Original Article

The Knowledge and Perception of Antiplatelet and Anticoagulant agents among Dentists in Northern Jordan

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Objectives: The aim of this study was to describe the attitude and perception toward antiplatelet/anticoagulant agents in patients with cardiovascular diseases among dentists in the northern district of Jordan and to compare the current practice of Jordanian dentists and the recently published guidelines regarding the management of patients taking antiplatelet/anticoagulant drugs before dental procedures. Materials and Methods: This is a cross-sectional study conducted on dentists and dental interns working at the dental clinics in northern Jordan, including dental clinics at Jordan University of Science and Technology (JUST) and the private sector. The total sample size comprised of 128 subjects (78 dentists from JUST and 50 private practitioners). The participants were interviewed using a preformed questionnaire to assess their knowledge and perceptions regarding the antiplatelets and the anticoagulant agents. Results: Approximately 61.5% of participants from JUST university and 20.0% of those in the private sector were aware of the use of clopidogrel (P < 0.0001). Although the overall awareness regarding other antiplatelets such as prasugrel was very low (8.6%), dentists from JUST (12.8%) showed a significantly higher level of awareness compared to the private practitioners (2.0%) (P = 0.049). More than 70% of the participants from JUST and only 46.0% of the private practitioners were aware of the consequences of interrupting treatment with clopidogrel in patients with coronary stents (P = 0.002). Almost both the participants from JUST (25.78%) and the private sector (24.22%) are consulting the cardiologists with similar frequencies before interrupting the treatment with the antiplatelet/anticoagulant agents. Participants who have clinical PhD qualifications are more aware of the recent clinical guidelines and the newest agents compared to others. Conclusions: The awareness regarding the newest antiplatelet/anticoagulant agents is poor among the dentists in northern Jordan. However, the majority (62.3%) of them realize the consequences of interrupting such treatments in patients with coronary stents. Unfortunately, only a quarter of the dentists are consulting the cardiologists before interrupting the treatment with the antiplatelet agents. Proper education, courses, and workshops should be performed to the dentists

KEYWORDS: Anticoagulants, antiplatelets, coronary stents, ischemic heart disease, dental procedures

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to improve their knowledge about this critical issue.

Introduction

oncommunicable diseases (NCDs) represent a modern epidemic. With changing lifestyles and an increase in life expectancy, there is a stable rise in the prevalence of NCDs all over the world. These diseases also include cardiovascular diseases (CVDs). Along with the rise in the prevalence of CVDs, the subject of cardiology has also evolved over the years. Interventional cardiology has represented several new treatment modalities such as the use of different kinds of stents. Because of that, many patients nowadays are using oral antiplatelet agents or anticoagulants for a longer duration than before.

The prolonged use of antiplatelet and anticoagulant drugs such as aspirin, clopidogrel, warfarin, or other new anticoagulant agents increases the risk of complications, mainly bleeding. [2] Although some studies showed that uninterrupted dual antiplatelet therapy with aspirin and clopidogrel is assumed to increase bleeding hazards after invasive dental procedures, other studies showed no significant increase. Although newer studies may state that there is increased bleeding risk, it is either not statistically significant or appropriately controlled with local homeostatic measures.[3-5] On the contrary, current data suggested that antiplatelet monotherapy with aspirin can be safely continued during oral surgical procedures like simple tooth extraction.^[5,6] However, it has to be noted that there is limited evidence on the intraoperative and postoperative pharmacodynamics of prasugrel and ticagrelor in dental and oral surgeries.^[7]

Therefore, the current recommendations state that there is no need to stop mono (aspirin) or dual antiplatelet therapies (aspirin and clopidogrel) before invasive dental procedures, if correct homeostatic measures are implemented, and unless the patient is about to undergo large maxillofacial surgeries, or unless the patient is at low thromboembolic risk.[5] Besides, based on the available evidence, the interruption of vitamin K antagonists (Warfarin) treatment before dental procedures is not recommended for interventions that are unlikely to cause bleeding, and for low and high bleeding risk procedures if the international normalized ratio (INR) < 3.5 during the 24 h before the planned intervention. If INR ≥ 3.5, dose adjustment is required, and the procedure should be delayed until the patient's INR has been reduced to less than 3.5.[7] However, current guidelines are lacking or insufficient for the new oral anticoagulant agents.^[7]

Similar studies have been conducted before in Turkey and Saudi Arabia which showed a wide range of knowledge related to the management of patients taking antiplatelet/anticoagulant agents before dental procedures and the consequences of interrupting antiplatelet agents. [8,9] However, there are variable practices among dentists, whereas some would prefer to discontinue the antiplatelets or the anticoagulant agents before the procedure; others will not take the risk of thrombotic complications upon discontinuing these drugs. [10]

Therefore, our study aimed to evaluate the attitudes and perceptions of dentists in the northern part of Jordan concerning the antiplatelets and the anticoagulant agents, especially the newest ones, in patients with CVDs. As well, we aimed to compare the current practice of Jordanian dentists and the recently published guidelines regarding the management of patients taking antiplatelet/anticoagulant drugs before dental procedures.

MATERIALS AND METHODS

This is a cross-sectional study conducted among dentists and dental interns. A convenient sample size of 128 (including all the dentists who were willing to participate) was adopted for the current study. The study participants included dentists and dental interns working at the dental clinics in Jordan University of Science and Technology (JUST), and private dentists in the northern part of Jordan. The study samples were collected over one month. Approvals from our local institutional review board (IRB) at King Abdullah University Hospital (KAUH) was ensured before commencing the project.

The data was collected with a preformed and validated questionnaire. The questionnaire was taken from a previous trial performed in Turkey^[8] with some modification which included questions for evaluation of knowledge and perception of dentists and interns regarding antiplatelet and anticoagulant agents. Faceto-face interviews with the study participants were conducted after obtaining consent from them. It was ensured that each participant was interviewed for at least 20 min. The questionnaire was kept anonymous. The data were entered in MS Excel file and analyzed using Statistical Package for the Social Sciences (SPSS) software program, version 20.0 statistical software. The results were expressed as frequencies and percentages. The chi-square test and Fisher's F test were applied to find the level of significance of the difference between different variables. A value of P < 0.05 was considered statistically significant.

RESULTS

The average age of the participants was 32.46 ± 10.17 years old. As shown in Table 1, the majority of the participants (71, 55.5%) belonged to the age group of 21–30 years old. Approximately 6.2% of the participants were more than 50 years old. As well, most of the participants (74, 57.8%) were males. Moreover, approximately 61% of the participants were working at JUST University and the remaining of them were private practitioners. Approximately 23.4% of the participants were interns and were all working at JUST University. Almost half of the participants had a clinical experience of fewer than 5 years and approximately 9.4% of them had a clinical experience of more than 20 years. Finally, the majority of the participants (67.2%) were lacking any advanced qualification, however, approximately

Table 1: Sociodemographic profile of the study participants Characteristics Frequency Percentage Age groups (years) 21 - 3071 55.5 31 - 4036 28.1 13 41 - 5010.2 51 - 604 3.1 61 or more 4 3.1 Gender 54 Females 42.2 Males 74 57.8 Place of work **JUST** 78 60.9 Private 50 39.1 Current status 98 Fully licensed dentist 76.6 30 23.4 Duration since graduation 29 22.7 Recently graduated (less than 1 year) 34 26.6 2-5 years 19 14.8 5-10 years 34 10-20 years 26.6 12 >20 years 9.4 Experience of clinical practice 65 50.8 <5 years 22 17.2 5-10 years 29 10-20 years 22.7 >20 years 12 9.4 Additional academic qualification No 86 67.2 Master 36 28.1 Doctor of Philosophy 6 4.7 Teaching experience (to dental students) No 94 73.4 Yes 34 26.6

28% of them had a Master's degree and approximately 4.7% of them were PhD holders.

Table 2 shows the comparison of the knowledge regarding the antiplatelet/anticoagulant drugs between dentists from different workplaces. Approximately 61.5% of the participants from JUST University and 20.0% of the private practitioners were aware of clopidogrel usage. This difference was found to be statistically significant (P < 0.0001). Similarly, the awareness regarding prasugrel was overall low (8.6%) among private clinicians. However, more participants (12.8%) from JUST were aware of it compared to private practitioners (2.0%) with a statistically significant difference (P = 0.049). In response to the question "Do you know what is the optimal duration of clopidogrel therapy after drug-eluting stents for patients with ischemic heart disease?," 29.5% of participants from JUST and 10.0% of the private practitioners could respond positively (P = 0.009). Approximately 17.9% of the participants from JUST and 20.0% of the private practitioners were used to suspend treatment with clopidogrel before a dental invasion procedure in their patient (P = 0.005). Almost 26.9% of participants from JUST and 46.0% of the private practitioners were used to wait until the completion of antiplatelet treatment before performing a dental procedure. More than 70% of the participants from JUST and only 46.0% of the private practitioners were aware of the consequences of interrupting treatment with clopidogrel in patients with ischemic heart disease who are having a stent (P = 0.002). Overall the knowledge regarding the guidelines recommendations concerning the management of patients with antiplatelet agents before the dental procedure was found to be significantly (P = 0.031) higher among participants from JUST (44.9%) compared to private clinicians (28.1%). Similarly, the knowledge regarding the targeted INR for patients with prosthetic heart valves and those with atrial fibrillation was also higher among participants from JUST (44.9% and 29.5%, respectively), compared to private practitioners (24.0% and 12.0%, respectively).

Figure 1 suggests that the participants from JUST were consulting the cardiologists slightly more frequently (25.78%), compared to private practitioners (24.22%). As well, approximately 19.53% of the dentists from JUST and 7.03% of the private practitioners said that they would not suspend any of the antiplatelet drugs before dental procedures.

Table 3 shows the association between the experience of teaching for dental students and the knowledge regarding the antiplatelet/anticoagulant agents. A statistically significant association was found for

Table 2: Comparison of knowledge regarding antiplatelet/anticoagulant drugs (correct/positive responses) among dentists working at JUST and private clinic

Question	g at JUST and pri	P Value chi-		
Question	JUST N = 78	Private clinic $N = 50$	Total $N = 128$ frequency (%)	square test/
	frequency (%)	frequency (%)	1.1.1	Fisher's F test
Do you know what Clopidogrel is?	48 (61.5)	10 (20.0)	58 (45.3)	< 0.0001
Do you know what Prasugrel is?	10 (12.8)	1(2.0)	11 (8.6)	0.049*
Do you know what Ticagrelor is?	14 (17.9)	3 (6.0)	17 (13.3)	0.052
Do you know Warfarin?	77 (98.7)	46 (92.0)	123 (96.1)	0.056
Do you know Dabigatran?	7 (9.0)	7 (14.0)	14 (10.9)	0.374
Do you know Apixaban?	7 (9.0)	4 (8.0)	11 (8.6)	1.000*
Do you know what the optimal duration of	23 (29.5)	5 (10.0)	28 (21.9)	0.009
Clopidogrel therapy is after drug-eluting stents for				
patients with ischemic heart disease?				
Do you suspend treatment with Aspirin before a dental invasion in your patients?	16 (20.5)	16 (32.0)	32 (25.0)	0.143
Do you suspend treatment with Clopidogrel before	14 (17.9)	10 (20.0)	24 (18.8)	0.005
a dental invasion in your patient?				
Do you consult with a cardiologist before	50 (64.1)	38 (76.0)	88 (68.8)	0.157
interrupting antiplatelet medication(s)?				
Do you ever wait until antiplatelet treatment is	21 (26.9)	23 (46.0)	44 (34.4)	0.027
completed before performing the procedure?	/ 1)		00 (60 0)	
Do you know the consequences of interrupting	57 (73.1)	23 (46.0)	80 (62.5)	0.002
treatment with Clopidogrel in a patient with				
ischemic heart disease and he is having a stent?	25 (44.0)	12 (26.0)	40 (27.5)	0.021
Are you aware of the recent guidelines	35 (44.9)	13 (26.0)	48 (37.5)	0.031
recommendations regarding the management of patients on antiplatelet agents before the dental				
procedure?				
Do you know what the target INR is for patients	35 (44.9)	12 (24.0)	47 (36.7)	0.017
with prosthetic heart valves?	33 (44.9)	12 (24.0)	47 (30.7)	0.017
Do you know what the target INR is for patients	23 (29.5)	6 (12.0)	29 (22.7)	0.021
with atrial fibrillation?	23 (27.3)	0 (12.0)	27 (22.7)	0.021
Do you suspend treatment with Warfarin before a	31 (39.7)	20 (40.0)	51 (39.8)	0.977
dental invasion in your patient?	(,-)	()	0 - (0 / 10)	
Do you consult with a cardiologist before	70 (89.7)	41 (82.0)	111 (86.7)	0.208
interrupting anticoagulant medication?	` ,	, ,	, ,	
Do you know the consequences of interrupting	58 (74.4)	39 (78.0)	97 (75.8)	0.639
treatment with Warfarin for patients with				
prosthetic heart valves or atrial fibrillation?				
Are you aware of the recent guidelines	30 (38.5)	6 (12.0)	36 (28.1)	0.001
recommendations regarding the management				
of patients on anticoagulants before the dental				
procedure?	,	40.40		
Do you recommend adding the guidelines and	77 (98.7)	48 (96.0)	125 (97.7)	0.560
recommendations of the management of patients				
on antiplatelet or anticoagulants before a dental				
invasion to the curriculum of dental students while				
they are in college? *Figh or's E tout				

^{*}Fisher's F test

questions (related to knowledge) "Do you know what Clopidogrel is?," "Do you know what Prasugrel is?" and "Do you know what the optimal duration of Clopidogrel therapy is after drug-eluting stents for patients with ischemic heart disease?." For almost all the above questions, the knowledge was found to be more among those not having teaching experience.

Similarly, the correct practices and correct responses were mostly found among those not having teaching experience.

Table 4 shows the association between knowledge and additional advanced qualifications. A higher percentage of participants who have PhD qualifications (33.3%)

were aware of prasugrel. Similarly, a higher percentage of the participants who have PhD qualifications (50.0%), followed by participants with a Master's degree (33.3%)

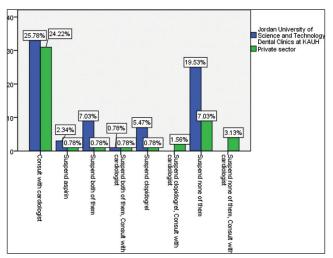


Figure 1: Response in reply to the question "If the patient is taking both Aspirin and Clopidogrel, what do you do before a dental invasion in your patient?"

knew the optimal duration of clopidogrel therapy after drug-eluting stents for patients with ischemic heart disease. As well, a higher percentage of the participants who have PhD qualifications (33.3%), were used to suspend clopidogrel before dental procedures.

DISCUSSION

Several pieces of evidence are there to suggest that stopping antiplatelet/anticoagulant therapies can increase the incidence of thromboembolic events.^[11,12] With the increasing number of invasive interventions for patients with CVDs, more and more dental patients come to clinics with on-going antiplatelet/anticoagulant treatments.^[7] Therefore, dentists must have adequate knowledge about the recent guidelines regarding the usage of those agents before and after invasive dental procedures. As well, they should be aware of when to refer those patients and consult with cardiologist specialists.

A previous study^[13] found that the most familiar antiplatelet drug to the dentists was aspirin/clopidogrel.

Table 3: Comparison of knowledge regarding antiplatelet/anticoagulant drugs (correct/positive responses) among dentists having teaching experience and not having teaching experience

Question	Are you involved		P Value chi-square
	in teaching dental		test/Fisher's F test
	students?		
	No N (%)	Yes N (%)	
Do you know what Clopidogrel is?	35 (60.3)	23 (39.7)	0.002
Do you know what Prasugrel is?	4 (36.4)	7 (63.6)	0.008*
Do you know what Ticagrelor is?	9 (52.9)	8 (47.1)	0.072
Do you know Warfarin?	90 (73.2)	33 (26.8)	1.000*
Do you know Dabigatran?	8 (57.1)	6 (42.9)	0.197*
Do you know Apixaban?	6 (54.5)	5 (45.5)	0.160*
Do you know what the optimal duration of Clopidogrel therapy is after drug-	15 (53.6)	13 (46.4)	0.007
eluting stents for patients with ischemic heart disease?			
Do you suspend treatment with Aspirin before a dental invasion in your patients?	25 (78.1)	7 (21.9)	0.488
Do you suspend treatment with Clopidogrel before a dental invasion in your patient?	17 (70.8)	7 (29.2)	0.001
Do you consult with a cardiologist before interrupting antiplatelet medication(s)?	63 (71.6)	25 (28.4)	0.483
Do you ever wait until antiplatelet treatment is completed before performing the procedure?	36 (81.8)	8 (18.2)	0.120
Do you know the consequences of interrupting treatment with Clopidogrel in a	56 (70.0)	24 (30.0)	0.256
patient with ischemic heart disease and he is having a stent?			
Are you aware of the recent guidelines recommendations regarding the management	28 (58.3)	20 (41.7)	0.003
of patients on antiplatelet agents before the dental procedure?			
Do you know what the target INR is for patients with prosthetic heart valves?	26 (55.3)	21 (44.7)	< 0.005
Do you know what the target INR is for patients with atrial fibrillation?	15 (51.7)	14 (48.3)	0.003
Do you suspend treatment with Warfarin before a dental invasion in your patient?	39 (76.5)	12 (23.5)	0.527
Do you consult with a cardiologist before interrupting anticoagulant medication?	80 (72.1)	31 (27.9)	0.557*
Do you know the consequences of interrupting treatment with Warfarin for patients	72 (74.2)	25 (25.8)	0.721
with prosthetic heart valves or atrial fibrillation?			
Are you aware of the recent guidelines recommendations regarding the management	18 (50.0)	18 (50.0)	< 0.005
of patients on anticoagulants before the dental procedure?			
Do you recommend adding the guidelines and recommendations of the management	92 (73.6)	33 (26.4)	1.000*
of patients on antiplatelet or anticoagulants before a dental invasion to the			
curriculum of dental students while they are in college?			

^{*}Fisher's F test

Table 4: Comparison of knowledge regarding antiplatelet/anticoagulant drugs (correct/positive responses) among dentists having an advanced degree and not having an advanced degree

Question		Advanced degree		
	None N	Masters N	PhD N	(Fisher's
	(%) #	(%) #	(%) #	F test)
Do you know what Clopidogrel is?	35 (40.7)	19 (52.8)	4 (66.7)	0.257
Do you know what Prasugrel is?	3 (3.5)	6 (16.7)	2 (33.3)	0.004
Do you know what Ticagrelor is?	8 (9.3)	8 (22.1)	1 (16.1)	0.112
Do you know Warfarin?	82 (95.3)	36 (100.0)	5 (83.3)	0.101
Do you know Dabigatran?	6 (7.0)	6 (16.7)	2 (33.3)	0.050
Do you know Apixaban?	5 (5.8)	5 (13.9)	1 (16.7)	0.184
Do you know what the optimal duration of Clopidogrel therapy is after drug-eluting	13 (15.1)	12 (33.3)	3 (50.0)	0.015
stents for patients with ischemic heart disease?				
Do you suspend treatment with Aspirin before a dental invasion in your patients?	21 (24.4)	9 (25.0)	2 (33.3)	0.818
Do you suspend treatment with Clopidogrel before a dental invasion in your patient?	17 (19.8)	5 (13.9)	2 (33.3)	0.005
Do you consult with a cardiologist before interrupting antiplatelet medication(s)?	62 (72.1)	24 (66.7)	2 (33.3)	0.153
Do you ever wait until antiplatelet treatment is completed before performing the	33 (38.4)	11 (30.6)	0(0)	0.133
procedure?				
Do you know the consequences of interrupting treatment with Clopidogrel in a patient	51 (59.3)	25 (69.4)	4 (66.7)	0.554
with ischemic heart disease and he is having a stent?				
Are you aware of the recent guidelines recommendations regarding the management of	34 (39.5)	11 (30.6)	3 (50.0)	0.492
patients on antiplatelet agents before the dental procedure?				
Do you know what the target INR is for patients with prosthetic heart valves?	27 (31.4)	19 (52.8)	1 (16.7)	0.049
Do you know what the target INR is for patients with atrial fibrillation?	17 (19.8)	9 (25.0)	3 (50.0)	0.187
Do you suspend treatment with Warfarin before a dental invasion in your patient?	33 (38.4)	16 (44.4)	2 (33.3)	0.769
Do you consult with a cardiologist before interrupting anticoagulant medication?	73 (84.9)	32 (88.9)	6 (100.0)	0.728
Do you know the consequences of interrupting treatment with Warfarin for patients	64 (74.4)	28 (77.8)	5 (83.3)	0.933
with prosthetic heart valves or atrial fibrillation?				
Are you aware of the recent guidelines recommendations regarding the management of	22 (25.6)	11 (30.6)	3 (50.0)	0.441
patients on anticoagulants before the dental procedure?				
Do you recommend adding the guidelines and recommendations of the management of	85 (98.8)	34 (94.4)	6 (100.0)	0.315
patients on antiplatelet or anticoagulants before a dental invasion to the curriculum of				
dental students while they are in college?				

[#] Column percentage

This is in agreement with our current study where we found similar results. One of the reasons can be that aspirin is the oldest antiplatelet agent available in medical practice. Moreover, it can be related to the excessive use of aspirin as prophylactic therapy in patients with CVDs, either primary prophylactic agent for high-risk CV patients or as secondary prophylactic therapy in patients with established CVDs. Another study conducted by Fareen et al.,[14] had found that approximately 45% of the dentists prefer to stop aspirin before the dental procedures. However, our current study found that only approximately 25% of the dentists believed in stopping the aspirin before dental procedures. This could be related to the improved dental services from one side and the fear of the cardiovascular consequences after stopping those medications.[11,12]

On the contrary, prasugrel and ticagrelor are relatively newer drugs. It was interesting to see that one of the studies conducted in Turkey revealed that none of the interviewed dentists were aware of those drugs.^[8] In agreement with that, our current study also found a very low level of awareness about these two drugs among the studied participants. As previously mentioned, this could be related to the fact that those are newly used drugs in the market. As well, it indicates the need for more workshops and training for dentists on the newly used drugs especially those which are used for cardiovascular patients. Moreover, this alerts us on the importance of keeping active communications and consultations with cardiovascular specialists before working with CVD patients at dental clinics.

This study revealed that approximately 46% of the dentists were aware of the recent guidelines and recommendations for the management of patients who are using antiplatelets or anticoagulants before dental invasive procedures. This finding was comparatively higher than what was found by Shah *et al.*,^[9] who revealed that only around 17% of dentists were aware of such guidelines. However, it appeared that our

participants are aware of the guidelines without proper knowledge or understanding of how to apply it properly and without being updated on the concerns related to the newly discovered drugs. This again highlighted the importance of consulting with the cardiovascular specialists before conducting invasive procedures on those patients.^[15] Unfortunately, we found in our study that only approximately 25% of the study participants were consulting cardiologists before interfering with antiplatelets or anticoagulants therapies. In comparison with that, Kumar et al.,[16] found that the majority of their participants were consulting the cardiologists before interfering with the antiplatelets or the anticoagulant therapies of their patients. Such a protocol should be encouraged in our country and possibly should be mandatory through the legislation of clear policies. In agreement with that, almost all the participants of this study believed that the "guidelines and recommendations of management of patients on antiplatelet or anticoagulants before a dental invasion" should be part of the curriculum of dental students, whereas they are in college. Such a belief was also expressed by the participants of the study conducted by a previous study,[13] in which approximately 88% of them believed in the same concepts.

Finally, we found that participants with higher degrees of dental education were more knowledgeable about the guidelines, the newest agents, and the proper use of antiplatelet/anticoagulant therapies in dental patients with CVDs. This is expected and accepted. However, it was unfortunate that those dentists who are currently having teaching experience were less aware of the same concepts. This could be related to the fact that most of our participants were dental interns or freshly graduated with less than 5 years' experience. We believe that those teaching interns may have been overloaded with the teaching duties and may not have proper time for updating themselves with the current guidelines and practices related to those therapies. As well, the knowledge of those interns and freshly graduated dentists maybe still related to what they used to learn during their bachelor studies where many updates and new drugs in the market did not exist at that time.

Our study has some limitations where the numbers of participants may better be improved. As well, calculating the response rate was not possible while keeping the identity of the participants totally anonymous. Moreover, high numbers of young and male participants may affect the study results. Finally, including practitioners from the public health sector may give more indication about the general dental practice in Jordan.

CONCLUSION

Following the findings of this study, it is recommended that the knowledge about "guidelines recommendations of management of patients on antiplatelet or anticoagulants before a dental invasion" is poor, especially in the private sector. There is a need of increasing the awareness about the evidencebased practices for the management of anticoagulant therapies among dentists before invasive dental procedures. Proper workshops, updated courses and curriculums, and more training for dentists especially those who have teaching duties should be provided. Almost all the participants believed that the guidelines and recommendations of the management of patients on antiplatelet or anticoagulants before a dental invasion should be added to the curriculum of dental students while they are in college.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

All the authors have contributed equally to the manuscript for conceptualization, formal analysis, investigation, methodology, writing, and final editing. All authors have read and agreed to the published version of the manuscript.

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