, n (%)		33 (64.7)		20 (41.7)	
Lateral, n (%)		5 (9.8)		9 (18.7)	
Culprit vessel, n (%)	n = 51		n = 48		0.28
LM		0		0	
RCA		31 (60.8)		22 (45.8)	
LAD		13 (25.5)		19 (39.6)	
LCx		7 (13.7)		7 (14.6)	
Non-culprit vessel stenosis ≥ 50%, n (%)	n = 32		n = 32		
RCA		7 (33.3)	n = 26	16 (61.5)	0.05
LAD		18 (47.4)	n = 29	17 (58.6)	0.36
LCx		16 (36.4)	n = 41	18 (43.9)	0.48
Patient outcomes					
Symptom onset to FMC (min), mean ± SE	n = 41	189.71 ± 70.18	n = 44	530.00 ± 143.53	0.02
Time to EKG (min), mean ± SE	n = 38	7.66 ± 2.31	n = 35	8.26 ± 2.54	0.81
Door to balloon (min), mean ± SE	n = 50	56.78 ± 5.65	n = 46	53.67 ± 3.43	0.73
FMC to balloon (min), mean ± SE	n = 50	89.14 ± 5.55	n = 42	90.02 ± 6.49	0.99

Hospital LOS (days), mean \pm SE	<i>n</i> = 52	4.40 \pm 0.88	<i>n</i> = 47	4.57 \pm 0.50	0.87
Cardiogenic shock, relative risk				1.81	
<i>n</i> (%)	<i>n</i> = 52	3 (5.8)	<i>n</i> = 48	5 (10.4)	0.23
In-hospital MACE (death, MI, cardiac arrest, stroke), relative risk				2.49	
<i>n</i> (%)	<i>n</i> = 52	8 (15.4)	<i>n</i> = 47	18 (38.3)	0.01
MACE < 14 d from admission, relative risk				3.03	
<i>n</i> (%)	<i>n</i> = 52	8 (15.4)	<i>n</i> = 45	21 (46.7)	< 0.001

SE: Standard error; LM: Left main; RCA: Right coronary artery; LAD: Left anterior descending; LCx: Left circumflex; FMC: First medical contact; EKG: Electrocardiogram; MACE: Major adverse cardiac events; LOS: Length of stay; COVID: Coronavirus disease.

which was reflected by the significantly higher symptom onset to FMC time in the COVID-19 group.

Although we noticed significantly delayed presentation of patients with STEMI and higher MACE during the COVID-19 pandemic, we found that STEMI clinical performance and quality measures were maintained at the system level despite following extra infection protocol measures.

Our study has inherent limitations of a retrospective study and moreover the small sample size limits generalization of our results. While we could expect the time from symptom onset to FMC to hold, we should be cautious in assuming that the degree of delay and clinical outcomes can be generalized to healthcare facilities globally.

CONCLUSION

This study provides insight into quality control and performance metrics of an acute medical condition like STEMI during the unprecedented pandemic that has largely affected every aspect of healthcare. At our academic institute, we found that there is a delay in STEMI patients seeking medical attention during the COVID-19 pandemic which could be translating into worse clinical outcomes. Our study allows for an early experience of how this pandemic could affect treatment of acute medical conditions like STEMI.

ARTICLE HIGHLIGHTS

Research background

Treatment of time sensitive medical conditions like ST elevation myocardial infarction (STEMI) could have been adversely affected during the coronavirus disease 2019 (COVID-19) pandemic. This could be due to fear of contracting COVID-19 in the hospital setting, along with healthcare challenges such as lack of personal protective equipment and shifting policies on rapid COVID-19 testing in these acutely sick patients. All of these factors could prolong symptom onset to first medical contact (FMC) and FMC to balloon times. Prolonged time to coronary reperfusion has been shown to be related to increased mechanical complications and worse outcomes.

Research motivation

Currently no data from an academic United States institute exist on STEMI performance measures such as time to electrocardiogram, FMC to balloon, etc. during the current pandemic. There is also lack of STEMI outcomes data during the pandemic which could have been adversely affected.

Research objectives

We evaluated STEMI performance benchmarks and clinical outcomes of all patients who presented to our facility during the COVID-19 pandemic. These were compared to the same time cohort from 2019. Knowing, whether these standards are preserved currently during the pandemic is critical as it allows us to further investigate the mechanistic aspect of it and offer solution.

Research methods

All patients who presented to our facility with STEMI during the pandemic were compared to a matched cohort from 2019. STEMI with unknown time of symptom onset and inpatient STEMI patients were excluded. Primary outcome was major adverse cardiac events (MACE) in-hospital and up to 14 d after STEMI, including death, myocardial infarction, cardiac arrest, or stroke. Significant differences among groups for continuous variables were tested through ANOVA, using SYSTAT, version 13. Chi-square tests of association were used to compare patient characteristics among groups using SYSTAT. Relative risk scores and associated tests for significance were calculated for discrete variables using MedCalc (MedCalc Software, Ostend, Belgium).

Research results

Symptom onset to FMC time interval was significantly longer in the COVID-19 group ($P < 0.02$) when compared to 2019 cohort. Time to first electrocardiogram, door-to-balloon time, and FMC to balloon time were not significantly affected. The right coronary artery was the most common culprit for STEMI in both the cohorts. Over 60% of patients had one or more obstructive ($> 50\%$) lesion(s) remote from the culprit site. In-hospital and 14 d MACE were more prevalent in the COVID-19 group ($P < 0.01$ and $P < 0.001$).

Research conclusions

This single academic center study conducted in the United States during the current pandemic reports longer time interval from symptom onset to first medical contact in patients presenting with STEMI. This is likely resulting in worse MACE outcomes when compared to the pre-COVID era as reflected from this report.

Research perspectives

Although a 'randomized control study' to assess the potential adverse impact on STEMI outcomes during the pandemic is not practical, our study provides observations from a teaching center during the 'natural experiment' conditions created by the current pandemic. Our findings suggest a need for data from bigger studies to confirm our study's pattern and outcomes.

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Dabigatran, rivaroxaban, and apixaban are superior to warfarin in Asian patients with non-valvular atrial fibrillation: An updated meta-analysis

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Abstract

BACKGROUND

Most of the randomized clinical trials that led to the wide use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation (AF) originated from western countries.

AIM

To systematically review and quantitatively synthesize the real-world data regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban compared to warfarin for stroke prevention in Asian patients with non-valvular AF.

METHODS

Medline, Cochrane, and ClinicalTrial.gov databases were reviewed. A random-effect model meta-analysis was used and I-square was utilized to assess the heterogeneity. The primary outcome was ischemic stroke. The secondary outcomes were all-cause mortality, major bleeding, intracranial hemorrhage, and

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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gastrointestinal bleeding.

RESULTS

Twelve studies from East Asia or Southeast Asia and 441450 patients were included. Dabigatran, rivaroxaban, and apixaban were associated with a significant reduction in the incidence of ischemic stroke [hazard ratio (HR) = 0.78, 95% confidence interval (CI): 0.65-0.94; HR = 0.79, 95%CI: 0.74-0.85, HR = 0.70, 95%CI: 0.62-0.78; respectively], all-cause mortality (HR = 0.68, 95%CI: 0.56-0.83; HR = 0.66, 95%CI: 0.52-0.84; HR = 0.66, 95%CI: 0.49-0.90; respectively), and major bleeding (HR = 0.61, 95%CI: 0.54-0.69; HR = 0.70, 95%CI: 0.54-0.90; HR = 0.58, 95%CI: 0.43-0.78; respectively) compared to warfarin.

CONCLUSION

Dabigatran, rivaroxaban, and apixaban appear to be superior to warfarin in both efficacy and safety in Asians with non-valvular AF.

Key Words: Novel oral anticoagulant; Direct oral anticoagulant; Atrial fibrillation; Asian population; Dabigatran; Rivaroxaban; Apixaban; Warfarin

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Core Tip: Dabigatran, rivaroxaban, apixaban have better efficacy (reduction in ischemic stroke and all-cause mortality) and are safer (reduction in major bleeding) than warfarin. Dabigatran is associated with a lower rate of intracranial hemorrhage than warfarin, while rivaroxaban and apixaban appear to have a trend towards reduced intracranial hemorrhage, without statistical significance. Dabigatran, rivaroxaban, and apixaban are associated with a lower rate of gastrointestinal bleeding.

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INTRODUCTION

Stroke is the second leading cause of death and a major cause of disability globally^[1,2]. It was estimated that more than 5.5 million people died secondary to stroke in 2016^[3]. One third of all ischemic strokes are attributed to atrial fibrillation (AF), which leads to cardioembolism of large cerebral arteries^[4]. As a consequence, AF-related strokes are more likely to be fatal or debilitating^[4]. AF is the most common sustained cardiac arrhythmia with an estimated global prevalence of 2.8% and an estimated life time risk of about 25%^[5]. The presence of AF is associated with a fivefold increase in stroke risk^[6]. AF and stroke are independently associated with dementia onset in this population^[7]. Therefore, anticoagulation therapy has been the mainstay of primary and secondary stroke prevention in patients with diagnosed AF for decades^[8,9]. Warfarin was the standard of care until 2009, when dabigatran, a non-vitamin K oral anticoagulant (NOAC) was found to be non-inferior to warfarin with regards to stroke prevention in patients with AF^[10]. Since then, three other NOACs have been approved, namely rivaroxaban, apixaban, and edoxaban, all of which have shown substantial clinical benefits in randomized clinical trials^[10-13]. The relative ease of prescribing and adhering to NOAC therapy has resulted in a more widespread use of NOACs as opposed to warfarin^[14]. However, most of the randomized clinical trials, which led to this substantial change in clinical practice, originated from western countries with underrepresentation of Asian population; yet a number of real-world studies have assessed the use of NOACs in Asians with AF. With this study we aimed to systematically review and quantitatively analyze the existing observational studies regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban compared

to warfarin for stroke prevention in Asians with non-valvular AF.

MATERIALS AND METHODS

The study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[15]. The study protocol was submitted for registration at the International Prospective Register for Systematic Reviews.

Literature search and study eligibility

Medline, Cochrane Library, and ClinicalTial.gov were systematically searched from their inception to April 27, 2020. Two independent investigators (Li WJ and Archontakis-Barakakis P) independently searched for eligible studies. In cases where there was a disagreement regarding the eligibility of a study, a third investigator (Kokkinidis DG) was involved in order consensus to be reached.

The search algorithm was (“novel oral anticoagulants” OR “direct oral anticoagulants” OR “non-vitamin K antagonist oral anticoagulants” OR NOAC OR DOAC OR dabigatran OR rivaroxaban OR apixaban OR warfarin OR coumadin OR “vitamin K antagonist”) AND (atrial fibrillation OR AF OR AFIB) AND (real-world OR “real world” OR observational OR cohort OR post-approval). The reference list of pertinent reviews and observational studies was also manually searched for further potentially eligible studies. Duplicate publications were removed at the end of the literature search.

The pre-specified inclusion criteria were: (1) Retrospective or prospective observational studies; (2) Studies where the majority or all study participants were of Asian race; (3) Studies comparing warfarin to one of the NOACs; and (4) Studies examining at least one of the following outcomes: Thromboembolic stroke, intracranial hemorrhage, any bleeding, major bleeding, gastrointestinal bleeding. We excluded randomized control trials and studies that presented comparisons between different NOACs. Studies on valvular AF (*i.e.*, diagnosis of mitral stenosis or mitral valve replacement or repair) were also excluded.

Data extraction and outcomes

Data extraction was performed based on a pre-defined data extraction form by two independent investigators (Li WJ and Kokkinidis DG) blinded to each other. Disagreements were resolved following discussion and final decision was reached by consensus and as needed with the addition of a third reviewer (Archontakis-Barakakis P). The primary outcome was ischemic stroke (as defined by the individual studies) occurring during study follow up period. The secondary outcomes were all-cause mortality, major bleeding (as defined by the included studies), intracranial hemorrhage, and gastrointestinal bleeding.

Risk of bias assessment

Two independent reviewers (Palaiodimos L and Tzelvels L) assessed the risk of bias of the included studies with the Risk of Bias in Non-Randomized Studies - of Interventions tool^[16]. Studies were assessed as having low, moderate, serious or critical risk of bias for the following domains: Confounding measurement and account, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and results reporting.

Statistical analysis

When potentially duplicated populations were encountered, studies were not analyzed together under the same comparison and outcome. The larger one of the two studies was the one that was prioritized. Hazard ratios (HRs) with the corresponding 95% confidence interval (CI) were used for evaluation of outcomes. A random effects model was used to account for heterogeneity among studies. Heterogeneity was assessed with the Higgins I-square (I^2) statistic. $I^2 > 75\%$ indicated significant heterogeneity. Forest plots were used to graphically display the effect size in each study and the pooled estimates. Funnel plots and the Egger's test were used for assessment of publication bias. A P value < 0.05 was considered significant. R 3.4 version (RStudio software, RStudio, Inc.) was used as statistical software.

RESULTS

Our literature search has yielded 127 potentially relevant records after duplicates were removed. After excluding studies for multiple reasons (Figure 1), twelve studies were included in our analysis. All of the studies were conducted in countries or regions located in East Asia or Southeast Asia with the majority of their study participants being Asians. Most of the studies were products of large databases/registries (9 out of 12). In ClinicalTrials.gov database, we only found DARING-AF trial (comparison of efficacy and safety among dabigatran, rivaroxaban, and apixaban in non-valvular AF) which attempted to evaluate the efficacy and safety of NOACs in Asian patients but no results were posted. The baseline study characteristics are presented in Table 1. The patient characteristics are presented in Table 2. The risk of bias assessment is presented in Figure 2.

Dabigatran vs warfarin

Dabigatran was associated with a significant reduction in the incidence of ischemic stroke (HR = 0.78, 95%CI: 0.65-0.94, Figure 3), all-cause mortality (HR = 0.68, 95%CI: 0.56-0.83, Figure 3), major bleeding (HR = 0.61, 95%CI: 0.54-0.69, Figure 3), intracranial hemorrhage (HR = 0.51, 95%CI: 0.42-0.62, Figure 3), and gastrointestinal bleeding (HR = 0.65, 95%CI: 0.46-0.94, Figure 3), compared to warfarin.

Rivaroxaban vs warfarin

Rivaroxaban was associated with a statistically significant lower rate of ischemic stroke (HR = 0.79, 95%CI: 0.74-0.85, Figure 4), all-cause mortality (HR = 0.66, 95%CI: 0.52-0.84, Figure 4), major bleeding (HR = 0.70, 95%CI: 0.54-0.90, Figure 4), and gastrointestinal bleeding (HR = 0.79, 95%CI: 0.69-0.90, Figure 4), compared with the warfarin group. Although there was a tendency towards reduction in the rate of intracranial hemorrhage (HR = 0.76, 95%CI: 0.52-1.11, Figure 4) in rivaroxaban group, the result was not statistically significant.

Apixaban vs warfarin

Apixaban was associated with a lower rate of ischemic stroke (HR = 0.70, 95%CI: 0.62-0.78, Figure 5), all-cause mortality (HR = 0.66, 95%CI: 0.49-0.90, Figure 5), major bleeding (HR = 0.58, 95%CI: 0.43-0.78, Figure 5), and gastrointestinal bleeding (HR = 0.39, 95%CI: 0.17-0.89, Figure 5). However, there was no difference in the intracranial hemorrhage, although a clear trend was noticed (HR = 0.64, 95%CI: 0.40-1.02, Figure 5) towards apixaban superiority.

DISCUSSION

This study was a systematic review and meta-analysis of observational studies comparing the efficacy and safety of NOACs to warfarin in Asians with non-valvular AF. To the best of our knowledge, this is the first real-world data meta-analysis on this topic that is focused on Asian patient population. Our findings can be summarized as following: (1) Dabigatran, rivaroxaban, and apixaban were associated with significantly lower incidence of ischemic stroke and all-cause mortality compared to warfarin; (2) NOACs were associated with significantly fewer major bleeding events and gastrointestinal bleeding events compared to warfarin; and (3) Dabigatran was associated with significantly fewer intracranial bleeding events compared to warfarin; no significant difference in intracranial bleeding between the other two studied NOACs and warfarin was found, but a trend favoring rivaroxaban and apixaban was noted.

Dabigatran is a direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin and has been used for stroke and systemic embolism prevention in non-valvular AF since 2010^[8]. The landmark trial that led to the approval and wide use of dabigatran, the randomized evaluation of long-term anticoagulation therapy (RE-LY) study, demonstrated that patients in the dabigatran arm (dose 150 mg twice daily) had significantly lower risk for stroke or systemic embolism [relative risk (RR) = 0.66, 95%CI: 0.53-0.82] and intracranial bleeding (RR = 0.40, 95%CI: 0.27-0.60) compared to warfarin arm in the two-year follow-up^[10]; these findings are consistent with the results of our meta-analysis. The RE-LY trial did not show a significant difference between dabigatran and warfarin in terms of all-cause mortality and major bleeding but revealed higher gastrointestinal bleeding event rates in the dabigatran arm^[10]. Real-world studies, which mainly included non-Asians, have confirmed that dabigatran has

Table 1 Baseline characteristics of included studies

Ref.	Design	Setting/data source	Country/region	Study period	Major eligibility criteria	Major exclusion criteria	OAC comparison groups	Outcomes of interest
Chan <i>et al</i> ^[25] , 2016	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2013	NVAF patients, age ≥ 30 years old	PE or DVT, joint replacement or valvular surgery within 6 mo before AF was diagnosed, ESRD, switcher from dabigatran to warfarin	Dabigatran <i>vs</i> warfarin	Ischemic stroke, intracranial hemorrhage, major GI bleeding, all-cause mortality
Yap <i>et al</i> ^[26] , 2016	Single-center, retrospective cohort study	Malaysia's National Heart Institute	Malaysia	January, 2009 to December, 2013	NVAF patients	Not mentioned	Dabigatran <i>vs</i> warfarin	Ischemic CVA, major bleeding
Cha <i>et al</i> ^[27] , 2017	Database, retrospective cohort study	Korean National Health Insurance Service database	Korea	January, 2014 to December, 2015	NVAF patients with CHA2DS2-VASc score ≥ 2 taking anticoagulants for primary prevention of stroke/systemic embolism	Thromboembolic event/TIA or ICH, patients received joint replacement, medications change between warfarin and NOACs	Dabigatran <i>vs</i> warfarin, rivaroxaban <i>vs</i> warfarin, apixaban <i>vs</i> warfarin	Ischemic stroke, intracranial hemorrhage, or all-cause mortality
Kohsaka <i>et al</i> ^[28] , 2017	Database, retrospective cohort study	275 acute care hospitals across Japan	Japan	March 1, 2011 to March 31, 2016	NVAF patients 18 yr or older without use of any OAC within 180 d before the index date	Valvular AF, post-operative AF, mechanical-valvular AF, rheumatic AF	Dabigatran <i>vs</i> warfarin, rivaroxaban <i>vs</i> warfarin, apixaban <i>vs</i> warfarin	Major bleeding
Chan <i>et al</i> ^[29] , 2018	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2016	NVAF patients ≥ 30 years old	More than 1 NOAC use during treatment course, diagnosis of valvular AF, VTE or joint replacement therapy, ESRD requiring renal replacement therapy within 6 mo before the index date	Dabigatran <i>vs</i> warfarin, rivaroxaban <i>vs</i> warfarin, apixaban <i>vs</i> warfarin	All-cause mortality, intracranial hemorrhage, GI bleeding, major bleeding
Huang <i>et al</i> ^[30] , 2018	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2015	NVAF patients ≥ 20 years old, at least 1 inpatient or 2 separate outpatient diagnoses of AF	Prosthetic heart valve or MV disease during the study period, pregnant, cancer, or chronic dialysis within 12 months prior to index date	Rivaroxaban <i>vs</i> warfarin	Ischemic stroke, intracranial hemorrhage, GI bleeding
Okumura <i>et al</i> ^[31] , 2018	Multi-center, prospective cohort study	63 institutions in the Tokyo area	Japan	September 1, 2013 to December 31, 2015	NVAF patients, age ≥ 20 years old, treatment with any anticoagulant drug for stroke prophylaxis	Not mentioned	Dabigatran <i>vs</i> warfarin, rivaroxaban <i>vs</i> warfarin, apixaban <i>vs</i> warfarin	Intracranial hemorrhage, major bleeding, all-cause mortality
Koretsune <i>et al</i> ^[32] , 2018	Database, retrospective cohort study	Hospital Information systems and administration database by Medical Data Vision	Japan	March 14, 2011 to June 30, 2016	NVAF patients, age ≥ 18 , new user of either dabigatran or warfarin	Dialysis, kidney transplant, atrial flutter, valvular AF, mechanical valve replacement, rheumatic AF or MV prolapse/regurgitation or stenosis; or DVT or PE < 6 months before the AF diagnosis	Dabigatran <i>vs</i> warfarin	Major bleeding, intracranial hemorrhage, GI bleeding
Chan <i>et al</i> ^[33] , 2019	Database, retrospective cohort study	National Health Insurance Research Database	Taiwan	June 1, 2012 to December 31, 2017	NVAF patients	More than one NOAC use, ESRD, DVT, PE, joint replacement therapy up to 6 mo prior to the index date.	Dabigatran <i>vs</i> warfarin, rivaroxaban <i>vs</i> warfarin, apixaban <i>vs</i> warfarin	Ischemic stroke, intracranial hemorrhage, major bleeding, major GI bleeding

Jeong <i>et al</i> ^[34] , 2019	Single-center, retrospective cohort study	Chonnam National University Hospital	Korea	January, 2014 to December, 2016	NVAF patients, CHA2DS2-VASc > 2	Valvular AF, or any OAC class change	Rivaroxaban <i>vs</i> warfarin	Ischemic stroke, major bleeding, GI bleeding, intracranial bleeding, all-cause mortality
Lee <i>et al</i> ^[35] , 2019	Database, retrospective cohort study	Korean Health Insurance Review Database	Korea	January, 2015 to December, 2017	NVAF patients naïve to OAC treatment	Not mentioned	Dabigatran <i>vs</i> warfarin, rivaroxaban <i>vs</i> warfarin, apixaban <i>vs</i> warfarin	Ischemic stroke, intracranial hemorrhage, GI bleeding, major bleeding
Cho <i>et al</i> ^[36] , 2019	Database, retrospective cohort study	Korean National Health Insurance Service	Korea	July 1, 2015 to December 31, 2016	NVAF patients with new prescription of anticoagulants, age ≥ 18	Less than 30 d of anticoagulants use, two or more types of anticoagulants user, CHA2DS2-VASc score < 2, prior PE or DVT, underwent joint replacement surgery, dialysis patients	Dabigatran <i>vs</i> warfarin, rivaroxaban <i>vs</i> warfarin, apixaban <i>vs</i> warfarin	All-cause mortality, major bleeding

NVAF: Nonvalvular atrial fibrillation; OAC: Oral anticoagulant; DVT: Deep venous thrombosis; PE: Pulmonary embolism; MV: Mitral valve; ESRD: End stage renal disease; GI: Gastrointestinal.

an overall better efficacy and safety profile compared to warfarin, however superiority of dabigatran in each of the individual outcomes was not consistent across studies^[17-19]. In contrast, our findings demonstrated that dabigatran was associated with 32% lower all-cause mortality, 39% lower risk for major bleeding, and 35% lower risk for gastrointestinal bleeding compared to warfarin. This meta-analysis focused on Asian population reveals consistent superiority of dabigatran compared to warfarin for all important outcomes.

Rivaroxaban acts by inhibiting activated factor Xa (FXa), a key molecule in the coagulation cascade^[8]. Rivaroxaban once daily oral direct FXa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in AF (ROCKET AF) trial was published in 2011 paving the way for approval of rivaroxaban for stroke prevention in patients with non-valvular AF^[11]. The rivaroxaban group was associated with significantly fewer stroke events compared to warfarin group (HR = 0.79, 95% CI: 0.66-0.96) which is in agreement with the findings of our meta-analysis but failed to demonstrate significant result in intention-to-treat population. No difference in major bleeding events between rivaroxaban and warfarin groups was demonstrated in ROCKET-AF (HR = 1.04, 95% CI: 0.90-1.20)^[11]. However, an increased risk of decrease in hemoglobin more than or equal to 2 g/dL in rivaroxaban group was seen. This is different from our study that found that Asian patients on rivaroxaban had 30% lower risk for major bleeding events occurrence compared to patients receiving warfarin. The findings from a large real-world study from Canada and the United States revealed no significant difference for stroke and bleeding outcomes between the rivaroxaban and warfarin groups^[20]. A propensity score matching analysis from Denmark demonstrated that patients on rivaroxaban had lower stroke rates but similar bleeding rates to patients on warfarin^[21]. Observational data from Coleman *et al*^[22] showed that rivaroxaban reduced stroke rates in patients with non-valvular AF compared to warfarin without any significant difference in bleeding rates. While

Table 2 Patient characteristics of included studies

Ref.	Patient Number (Api)	Patient Number (Riv)	Patient Number (Dab)	Patient Number (War)	Age (Api)	Age (Riv)	Age (Dab)	Age (War)	HAS-BLED (Api)	HAS-BLED (Riv)	HAS-BLED (Dab)	HAS-BLED (War)	CHA2DS2-VASc (Api)	CHA2DS2-VASc (Riv)	CHA2DS2-VASc (Dab)	CHA2DS2-VASc (War)
Chan <i>et al</i> ^[25] , 2016	N/A	N/A	9940	9913	N/A	N/A	75 ± 10	76 ± 10	N/A	N/A	2.57 ± 1.01	2.58 ± 1.06	N/A	N/A	4.13 ± 1.59	4.16 ± 1.75
Yap <i>et al</i> ^[26] , 2016	N/A	N/A	500	500	N/A	N/A	65.3 ± 11.3	66.8 ± 11.3	N/A	N/A	1.57 ± 0.96	1.67 ± 0.94	N/A	N/A	2.69 ± 1.54	3.40 ± 1.54
Cha <i>et al</i> ^[27] , 2017	2189	5681	3741	23222	70.3 ± 10.0	70.5 ± 9.9	69.3 ± 10.0	68.82 ± 11.1	N/A	N/A	N/A	N/A	3.57 ± 1.29	3.60 ± 1.32	3.51 ± 1.28	3.57 ± 1.31
Kohsaka <i>et al</i> ^[28] , 2017	5977	5090	6726	6726 (War-Dab matched); 5090 (War-Riv matched); 5977 (War-API matched)	77.4 ± 10.0	75.8 ± 10.0	73.1 ± 9.9	73.3 ± 10.5 (War-Dab matched); 76.2 ± 10.5 (War-Riv matched); 77.7 ± 10.0 (War-API matched)	N/A	N/A	N/A	N/A	3.5 ± 1.6	3.3 ± 1.6	3.0 ± 1.6	3.0 ± 1.6 (War-Dab matched); 3.4 ± 1.6 (War-Riv matched); 3.5 ± 1.5 (War-API matched)
Chan <i>et al</i> ^[29] , 2018	5843	27777	20079	19375	76 ± 10	76 ± 10	76 ± 10	76 ± 10	2.96 ± 1.12	2.96 ± 0.51	2.96 ± 0.59	2.97 ± 0.61	3.89 ± 1.56	3.89 ± 0.71	3.88 ± 0.82	3.89 ± 0.88
Huang <i>et al</i> ^[30] , 2018	N/A	9637	N/A	9637	N/A	75.2 ± 10.24	N/A	74.98 ± 10.6	N/A	2.21 ± 1.46	N/A	2.33 ± 1.49	N/A	4.02 ± 1.92	N/A	4.11 ± 2
Okumura <i>et al</i> ^[31] , 2018	428	761	456	1561	73.2 ± 10.1	71.5 ± 9.1	70.9 ± 9.5	72.2 ± 9.3	1.42 ± 0.81	1.32 ± 0.77	1.07 ± 0.71	1.61 ± 0.88	3.12 ± 1.47	2.87 ± 1.45	2.83 ± 1.46	3.08 ± 1.51
Koretsune <i>et al</i> ^[32] , 2018	N/A	N/A	4606	4606	N/A	N/A	74 ± 10	73 ± 11	N/A	N/A	2.1 ± 1.0	2.1 ± 1.1	N/A	N/A	3.3 ± 1.7	3.3 ± 1.7
Chan <i>et al</i> ^[33] , 2019	9952	33022	22371	19761	76 ± 10.5	75.3 ± 10.6	74.2 ± 10.4	70.6 ± 13.4	2.9 ± 1.1	2.9 ± 1.1	2.8 ± 1.1	2.6 ± 1.3	3.9 ± 1.6	3.8 ± 1.6	3.7 ± 1.5	3.2 ± 1.8
Jeong <i>et al</i> ^[34] , 2019	N/A	804	N/A	804	N/A	71.4 ± 10.5	N/A	70.4 ± 10.2	N/A	N/A	N/A	N/A	N/A	3.3 ± 1.8	N/A	3.4 ± 1.8
Lee <i>et al</i> ^[35] , 2019	22177	35965	17745	25420	72.7 ± 10.2	72.0 ± 9.9	70.8 ± 9.9	67.3 ± 12.6	2.75 ± 1.04	2.77 ± 1.02	2.67 ± 1.01	2.58 ± 1.14	3.76 ± 1.41	3.63 ± 1.40	3.55 ± 1.37	3.18 ± 1.61
Cho <i>et al</i> ^[36] , 2019	12502	21000	12593	10409	74.3 ± 8.9	73.8 ± 8.8	72.9 ± 8.9	70.8 ± 11	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	2.6 ± 1.0	3.7 ± 1.2	3.6 ± 1.2	3.5 ± 1.2	3.5 ± 1.2

HAS-BLED: Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; War: Warfarin; Dab: Dabigatran; Riv: Rivaroxaban; Api: Apixaban; N/A: Not applicable.

another study from the United States showed higher risk of gastrointestinal bleeding in the rivaroxaban group^[23], our study yielded favorable result pointing toward reduction of gastrointestinal bleeding of rivaroxaban in Asian patients. In summary,

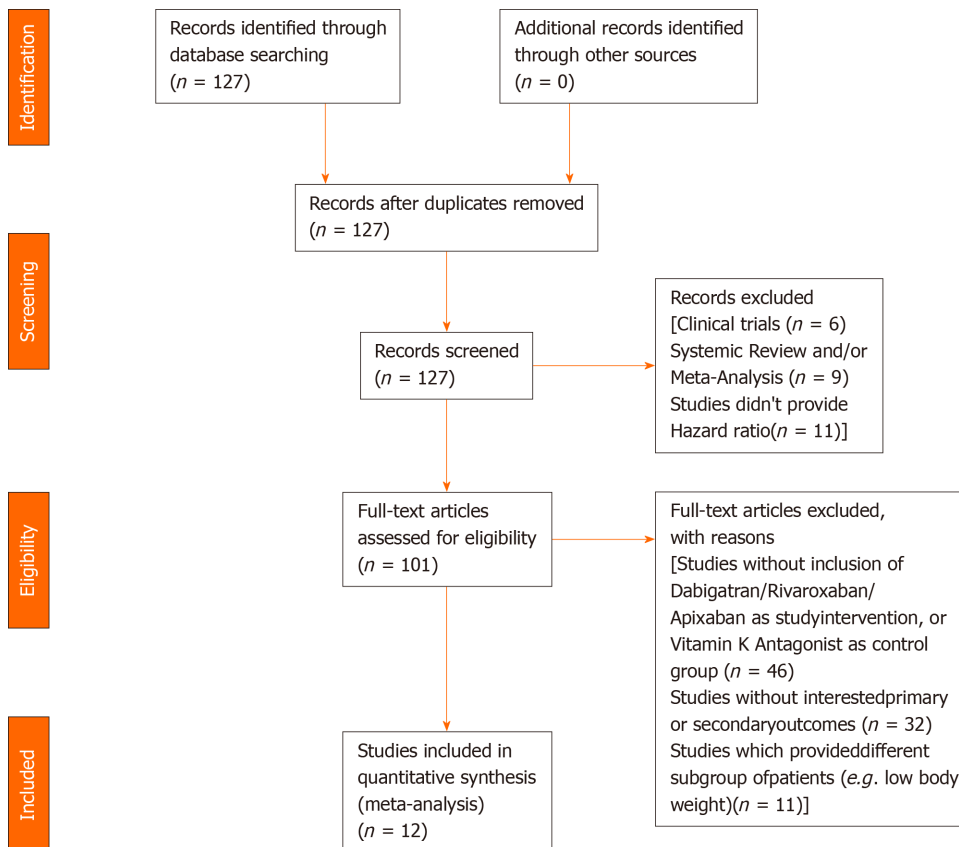


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

our meta-analysis showed that Asian patients with non-valvular AF on rivaroxaban had less stroke and bleeding rates compared to those on warfarin.

Apixaban is another FXa inhibitor approved for stroke prevention in patients with non-valvular AF^[8]. The publication of the results of the apixaban for reduction in stroke and other thromboembolic events in AF (ARISTOTLE) trial was the milestone after which apixaban became one of the most widely prescribed oral anticoagulants^[12]. In ARISTOTLE trial, patients with non-valvular AF were randomized in the apixaban and warfarin groups. The apixaban group had significantly lower stroke and major bleeding events rates, and lower mortality compared to warfarin group. Large real-world studies mainly in non-Asians confirmed the randomized trial data^[18,24]. With this meta-analysis, we demonstrate that apixaban is more efficacious and safer than warfarin in our Asian population, as well.

The main strengths of our study are its strict methodology, robust analysis, and the relatively large number of included studies and overall patient sample. Our study has a number of limitations, mainly associated with the observational nature of the included studies. The patient populations of the individual studies were heterogeneous despite the fact that the vast majority was of Asian race. We were unable to adjust for baseline comorbidities because we did not have access to patient level data. For some of the outcomes, the number of eligible studies was limited which decreases the certainty in our findings.

CONCLUSION

In conclusion, the present systematic review and meta-analysis revealed that dabigatran, rivaroxaban, and apixaban, appear to be superior to warfarin in terms of efficacy (stroke prevention, all-cause mortality) and safety outcomes (bleeding events) in Asians with non-valvular AF.

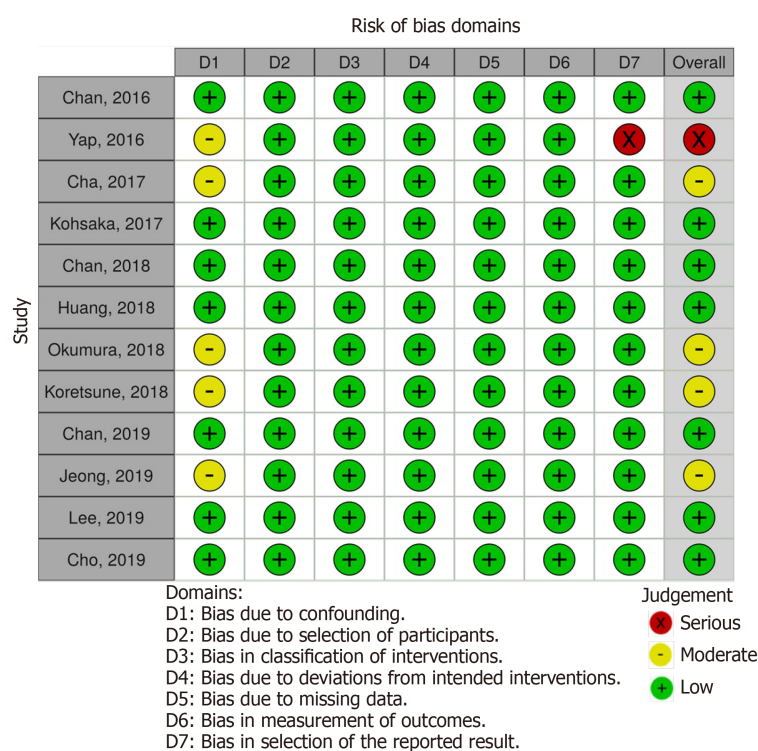
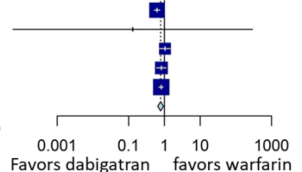


Figure 2 Risk of bias assessment of included studies using risk of bias in non-randomized studies-of interventions tool.

Ischemic stroke

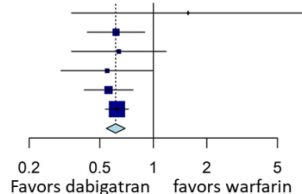
Source	HR (95% CI)
Chan et al. Stroke	0.62 [0.52; 0.73]
Yap et al.	0.13 [0.00; 291.41]
Cha et al.	1.03 [0.73; 1.46]
Chan et al. Chest	0.82 [0.61; 1.10]
Lee et al.	0.81 [0.71; 0.92]
Total	0.78 [0.65; 0.94]

Heterogeneity: $\chi^2_4 = 10.01$ ($P = 0.04$), $I^2 = 60\%$

**Major bleeding**

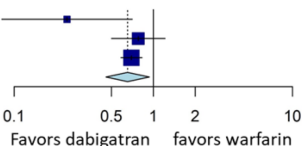
Source	HR (95% CI)
Yap et al.	1.57 [0.35; 7.11]
Kohsaka et al.	0.62 [0.43; 0.90]
Okumura et al.	0.64 [0.35; 1.18]
Koretsune et al.	0.55 [0.30; 1.00]
Chan et al. Chest	0.56 [0.41; 0.77]
Lee et al.	0.62 [0.54; 0.72]
Total	0.61 [0.54; 0.69]

Heterogeneity: $\chi^2_5 = 2.01$ ($P = 0.85$), $I^2 = 0\%$

**Gastrointestinal bleeding**

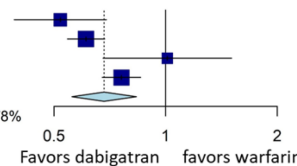
Source	HR (95% CI)
Koretsune et al.	0.24 [0.08; 0.70]
Chan et al. Chest	0.78 [0.50; 1.21]
Lee et al.	0.70 [0.59; 0.83]
Total	0.65 [0.46; 0.94]

Heterogeneity: $\chi^2_2 = 4.00$ ($P = 0.14$), $I^2 = 50\%$

**All-cause mortality**

Source	HR (95% CI)
Cha et al.	0.52 [0.39; 0.69]
Chan et al. JAHA	0.61 [0.54; 0.68]
Okumura et al.	1.01 [0.68; 1.51]
Cho et al.	0.76 [0.67; 0.86]
Total	0.68 [0.56; 0.83]

Heterogeneity: $\chi^2_3 = 13.90$ ($P = 0.003$), $I^2 = 78\%$

**Intracranial hemorrhage**

Source	HR (95% CI)
Cha et al.	0.44 [0.25; 0.77]
Okumura et al.	0.49 [0.15; 1.62]
Koretsune et al.	0.67 [0.47; 0.96]
Chan et al. Chest	0.48 [0.29; 0.80]
Lee et al. Stroke	0.45 [0.33; 0.60]
Total	0.51 [0.42; 0.62]

Heterogeneity: $\chi^2_4 = 3.33$ ($P = 0.50$), $I^2 = 0\%$

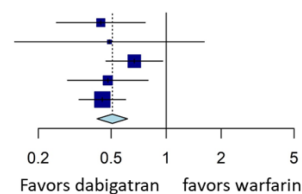


Figure 3 Forest plots comparing dabigatran with warfarin regarding hazard ratios of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

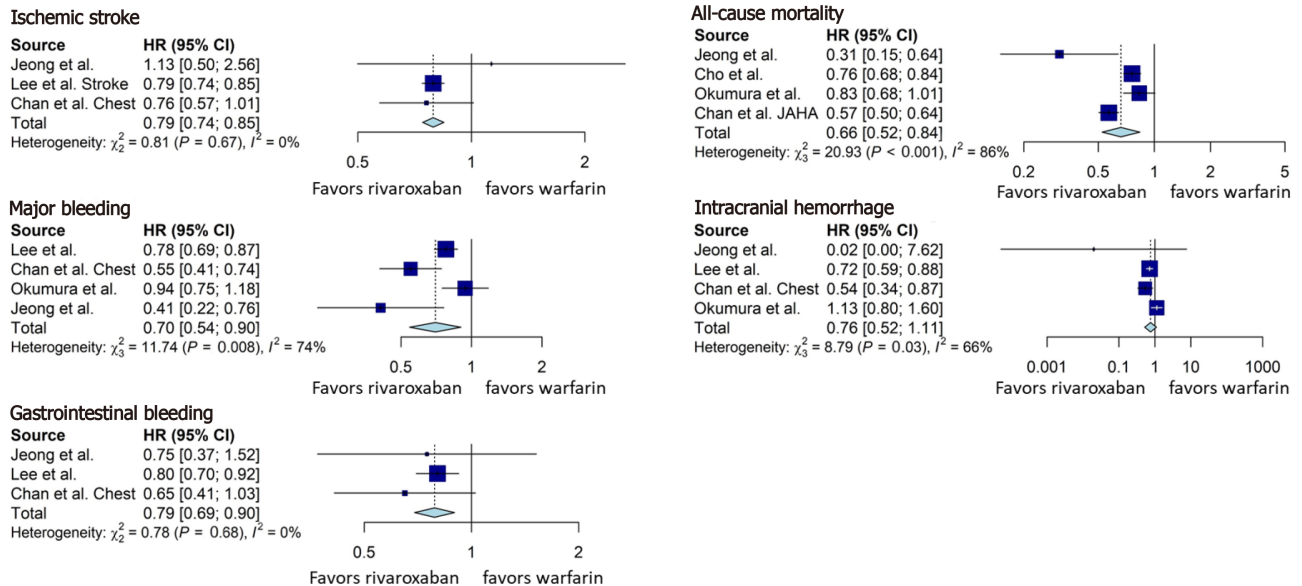


Figure 4 Forest plots comparing rivaroxaban with warfarin regarding hazard ratio of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

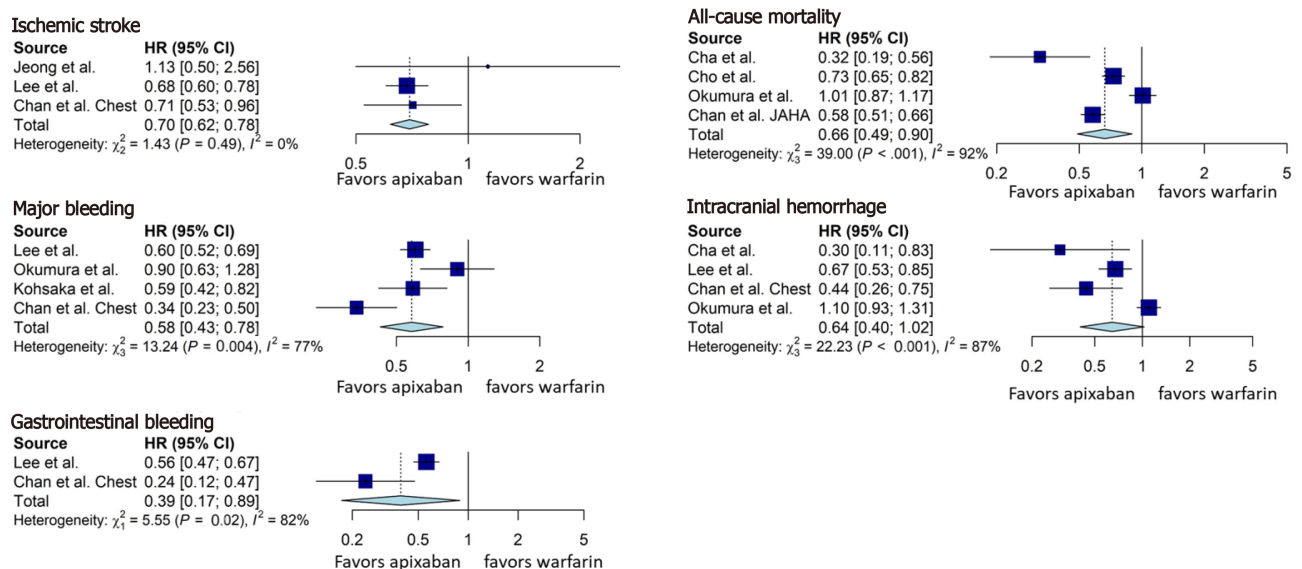


Figure 5 Forest plots comparing apixaban with warfarin regarding hazard ratio of ischemic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. HR: Hazard ratio; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Stroke is the second leading cause of mortality and disability worldwide with one-third of all ischemic stroke cases attributed to atrial fibrillation (AF).

Research motivation

Warfarin was the standard of care of stroke prevention in patients with nonvalvular AF but novel oral anticoagulants including dabigatran, rivaroxaban, and apixaban have demonstrated better efficacy and safety than warfarin in randomized clinical trials but they originated from Western countries where the Asian population was underrepresented.

Research objectives

We aimed to systematically review and quantitatively analyze the existing real-world observational studies regarding the efficacy and safety of dabigatran, rivaroxaban, and apixaban when they are compared with warfarin for stroke prevention in Asian patients with non-valvular AF.

Research methods

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Medline, Cochrane, and ClinicalTrial.gov databases were systematically searched. A random-effect model meta-analysis was used and I^2 was utilized to assess heterogeneity. Risk of bias assessment was performed for every study included.

Research results

Twelve studies were qualified for our study. Dabigatran, rivaroxaban, and apixaban were all associated with significantly reduced incidence of ischemic stroke, all-cause mortality, major bleeding, and gastrointestinal bleeding. Dabigatran was also found associated with a lower risk of intracranial hemorrhage.

Research conclusions

Dabigatran, rivaroxaban, and apixaban have better efficacy and safety profile than warfarin for stroke prevention in Asian patients with non-valvular AF.

Research perspectives

Future research which conducts a head-to-head comparison between different novel oral anticoagulants is necessary to determine the best option for Asian patients with non-valvular AF.

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Intracoronary brachytherapy for the treatment of recurrent drug-eluting stent in-stent restenosis: A systematic review and meta-analysis

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Abstract

BACKGROUND

We performed a meta-analysis on observational studies since randomized control trials are not available. We studied intracoronary brachytherapy (ICBT) and recurrent drug eluting stent in-stent restenosis (DES-ISR) to evaluate the procedural success, target lesion revascularization (TLR), incidence of myocardial infarction (MI) and all-cause mortality at 2 years follow-up.

AIM

To perform meta-analysis for patients undergoing ICBT for recurrent DES-ISR.

METHODS

We performed a systematic search of the PubMed/MEDLINE, Cochrane and DARE databases to identify relevant articles. Studies were excluded if intra-

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coronary brachytherapy was used as a treatment modality for initial ISR and studies with bare metal stents. We used a random-effect model with DerSimonian & Laird method to calculate summary estimates. Heterogeneity was assessed using I^2 statistics.

RESULTS

A total of 6 observational studies were included in the final analysis. Procedural angiographic success following intra-coronary brachytherapy was 99.8%. Incidence of MI at 1-year was 2% and 4.1% at 2-years, respectively. The incidence of TLR 14.1% at 1-year and 22.7% at 2-years, respectively. All-cause mortality at 1- and 2-year follow-up was 3% and 7.5%, respectively.

CONCLUSION

Given the observational nature of the studies included in the analysis, heterogeneity was significantly higher for outcomes. While there are no randomized controlled trials or definitive guidelines available for recurrent ISR associated with DES, this analysis suggests that brachytherapy might be the alternative approach for recurrent DES-ISR. Randomized controlled trials are required to confirm results from this study.

Key Words: Intracoronary brachytherapy; In-stent restenosis; Meta-analysis; Drug eluting stent; Systematic review; Brachytherapy

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Core Tip: Information is not readily available for the management of recurrent drug-eluting in-stent restenosis. There have been recent advances in the management of in-stent restenosis. While the use of a drug-eluting stent is still associated with in-stent restenosis, the use of intracoronary brachytherapy (ICBT) has resurged as one of the modalities in the management of such a complex problem. This analysis focuses on myocardial infarction and target lesion revascularization after the use of ICBT with a follow-up out to 2 years. Future studies with longer follow up are required to see if these benefits last longer.

Citation: Ilyas I, Kumar A, Adalja D, Shariff M, Desai R, Sattar Y, Vallabhajosyula S, Gullapalli N, Doshi R. Intracoronary brachytherapy for the treatment of recurrent drug-eluting stent in-stent restenosis: A systematic review and meta-analysis. *World J Cardiol* 2021; 13(4): 95-102

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INTRODUCTION

As percutaneous coronary intervention has evolved, drug eluting stents (DES) have become the mainstay of therapy given their lower rates of in-stent restenosis (ISR) and other complications in comparison to bare metal stents (BMS). ISR occurs due to vascular remodeling and neointimal hyperplasia which can lead to the reoccurrence of anginal symptoms^[1]. Various clinical factors, including stent type, other comorbidities and patient characteristics, contribute to the development of ISR. This makes it difficult to ascertain the exact incidence of ISR, however, with the advent of second-generation DES, ISR rates have decreased to approximately 8%^[2]. Patients with ISR will often undergo revascularization with repeat stenting per guideline, however, the recommendations are less clear for 2 or more previously implanted stents^[3,4]. There have been several modalities used for such lesion without clear benefits which includes but not limited to the use of laser atherectomy, intracoronary brachytherapy (ICBT), and drug coated balloons. The intracoronary irradiation may limit intravascular smooth muscle proliferation by promoting novel cell cycle regulation and eventually reduces the rate of ISR^[5]. There have been promising results with the use of ICBT for recurrent DES-ISR^[6-8]. Given the inherent limitations and logistic issues

associated with the use of ICBT, the use has been very limited to a few centres in the United States. We performed a meta-analysis on observational studies studying ICBT in the absence of randomized controlled trials and recurrent DES-ISR to evaluate the procedural success, target lesion revascularization (TLR), incidence of myocardial infarction (MI) and all-cause mortality at 1- and 2-years follow-up.

MATERIALS AND METHODS

Literature search

We performed a systematic search of the PubMed/MEDLINE, Cochrane and DARE databases to identify relevant articles. The literature search was performed from the inception of the database to January 2019. Since studies included in the present meta-analysis were approved by institutional ethical committee, no additional ethical clearance was required for the present meta-analysis. The reporting of the present systematic review and meta-analysis was in accordance with the PRISMA guidelines^[9].

Study selection

Each of the three databases were searched using the search terms "Intra-coronary Brachytherapy", "ICBT" OR "Intra-vascular Brachytherapy" "Intravascular Brachytherapy", "Drug eluting stent", "Drug-eluting stent", DES, "In-stent restenosis", ISR, to identify citations without language restrictions ([Supplementary Table 1](#)). Studies were not excluded based on sample size. The identified studies were imported into Mendeley reference manager and checked for duplicates. The reference list of the relevant articles searched were reviewed to identify additional articles.

The inclusion criteria were (1) observational studies of ICBT; and (2) for recurrent ISR of DES reporting either one of the following event rates: Procedural success; TLR, MI and all-cause mortality at 1 and/or 2 years follow up. Studies were excluded if intra-coronary brachytherapy was used as a treatment modality for initial ISR and studies with BMS ([Supplementary eMethod1](#)).

Data extraction

The screening of searched citations was performed at two levels. At the first level, two reviewers independently screened the title and abstracts of citations searched. At the second level, full text of citations identified by first level of screening was reviewed by two independent reviewers and included if the studies met the inclusion criteria. Any disparity during the review process was rectified by mutual consensus. Data extraction from included studies was performed by two reviewers independently. The following information was extracted from each included study, author's name, year, number of patients, mean age, percentage male, procedural angiographic success rates, TLR, MI and all-cause mortality rates at 1- and 2-year follow-up that were reported.

Statistical analysis

We used random effect model with DerSimonian & Laird method to calculate summary estimates. Heterogeneity was assessed using I^2 statistics. Estimates with $I^2 > 50\%$ was considered statistically heterogeneous. To allow for inclusion in the meta-analysis, a correction of 0.5 was added to the events of studies reporting event rate of 0%. All statistical analysis was carried out using R statistical software version 3.6.2.

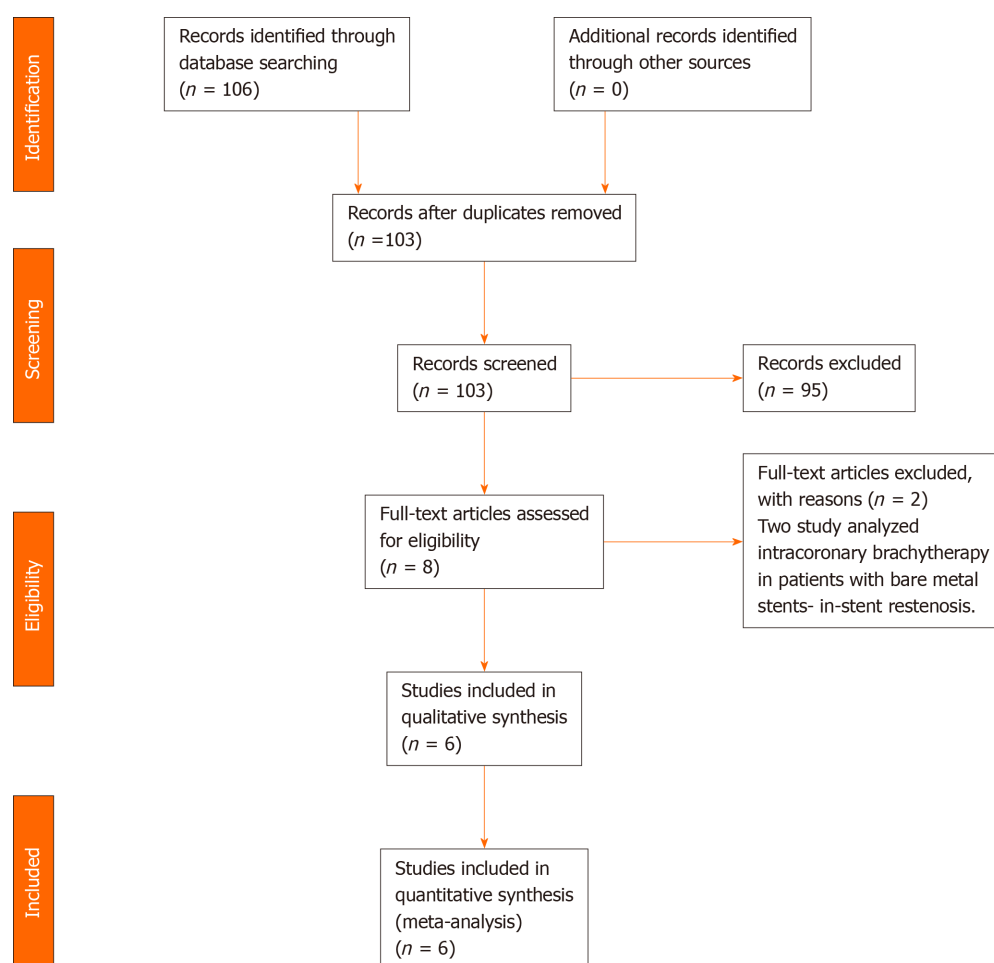
RESULTS

Summary of included studies

The database search identified a total of 26 citations. After applying the inclusion criteria, 6 studies were included in the final analysis^[6,7,10-12]. The PRISMA flow chart for inclusion of studies is provided in [Figure 1](#). All studies included in the present study analysed intra-coronary brachytherapy as treatment strategy in patients with recurrent ISR. The baseline characteristics of included studies are provided in [Table 1](#). The mean age of the patients ranges from 65-67 years in all studies. All studies included patients with ≥ 2 stents. However, information regarding previous stent DES or BMS was not clear in any of the manuscript. Males were significantly higher in all studies. All studies utilized Strontium/yttrium-90 beta radiation system at the depth of 2 mm in almost all studies. Mean radiation dose was 18-23 gray in all studies. All the studies performed brachytherapy on DES as the most recent layer of the stent. Although

Table 1 Baseline characteristics of included studies

Ref.	Year	Number of patients (n)	Mean age (years)	Percentage male (%)	DM (%)	Hypertension (%)	Type of brachytherapy	Mean/median radiation dose
1 Negi <i>et al</i> ^[6]	2016	186	65	62	47	95	Strontium/yttrium-90 beta radiation	23-25 Gray
2 Ohri <i>et al</i> ^[8]	2016	134	65	75	59	99	Strontium/yttrium-90 beta radiation	18.4 or 23 Gray
3 Mangione <i>et al</i> ^[7]	2017	101	66	67	53	98	Strontium/yttrium-90 beta radiation	18-23 Gray
4 Varghese <i>et al</i> ^[12]	2018	197	65	75	60	99	Strontium/yttrium-90 beta radiation	22 Gray
5 Megaly <i>et al</i> ^[10]	2021	116	66	69	-	-	Strontium/yttrium-90 beta radiation	22.6 Gray
6 Meraj <i>et al</i> ^[11]	2021	290	67	66	58	97	Strontium/yttrium-90 beta radiation	23 Gray

**Figure 1** PRISMA flow chart for the selection of studies included in the meta-analysis.

studies did not mention which stent was utilized prior to this brachytherapy procedure, all studies included patients after calendar year 2011, and hence, we can safely assume that all studies utilized second generation DES stent after the procedure.

Results of analysis of outcomes

Procedural angiographic success following intra-coronary brachytherapy was 99.8% (95%CI: 99.5%-100.1%) (Figure 2A). TLR at 1-year follow-up was 14.1% (95%CI: 9.2%-19%) (Figure 2B) and at 2-year follow-up was 22.7% (95%CI: 15.4%-30%) (Figure 3A) following intra-coronary brachytherapy. MI at 1- and 2-year follow-up were 2%

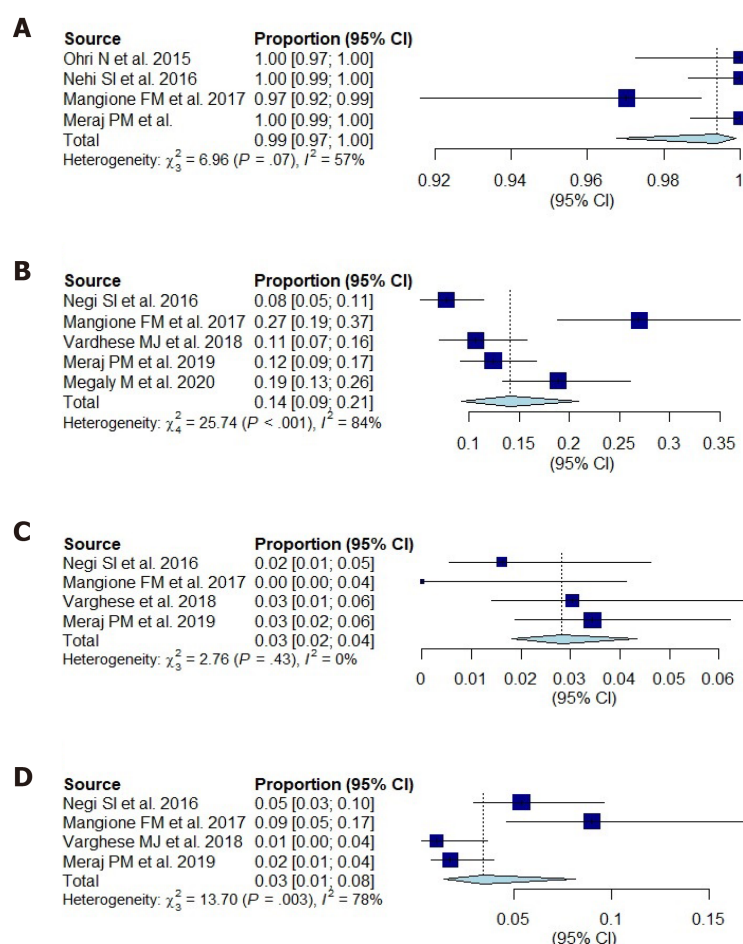


Figure 2 Forest plot for the clinical outcomes at 1 year. A: Demonstrated procedural success at 1 year; B: Demonstrates target lesion revascularization at 1 year; C: Demonstrates myocardial infarction at 1 year; D: Demonstrates all-cause mortality at 1 year.

(95% CI: 0.6%-3.3%) and 4.1% (95% CI: 2.5%-5.8%) (Figures 2C and 3B), respectively. All-cause mortality rates were 3% (95% CI: 0.8%-5.3%) and 7.5% (95% CI: 0.8%-14.3%) (Figures 2D and 3C), at 1- and 2-year follow-up, respectively.

DISCUSSION

In the absence of randomized controlled trials, we analysed observational studies demonstrating the favourable outcomes of brachytherapy following DES-ISR. The findings demonstrate high rates of procedural success, with TLR (14.1%) at 1-year and (22.7%) at 2-years, respectively. Incidence of MI at 1-year was 2% and 4.1% at 2-years, respectively. All-cause mortality at 1- and 2-year follow-up was 3% and 7.5%, respectively.

Brachytherapy targets adventitial fibrocytes that is the main source for neoproliferation of the tissue and causes apoptosis. Since there is overall suppression of neointimal growth by DES, DES-ISR tends to be focal, predominantly occurring at the stent edge^[13]. ICBT inhibits neointimal formation within the stent by delivering radioactive strontium-90 beta-radiation *via* a hydraulic mechanism. This may not be as effective at the stent edge which may account for the minority of patients requiring revascularization at the 1- and 2-year follow-up^[14]. Between the 1- and 2-year marks, there has been a remarkable increase in TLR, 14.1% *vs* 22.7%, leading to increases in MI and all-cause mortality at the two-year mark. This suggests that radiation may delay but does not eliminate the development of restenosis, leading to higher occurrences of MI and all-cause mortality at the two-year mark.

Management of resistant DES-ISR remains challenging and the best therapeutic option is still unclear. Some experts suggested that combined use of excimer laser coronary atherectomy may improve further clinical outcomes, however, the data is limited. Another option would be to use drug coated balloons; however, more data is

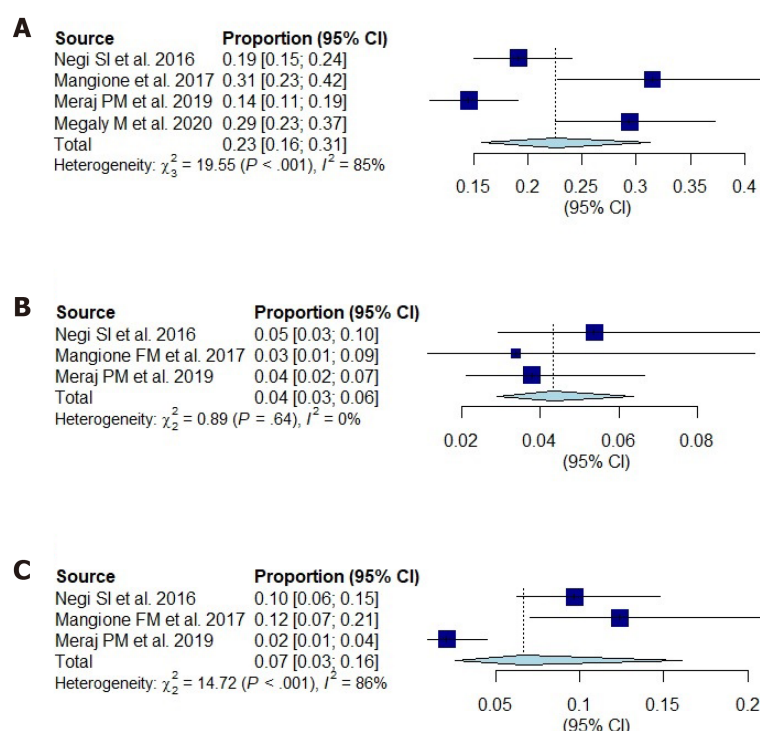


Figure 3 Forest plot for the clinical outcomes at 2 year. A: Demonstrates target lesion revascularization at 2 years; B: Demonstrates myocardial infarction at 2 years; C: Demonstrates all-cause mortality at 2 years.

needed to determine use of this technology. The use of rotational and orbital atherectomy is also on the rise. As technology is growing, use of third generation DES stent would be helpful in reducing ISR rates itself. Intravascular imaging is another growing field which might help determine pathophysiology in the development of DES-ISR. Since stent under-expansion is thought to be the main reason for DES-ISR, this can probably be prevented with the use of intravascular ultrasonography.

There are some limitations to our analysis. Three of the six studies included data for all the seven endpoints we analysed. This may have led to a smaller data pool. Additionally, we did not analyse the vessel diameter of the targeted lesion as this information was not readily available. Though, it should be a matter that, it should be investigated further given that ICBT has the greatest benefit in small vessel diameters^[15]. It has been previously established that patients with diabetes are more prone to develop ISR, yet it would be interesting to note the long-term procedural success in patients with co-morbid conditions following ICBT after DES-ISR^[16]. The number of stent varied in different studies. With each additional layer of stent, chances of ISR and other outcomes may increase. Finally, we do not have enough randomized control trials and we have to rely on observational studies to guide management in such patients. Overall, our analysis shows that ICBT is a feasible treatment option for the treatment of DES-ISR, is associated with high rates of procedural success and favourable efficacy at the one and two-year marks.

CONCLUSION

Currently, United States Food and Drug Administration has approved intracoronary radiation as an adjunctive treatment for ISR. While there are no definitive guidelines or recommendations for the management of recurrent ISR associated with DES, this analysis on brachytherapy with DES-ISR demonstrated that ICBT could be an effective alternate modality for such complex lesions. However, heterogeneity was significantly higher given the observational nature of the studies included in the analysis which must be kept in mind. Analysis shows that the initial intra-coronary brachytherapy procedure is highly successful. Brachytherapy is a practical treatment option for difficult to treat DES-ISR in patients with limited life expectancy or multiple comorbid states who may not be able to tolerate alternative treatment options, though, further analysis is needed on the long-term effects following ICBT in medically complex

patients.

ARTICLE HIGHLIGHTS

Research background

There is no established strategy for the management of in-stent restenosis which is common even when using drug eluting stents. There is a resurgence of the use of intracoronary brachytherapy (ICBT) for the treatment of drug eluting stent in-stent restenosis (DES-ISR).

Research motivation

The use of ICBT was common in the late 1990s era. Even with the use of second and third generation drug-eluting stents, in-stent restenosis have remained a significant problem. There have been multiple strategies used to manage this complex problem. Along with other strategies, ICBT has re-emerged as a potential solution.

Research objectives

The main objective was to perform a meta-analysis for patients undergoing ICBT for recurrent DES-ISR and analyze clinically important outcomes.

Research methods

We have reviewed PubMed/MEDLINE, Cochrane and DARE databases to identify studies that used ICBT for the management of in-stent restenosis. We used a random-effect model with DerSimonian & Laird method to calculate summary estimates. Heterogeneity was assessed using I^2 statistics.

Research results

We included 6 observational studies in this meta-analysis. Procedural angiographic success following intra-coronary brachytherapy was 99.8%. The incidence of myocardial infarction and all-cause mortality was within acceptable range at 2 years. Incidence of target lesion revascularization (14.1%) at 1-year and (22.7%) at 2-years, respectively.

Research conclusions

Brachytherapy should be one of the preferred approach for recurrent DES-ISR.

Research perspectives

There is an unmet need for randomized control trial comparing brachytherapy *vs* another drug eluting stent with a longer follow-up.

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Pregnancy associated spontaneous coronary artery dissection: A case report and review of literature

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Abstract

BACKGROUND

Pregnancy-associated spontaneous coronary artery dissection (PSCAD) is an important cause of chest pain and acute myocardial infarction in pregnant and postpartum women. Pregnancy is considered an isolated risk factor for spontaneous coronary artery dissection. The etiology, pathogenesis, and incidence of PSCAD are not known.

CASE SUMMARY

We present a case of a 33-year-old postpartum female who presented with sudden onset chest pain and was diagnosed with spontaneous coronary artery dissection and needed urgent catheterization revealing left anterior descending coronary artery dissection. She underwent emergent coronary artery bypass graft surgery with good post-operative recovery.

CONCLUSION

Most patients with PSCAD can be managed conservatively with medical management and have good outcomes. Patients with high-risk presentations benefit from the invasive approach. Coronary artery bypass graft may be required in select few patients based on angiography findings. Due to the risk of recurrent spontaneous coronary artery dissection, subsequent pregnancies are discouraged.

Key Words: Pregnancy; Spontaneous artery dissection; Acute coronary syndrome; Coronary artery bypass surgery; Percutaneous coronary intervention; Pregnancy; Dissection; Myocardial Infarction; Case report

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Core Tip: Chest pain during pregnancy and peripartum period need a comprehensive workup. Pregnancy is an isolated risk factor for spontaneous coronary artery dissection. Patients with pregnancy-associated spontaneous coronary artery dissection often have an elevated rate of high-risk presentations and may require invasive treatment or coronary artery bypass graft in few cases. Multidisciplinary care coordinated by a team of experts including interventional cardiologists, high-risk obstetricians, internists, cardiothoracic surgeons and Critical care specialists is essential in managing these patients in the peripartum period. Early diagnosis and timely intervention are lifesaving in cases involving Pregnancy associated spontaneous coronary artery dissection.

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INTRODUCTION

Chest pain is the second most common chief complaint for emergency room visits^[1]. Common causes of chest pain presenting to the emergency department are gastrointestinal causes, musculoskeletal causes, acute coronary syndrome, pericarditis and pulmonary embolism^[2,3]. Spontaneous coronary artery dissection (SCAD) leading to coronary ischemia is an uncommon cause of chest pain predominantly seen in women. SCAD is defined as an epicardial coronary artery dissection that is not associated with trauma, atherosclerosis or due to iatrogenic causes. Many cases of SCAD in women happen during the peripartum period, and this can be life-threatening events in young females^[4,5].

Pregnancy-associated spontaneous coronary artery dissection (PSCAD) is an important cause of chest pain and acute myocardial infarction in pregnant and postpartum women. It remains rare in incidence overall, with a handful of case reports and few small case series reported in the literature. Pregnancy and puerperium are considered major risk factors for SCAD because of hormonal changes. The etiology of PSCAD is not clearly understood. Patients with PSCAD often have high-risk presentations and have a complicated course. Failure to diagnose and treat PSCAD timely may lead to worse outcomes.

Here, we report a case of a 33-year-old postpartum female who had a complicated course following SCAD requiring coronary artery bypass graft (CABG) and had an uneventful recovery. To further improve understanding of PSCAD, we conducted an extensive literature search of Medline database for articles published until October 2020 using the following search terms "Myocardial infarction", "Pregnancy", "Spontaneous Coronary artery dissection" and "postpartum" in various combinations. We have reviewed the etiology, clinical presentation, diagnosis and treatment strategy of PSCAD in this literature review.

CASE PRESENTATION

Chief complaints

Sudden onset chest pain.

History of present illness

A previously healthy 33-year-old Hispanic female with no significant medical history presented to the emergency room with sudden onset of chest pain while she was cooking dinner. The pain originated in the neck area on the left side and mid-back region, radiated to the anterior chest, was 10/10 intensity, pressure-like, lasted for 15 min, and resolved with aspirin. Chest pain was associated with nausea, vomiting, diaphoresis, shortness of breath, and lightheadedness. A month ago, she delivered her

third child by normal vaginal delivery at 37 wk of gestation. The review of systems was otherwise unremarkable.

History of past illness

The patient had no prior history of coronary artery disease, aortic dissection, or pulmonary embolism.

Personal and family history

She had no significant social history including smoking, alcohol or recreational substance use. She denied use of any over the counter medicines and denied use of any hormonal contraceptives before. Her only medications included prenatal vitamins and iron supplements. There was no history of sudden cardiac death or early myocardial infarction in the family.

Physical examination

Her physical examination was unremarkable. Blood pressure was 104/56 mmHg and heart rate was 82 beats per minute. Equal intensity pulses were palpable in both arms. There were no cardiac murmurs, jugular venous distension, crackles on auscultatory lung areas, and pedal edema.

Laboratory examinations

Laboratory markers showed low hemoglobin of 11.6 g/dL (normal 12-15.5 g/dL), white blood cell count of 6×10^9 cells/L, creatinine of 0.6 mg/dL, ESR of 16 mm/h (normal range, 0-20 mm/h) and CRP of 2.7 mg/L (normal range, 0-10 mg/L). Serial Troponins (Troponin T) were abnormal and trended up from 0.01 ng/mL and peaked at 15.5 ng/mL.

Imaging examinations

Her initial electrocardiogram (EKG) was normal. Subsequent EKGs showed dynamic T wave inversions. Chest radiography did not reveal mediastinal widening or any fractures and dislocations. Transthoracic echocardiogram revealed 48% LVEF, moderate-sized apical wall motion abnormality with akinesia of the anteroseptal segments.

MULTIDISCIPLINARY EXPERT CONSULTATION

A multidisciplinary team including cardiology, cardiothoracic surgery, critical care medicine was consulted, and they recommended starting heparin drip, high intensity statin therapy, and giving loading doses of aspirin and clopidogrel.

FINAL DIAGNOSIS

She underwent Left heart catheterization, which revealed spontaneous circumferential dissection extending from Ostia to mid-left anterior descending (LAD) with distal 90% stenosis (Figures 1 and 2). Diagnosis was made on the basis of symptoms of chest pain, elevated troponins, EKG findings of T-wave inversions, echocardiogram findings of wall motion abnormalities with low ejection fraction 48% and more importantly angiographic findings of dissection.

TREATMENT

An intra-aortic balloon pump was placed, IV nitroglycerine and metoprolol were started. Conservative management was not an option for her owing to ongoing ischemia. Percutaneous coronary intervention (PCI) was considered extremely high risk for her due to extensive involvement of left anterior descending and CABG was favored. The patient underwent a CABG (free left internal mammary artery to left anterior descending and saphenous vein graft to diagonal 1 and 2) and was transferred to the cardiac intensive care unit with an intra-aortic balloon pump and dopamine infusion.

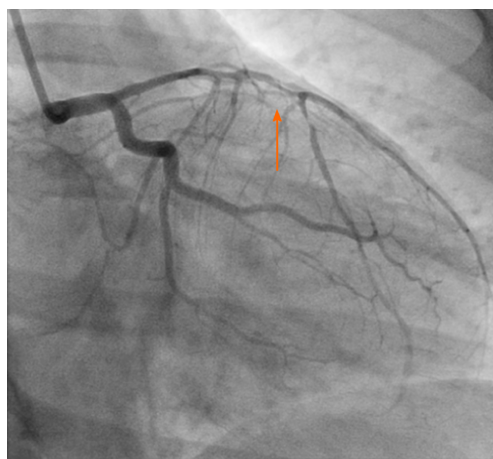


Figure 1 Right anterior oblique caudal view: Dissection extending from Ostium to mid LAD beyond the 2nd diagonal (arrow) with 90% stenosis (indicated by arrow).

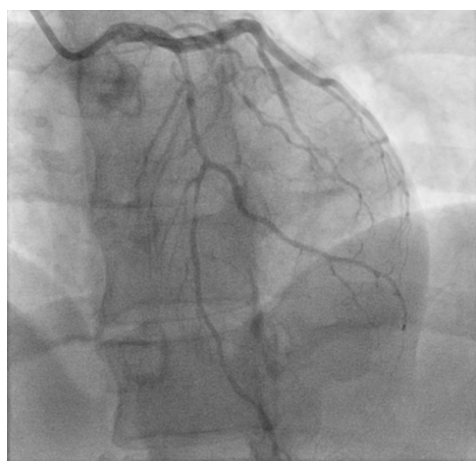


Figure 2 Right anterior oblique cranial view.

OUTCOME AND FOLLOW-UP

She had an uneventful post-operative recovery and was discharged home on Aspirin, Atorvastatin and Metoprolol with close clinic follow-up. Autoimmune workup including antinuclear antibody, anti-DS antibody, ANCA antibodies, anticardiolipin antibody, and diluted Russell Viper venom test was negative. Post-discharge clinic follow up in one and 3 mo were uneventful, and she was advised to continue medical management.

DISCUSSION

Pregnancy predisposes to an increased risk of myocardial infarction by three-fold compared to non-pregnant females in the reproductive age group^[4]. PSCAD comprises about 40% of pregnancy-associated myocardial infarction^[5]. PSCAD occurs in approximately 1.8 per 100000 pregnancies^[6].

Etiology and pathogenesis

Given the rarity of this condition, the etiology of PSCAD is largely unknown. Black race, hyperlipidemia, hypertension and migraine have been associated with the development of PSCAD^[6]. A meta-analysis of Genome wide studies has identified a common genetic locus PHACTR1-EDN1 implicated in the development of both fibromuscular dysplasia (FMD) and SCAD in affected patients^[7]. In a PSCAD cohort, Fibromuscular dysplasia was noted in greater than 40% of cases who underwent

imaging, revealing there may be a strong connection between FMD and PSCAD^[8,9]. Autopsy studies have suggested that SCAD may be an initial manifestation of FMD^[10,11]. Besides, several conditions that have been associated with SCAD including advanced maternal age, intense exercise, oral contraceptives, immunosuppressive therapy, menopause, sleep deprivation, cocaine abuse, connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome, polyarteritis nodosa and systemic lupus erythematosus may be related to PSCAD^[12-14]. PSCAD patients also have higher rates of prior infertility treatments.

Pregnancy and puerperium are considered major risk factors for SCAD because of hormonal changes^[15]. Changes in the levels of sex hormones leading to alterations in intima and media layers of arterial walls were proposed as a cause of PSCAD. Impaired collagen synthesis, myocyte proliferation and altered texture of mucopolysaccharides may weaken the layers of the coronary arterial wall. During pregnancy, a hyperdynamic circulatory state with increased shear stress on the labile coronary artery leads to coronary artery dissection^[16,17]. PSCAD is more commonly observed in the left anterior descending coronary artery and Left main artery^[15].

Clinical features and diagnosis

Clinical features are related to myocardial ischemia. Myocardial hypoperfusion is due to true luminal narrowing by false lumen compression caused by intramural hematoma. Clinical features depend on the anatomy of coronary involvement and the severity of involvement. The clinical spectrum varies from nonspecific chest pain, anginal equivalent, typical chest pain suggestive of unstable angina, cardiogenic shock leading to hemodynamic instability and sudden cardiac death.

Elevated cardiac biomarkers including troponins due to myocyte injury from ischemia may be seen. EKG may reflect changes corresponding to the involvement and extent of coronary territory and the severity of ischemia. Emergent coronary catheterization is essential for establishing a definitive diagnosis. Computed tomographic angiography coronary angiography may be useful in postpartum patients for diagnosing dissection and also during follow-up evaluation for resolution^[18]. Unlike SCAD, where mid and distal coronary artery occlusions are common, PSCAD patients are more likely to have proximal vessel (mainly left main and left anterior descending) or multivessel involvement^[19]. They present with worse LVEF compared with other SCAD patients. EKG could be normal but may also show a nonspecific ischemic pattern, T wave inversions, ST-segment depression, or ST-segment elevation.

Treatment and prognosis

The management strategy employed in PSCAD is similar to the management of SCAD with special attention to the stage of pregnancy and emphasis on fetal and maternal well-being. Both conservative treatment with medical therapy alone and percutaneous coronary intervention have been used in the management of PSCAD. There are no evidence-based guideline recommendations from professional societies yet as SCAD/PSCAD is rare. There have been no randomized controlled trials to guide management and so there is no established strategy to guide treatment. Emergent coronary angiography is the key in reviewing coronary arteries' anatomy and diagnosing SCAD and also to identify the severity and extent of the coronary artery dissection^[5]. Intravascular ultrasound and optical coherence tomography may help in differentiating true lumen *vs* false lumen. Conservative management strategy may be followed in stable PSCAD patients as in one case series of 750 patients, about 85% were managed conservatively and had good long-term outcomes^[20]. PCI may be considered in patients with proximal occlusions, cardiogenic shock, unstable rhythm and those who fail conservative treatment strategy^[15]. However, PCI in SCAD patients has higher rates of complications such as propagation of hematoma (noted in one-third of cases) and iatrogenic dissection^[21,22]. Difficulty in identifying true lumen limits the success rate with stenting in establishing the coronary flow. Coronary arteries may be more friable due to hormonal changes in pregnancy and PCI may further worsen dissection in PSCAD patients^[6].

CABG is reserved for patients with multivessel involvement or involvement of the left main coronary artery with ongoing ischemia/infarction^[5,23-25]. Thrombolytics should be avoided due to the risk of reexpansion of hematoma, causing expanding dissection leading to compression of the true lumen with worsening ischemia. Besides, thrombolytics fall in risk category C for use in pregnancy^[26,27]. Caution advised with medical management as certain drugs are contraindicated or not well studied during pregnancy. Antiplatelet agents such as aspirin, beta-blockers such as labetalol are safe during pregnancy. Available human data suggests the benefits of Clopidogrel use

outweigh risks during pregnancy and risk of fetal harm is not expected^[28,29]. Angiotensin converting enzyme inhibitors should be avoided during pregnancy.

Previously considered a universally fatal condition, survival outcomes of PSCAD have improved in the past decades due to advances in the management of acute myocardial infarction. Maternal mortality rates are still high and variable in PSCAD patients, with one recent study reporting in-hospital mortality rates of 4.5%^[30,31]. In another recent series of 750 patients containing 34 peripartum patients, PSCAD was associated with a higher rate of major adverse events (20.6%) such as Stroke/TIA, all-cause mortality, re-infection, Cardiogenic shock, congestive heart failure and cardiac arrest^[20]. Patients with PSCAD were found to have an elevated rate of high-risk presentations and also known to have low ejection fraction compared to females with acute myocardial infarction in the same age group. Recurrence after SCAD has been noted, although less common. There is a paucity of information on the risk of recurrent SCAD in patients with prior PSCAD. Due to the high risk of mortality and morbidity associated with PSCAD, pre-conceptional counseling is recommended for subsequent pregnancies. Coronary tortuosity, migraine headaches, fibromuscular dysplasia, hypertension are associated with recurrent PSCAD. Careful evaluation, low threshold for coronary angiography referral and early intervention may help reduce the rate of missed diagnosis in high-risk women during the peripartum period. Multidisciplinary care coordinated by a team of experts including interventional cardiologists, high-risk obstetricians, internists, cardiothoracic surgeons and critical care specialists is essential in managing these patients in the peripartum period^[32]. Targeted cardiac rehabilitation programs are preferred over strenuous high-intensity exercise programs in postpartum women^[33].

CONCLUSION

Strong suspicion and emergent catheterization should be considered when pregnant and postpartum women present with chest pain, electrocardiogram changes and elevated biomarkers. Emergent coronary catheterization is essential for establishing a definitive diagnosis. Although no standard guidelines exist, conservative therapy with medical management has been increasingly adopted in pregnancy-associated spontaneous coronary artery dissection with good outcomes. Selected cases with high-risk presentations like ours have definitive benefit from PCI and coronary artery bypass graft. Hence, PCI should be reserved only for high-risk patients and coronary artery bypass graft in extremely high-risk or PCI failure cases.

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Device closure of fistula from left lower pulmonary artery to left atrium using a vascular plug: A case report

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Abstract

BACKGROUND

Pulmonary artery-to-left atrial fistula is a variant of pulmonary arteriovenous fistula and is a developmental anomaly. Delayed presentation, cyanosis and effort intolerance are some of the important features. The diagnosis is confirmed by computed tomography or pulmonary artery angiography. Catheter-based closure is preferred to surgery.

CASE SUMMARY

Left pulmonary artery-to-left atrial fistula is rare. A 40-year-old male presented with effort intolerance, central cyanosis, and recurrent seizures. He had a large and highly tortuous left pulmonary artery-to-left atrial fistula associated with a large aneurysmal sac in the course. Catheter-based closure was performed using a vascular plug.

CONCLUSION

Left pulmonary artery-to-left atrial fistula is relatively uncommon compared to right pulmonary artery-to-left atrial fistula. Percutaneous closure by either a transeptal technique or guide wire insertion into the pulmonary vein through the pulmonary artery is preferred. The need for an arteriovenous loop depends on the tortuosity of the course of the fistula and the size of the device to be implanted because a larger device needs a larger sheath, necessitating firm guide wire support to facilitate negotiation of the stiff combination of the delivery sheath and dilator.

Key Words: Pulmonary artery; Left atrium; Fistula; Hemangioma; Catheter-based; Vascular plug; Case report

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Core Tip: Pulmonary artery-to-left atrial fistula is a variant of pulmonary arterio-venous fistula and is a developmental anomaly. Left pulmonary artery-to-left atrial fistula is rare. We report the case of a 40-year-old male who presented with effort intolerance, central cyanosis, and recurrent seizures. He had a large and highly tortuous left pulmonary artery-to-left atrial fistula associated with a large aneurysmal sac in the course. Catheter-based closure was performed using a vascular plug.

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INTRODUCTION

Left pulmonary artery-to-left atrial fistula is relatively rare compared to right pulmonary artery-to-left atrial fistula, as previously reported^[1]. The first case of pulmonary artery-to-left atrial fistula was reported in 1989 as an unusual cause of cyanosis in a newborn^[2]. A significant right-to-left shunt is clinically marked by effort intolerance, cyanosis, and polycythemia, as well as sometimes bleeding issues related to associated hemangioma^[3,4]. Pulmonary artery-to-left atrial fistula is a variant of pulmonary arteriovenous malformation. There is significant clinical suspicion of this condition when there is cyanosis without any obvious murmur in the precordium. Echocardiography shows a significant increase in pulmonary venous return to the left atrium, which is an additional clue and can be confirmed by cardiac catheterization or contrast-enhanced computed tomography. This case reports the relevant issues we encountered during the percutaneous device closure of a large and highly tortuous left pulmonary artery-to-left atrial fistula associated with a large aneurysmal sac in its course in an adult.

CASE PRESENTATION

Chief complaints

A 40-year-old male weighing 47 kg presented with effort intolerance, cyanosis, and clubbing.

History of present illness

The patient had a history of recurrent seizures and was on levetiracetam.

Personal and family history

The patient was a school teacher in profession and had no other significant comorbidities and no family history of congenital malformation.

Physical examination

The patient had central cyanosis and pandigital clubbing, and his room air oxygen saturation was 87%. There was no murmur on auscultation.

Laboratory examinations

The results of routine blood tests were normal. A genetic study could not be performed to exclude Osler-Weber-Rendu syndrome, which is also known as hereditary hemorrhagic telangiectasia^[4,5].

Imaging examinations

Chest X-ray examination showed a dilated and enlarged left perihilar region. There were multiple small hemangiomas in several organs, including the brain. Echo-

cardiography showed increased pulmonary venous return to the left atrium. Enhanced computed tomography of the pulmonary artery showed a left pulmonary artery-to-left atrial fistula with a highly tortuous course associated with an aneurysmal sac on its course from the pulmonary artery to the left atrium (Figure 1A, Video 1 and 2). The narrowest diameter of the fistula was 1 cm just proximal to the aneurysmal sac in its course. A significant branch of the pulmonary artery was supplying the posterior segment of the left lower lobe.

MULTIDISCIPLINARY EXPERT CONSULTATION

The cardiothoracic surgeon suggested device closure as the first option if possible.

FINAL DIAGNOSIS

The final diagnosis was a large left lower pulmonary artery-to-left atrial fistula associated with an aneurysmal sac.

TREATMENT

Because the patient had multiple hemangiomas and recurrent seizures related to cerebral hemangioma based on the magnetic resonance angiography findings of the brain, the cardiac team suggested that a catheter-based intervention would be preferred over surgery. Device closure was planned after informed consent was obtained. Under local anesthesia and after infective endocarditis prophylaxis, the patient was taken for percutaneous vascular plugging of the fistula. Right ventricular saturation was 78%, and left ventricular saturation was 92% in room air. The pulmonary artery systolic pressure was 37 mmHg. The angiograms of the frontal and lateral projections showed a significantly tortuous course of the left lower pulmonary artery-to-left atrial fistula with an aneurysmal sac of 6 cm in diameter in its course (Figure 1B). The landing zone diameter was 16 cm, and the landing zone length was 2 cm after the origin of the left lower lobe segmental pulmonary artery branch (Figure 2A). A Terumo wire 0.35 cm × 260 cm in size (Terumo, Tokyo, Japan) was passed across the fistula from the left pulmonary artery through the sac far into the upper right pulmonary vein (Figure 2B). The insertion of a compatible 8-Fr sheath with its dilator was up to the sac was attempted but was not possible because of the tortuous course. The dilator was exchanged with a 5-Fr multipurpose diagnostic catheter, and the sheath was placed just proximal to the neck of the fistula. A 20-mm Amplatzer vascular plug (St. Jude Medical, Minnesota, United States) was deployed without any residual shunting (Figure 3, Video 3 and 4). The arterial oxygen saturation immediately increased to 98%. The patient was discharged on aspirin on day three after the procedure. Oral anticoagulation was avoided in this case because of bleeding issues related to multiple hemangiomas.

OUTCOME AND FOLLOW-UP

At the 2-mo follow-up, contrast-enhanced computed tomography showed the position of the vascular plug *in situ*; there was no residual shunting, and the patient's room air saturation was 98%.

DISCUSSION

Incomplete degeneration of the partition between the arterial and venous plexus of the splanchnic pulmonary vascular bed leads to the formation of thin-walled sacs, resulting in the formation of pulmonary arteriovenous fistulas, which may sometimes be absorbed into the left atrium, causing the pulmonary artery to form a left atrial fistula. The potential right-to-left shunt and aneurysmal dilatation of the pathway can cause thromboembolism and death due to rupture of the sac. The incidence of this kind of fistula is higher in males. Routine frontal chest X-ray examination may show

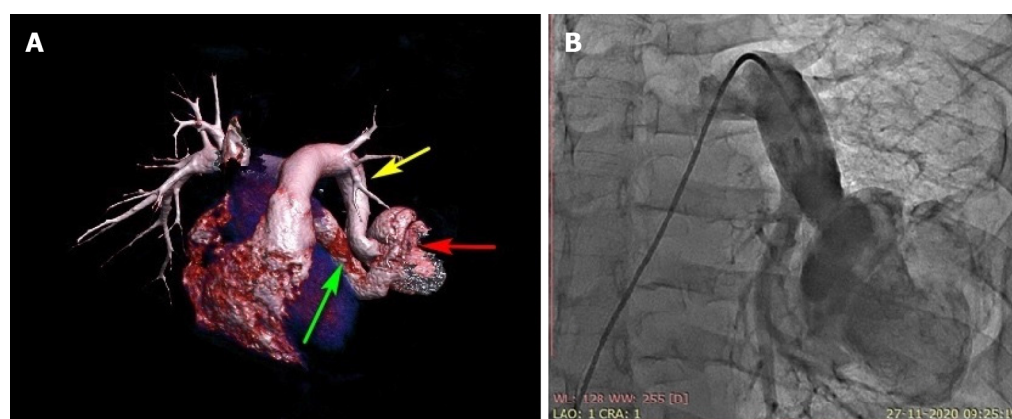


Figure 1 Three-dimensional computed tomography volume rendering and pulmonary artery angiogram. A: Contrast-enhanced computed tomography with three-dimensional reconstruction showing the left lower pulmonary artery-to-left atrial fistula with a highly tortuous course associated with an aneurysmal sac. Yellow arrow: left lower segmental artery; red arrow: aneurysmal sac; green arrow: last part of fistula connecting the left atrium; B: Anterior-posterior projection of pulmonary artery angiography using a 6-Fr pigtail catheter showing a highly tortuous large left pulmonary artery-to-left atrial fistula associated with a 6-cm aneurysmal sac. The right ventricular oxygen saturation was 79%, and the left ventricular saturation was 92% in room air without anesthesia.

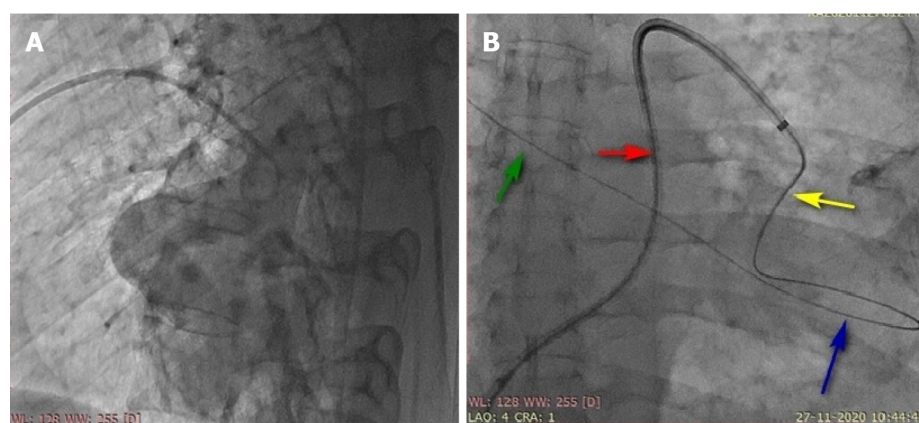


Figure 2 Lateral pulmonary angiography and the course of the guidewire. A: Lateral pulmonary artery angiography using a 6-Fr pigtail catheter showing a large left pulmonary artery-to-left atrial fistula associated with a large aneurysmal sac; B: A Terumo wire (0.35 cm × 260 cm) and 5-Fr multipurpose catheter helped to negotiate the highly tortuous course of the fistula to reach beyond the targeted landing zone and the site of guide wire placement in the upper right pulmonary vein via the aneurysmal sac for adequate support. Red arrow: 8-Fr sheath; yellow arrow: 5-Fr multipurpose catheter through the delivery sheath; blue arrow: guidewire in the aneurysmal sac; green arrow: upper right pulmonary vein.

perihilar vascular enlargement. Agitated saline contrast echocardiography could provide additional information when pulmonary artery-to-left atrial fistula is suspected. A close differential diagnosis of pulmonary arteriovenous fistula must always be kept in mind^[6]. Although invasive pulmonary angiography is diagnostic, it should be reserved for intervention because computed tomography angiography with three-dimensional reconstruction provides most of the information needed to decide whether a fistula can be percutaneously plugged by a device or requires surgical closure^[7]. Various plugging devices, such as vascular plugs, duct occluders and septal defect occluders, can be used depending upon the tortuosity of the course, availability of the landing zone and available delivery sheath and age of the patient. The plug can be deployed with or without an arteriovenous loop depending on the tortuosity of the course and size of the fistula^[8] with or without general anesthesia depending upon the age of the patient.

The proximal part of the left lower lobe pulmonary artery was tortuous before its division into anterior and posterior segmental branches. The sac was located along the course of the anterior segmental artery. We faced five major challenges to the catheter-based intervention in this case. (1) Negotiation of the 8-Fr sheath with its stiff default dilator was not possible; we overcame this difficulty by using a 5-Fr multipurpose catheter and substituting the dilator; (2) Although device implantation could have been performed using a transeptal approach with or without a loop, we could manage the antegrade approach from the pulmonary artery because of the good

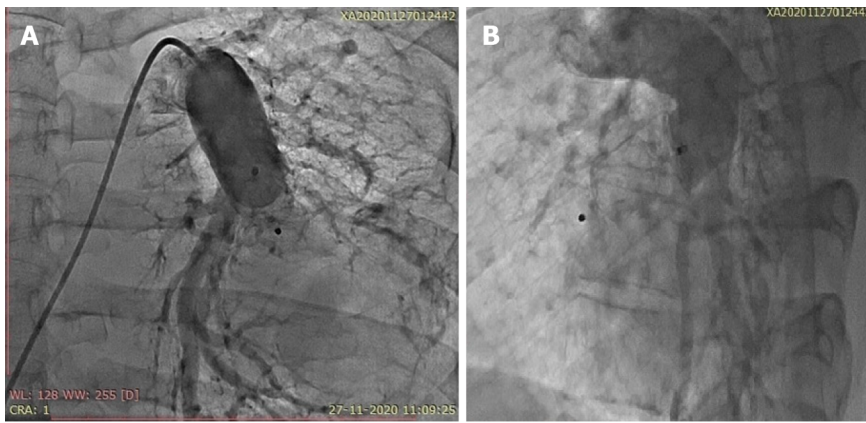


Figure 3 Pulmonary artery angiography after device deployment. Pulmonary artery angiography in the frontal projection and in the lateral projection showing perfect device positioning, no residual shunting and uncompromised blood flow in the left lower segmental artery. A: Frontal projection; B: Lateral projection.

support provided by the guidewire in the upper right pulmonary vein; (3) The proximal end of the landing zone in this case was quite close to the ostium of a large posterior segmental left pulmonary artery branch, but the procedure was completed well because of the proper device selection, which is evident in the provided video clips (Video 3 and 4); (4) The possibility of device embolization in this case was avoided by proper identification of the landing zone and its diameter and the selection of a well-fitting device; and (5) Although there was a fair indication for oral anticoagulation to prevent atheroembolism from the aneurysmal sac after device implantation, we only administered aspirin to avoid bleeding issues related to multiple hemangiomas. Percutaneous closure is preferred to open heart surgery whenever the anatomy allows, as in this case.

CONCLUSION

Left pulmonary artery-to-left atrial fistula is relatively uncommon compared to right pulmonary artery-to-left atrial fistula. Percutaneous closure by either a transeptal technique or guide wire insertion in the pulmonary vein through the pulmonary artery is preferred. The need for an arteriovenous loop depends upon the tortuosity of the course of the fistula and this size of the device to be implanted because a larger device needs a larger sheath, necessitating firm guide wire support to facilitate negotiation of the stiff combination of the delivery sheath and dilator.

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