Mediterranean Journal of Hematology and Infectious Diseases

Review Article

Clinical Care Pathway and Management of Major Bleeding Associated with Nonvitamin K Antagonist Oral Anticoagulants: A Modified Delphi Consensus from Saudi Arabia and UAE

Abdulrahman Al Raizah[1], Fakhr Alayoubi[2], Galal Hassan Abdelnaby[3], Hazzaa Alzahrani[4], Majid Farraj Bakheet[5], Mohammed A Alskaini[6], Rasha Buhumaid[7], Sameer Al Awadhi[8], Sara Nooruddin Kazim[9], Thiagarajan Jaiganesh[10], Mohamed Hamdy Hussein Naguib[14] and Zohair Al Aseri[11,12,13].

[1] Division of Adult Hematology, Department of Oncology, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, PO Box. 22490, 11426, Riyadh, Saudi Arabia.
[2] King Saud University, Riyadh, Saudi Arabia.
[3] Alqassimi Hospital, United Arab Emirates.
[4] King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.
[5] Neurology Department, King Abdullah Medical City, Mecca, Saudi Arabia.
[6] Department of Neurology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.
[7] Mohammed Bin Rashid University of Medicine and Health Science, Dubai, United Arab Emirates.
[8] Digestive Diseases Unit, Rashid Hospital, Dubai, United Arab Emirates.
[9] Department of Emergency Medicine, Rashid Hospital and Trauma Centre, Dubai Health Authority, Dubai, United Arab Emirates.
[10] Emergency Department, Tawam Hospital, Al Ain, United Arab Emirates.
[11] Department Emergency Medicine and Critical Care, College of Medicine, King Saud University, Riyadh, Saudi Arabia.
[12] Department of Clinical Sciences, College of Medicine and Riyadh Hospital, Dar Al Uloom University, Riyadh, Saudi Arabia.
[13] Therapeutic Deputyship, Ministry of Health, Riyadh, Saudi Arabia.
[14] AstraZeneca, Saudi Arabia.

Competing interests: The authors declare no conflict of Interest.

Abstract. ***Background.*** **The nonvitamin K antagonist oral anticoagulants (NOACs) have become the mainstay anticoagulation therapy for patients requiring oral anticoagulants (OACs) in the Gulf Council Cooperation (GCC) countries. The frequency of NOAC-associated major bleeding is expected to increase in the Emergency Department (ED). Nonetheless, we still lack local guidelines and recommendations for bleeding management in the region. The present Delphi-based consensus aims to establish a standardized and evidence-based clinical care pathway for managing NOAC-associated major bleeding in the Kingdom of Saudi Arabia (KSA) and the United Arab Emirates (UAE).**
Methods**: We adopted a three-step modified Delphi method to develop evidence-based recommendations through two voting rounds and an advisory meeting between the two rounds. A panel of 11 experts from the KSA and UAE participated in the consensus development.**
Results**: Twenty-eight statements reached the consensus level. These statements addressed key aspects of managing major bleeding events associated with NOACs, including the increased use of NOAC in clinical practice, clinical care pathways, and treatment options.**
Conclusion**: The present Delphi consensus provides evidence-based recommendations and protocols for the management of NOAC-associated bleeding in the region. Patients with major DOAC-induced bleeding should be referred to a well-equipped ED with standardized**

management protocols. A multidisciplinary approach is recommended for establishing the association between NOAC use and major bleeding. Treating physicians should have prompt access to specific reversal agents to optimize patient outcomes. Real-world evidence and national guidelines are needed to aid all stakeholders involved in NOAC-induced bleeding management.
Keywords: Nonvitamin K antagonist oral anticoagulants; Bleeding; Clinical care pathway; Consensus; Saudi Arabia; UAE.

Citation: Al Raizah A., Alayoubi F., Abdelnaby G.H., Alzahrani H., Bakheet M.F., A Alskaini M., Buhumaid R., Al Awadhi S., Kazim S.N., Jaiganesh T., Naguib M.H.H., Al Aseri Z. Clinical care pathway and management of major bleeding associated with nonvitamin K antagonist oral anticoagulants: a modified delphi consensus from Saudi Arabia and UAE. Mediterr J Hematol Infect Dis 2024, 16(1): e2024038, DOI: http://dx.doi.org/10.4084/MJHID.2024.038

Published: May 01, 2024 **Received: December 13, 2023** **Accepted: April 13, 2024**

Correspondence to: Zohair Al Aseri, FRCPC EM & CCM. Department Emergency Medicine and Critical Care, College of Medicine, King Saud University, Riyadh, Saudi Arabia. Department of Clinical Sciences, College of Medicine and Riyadh Hospital, Dar Al Uloom University, Riyadh, Saudi Arabia. Therapeutic Deputyship, Ministry of Health, Riyadh, Saudi Arabia. E-mail: Alaserizohair@gmail.com ORCID: http://orcid.com/0000-0001-9869-7544

Introduction. The nonvitamin K antagonist oral anticoagulants (NOACs) have become the mainstay anticoagulation therapy for patients requiring oral anticoagulants (OACs).[1,2] Current guidelines recommend the use of NOACs for a wide range of conditions, including non-valvular atrial fibrillation (NVAF), recurrent deep vein thrombosis (DVT), pulmonary embolism (PE), and cancer-associated thrombosis.[2,3] Despite their advantages, NOACs are not risk-free medications. A pooled analysis observed that the prevalence of major bleeding in patients on NOACs ranged from 1.6 to 3.6 per 100 patient-years,[4] which can lead to massive transfusion, irreversible neurological complications, hospitalization, death,[5,6] and increased healthcare resource utilization (HCRU).[7,8]

The management of NOAC-associated major bleeding is based on restoring hemodynamic stability and reversing hemostasis to normal functions before the reintroduction of NOACs.[9] Pivotal clinical trials confirmed the effectiveness of specific reversal agents in restoring factor Xa or direct thrombin activity in patients with life-threatening bleeding.[10,11] Several guidelines recommend specific reversal agents over PCC for NOAC users with life-threatening bleeding or bleeding at critical sites.[12,13]

The Gulf Cooperation Council (GCC) countries have experienced significant transformations in their healthcare systems over the past few decades. Recent reports indicated a notable increase in the use of NOACs, driven by the increased prevalence of NVAF, DVT, and other conditions requiring OACs.[14,15] Data from the GCC countries showed that rivaroxaban and apixaban were the most prescribed OACs for NVAF patients in the region.[16–19] As the use of NOACs continues to rise in the GCC countries, the absolute number of patients who experience major bleeding events while on these medications is also expected to rise. Single-center reports from the GCC countries showed that the rate of major bleeding in patients receiving apixaban was 2.8%.[20] Despite this burden, we still lack local guidelines and recommendations for bleeding management in the GCC region.

The present Delphi-based consensus aims to establish a standardized and evidence-based clinical care pathway for the management of NOAC-associated major bleeding in the Kingdom of Saudi Arabia (KSA) and the United Arab Emirates (UAE). This consensus gathered recommendations from regional experts to tailor the management pathway to the specific healthcare context of KSA and UAE, considering the local clinical practices.

Methods.

Study Design and Panel Recruitment. We adopted a three-step modified Delphi method to recruit a panel of 11 experts from KSA and UAE. The experts were selected using a non-probability convenient selection process to ensure a geographical representation of major academic institutions in the GCC region. The panel of experts comprised consultants with diverse and complementary expertise, ensuring a comprehensive and multidisciplinary approach to the consensus process. The expert panel included hematologists, neurologists, emergency medicine physicians, and clinical pharmacists. All experts participated voluntarily and were required to sign a disclosure statement before consensus development.

Literature Review and Statements Development. The survey development committee conducted a comprehensive search of electronic databases, including PubMed, Embase, and Cochrane Library, to retrieve relevant guidelines, consensus, and systematic reviews about the management of NOAC-associated bleeding. The literature search was performed using the following terms: ("dabigatran," "rivaroxaban," "apixaban," "edoxaban," OR "nonvitamin K antagonist oral

anticoagulant" OR "direct oral anticoagulant" OR "novel oral anticoagulant" OR "NOAC" OR "DOAC" OR "Vitamin K antagonists" OR "VKA" OR "warfarin" OR "dicoumarol" OR "acenocoumarol" OR "Coumadin") AND ("bleeding" OR "major bleeding" OR "hemorrhage" OR "intracranial bleeding" OR "adverse events") AND ("management" OR "prothrombin complex concentrate" OR "Andexanet alfa" OR "Idarucizumab"). A secondary search was conducted using the abovementioned keywords in combination with the following GCC-related keywords to retrieve relevant citations from the GCC region: ("Gulf Council" OR "Gulf Council Cooperation" OR "GCC" OR "Saudi Arabia" OR "Kuwait" OR "United Arab Emirates" OR "Qatar" OR "Bahrain" OR "Oman").

The search was supplemented by screening relevant publications from the hematology, cardiology, or stroke journals based in one of the GCC or Middle East regions, such as the Saudi Heart Journal, Journal of the Saudi Heart Association, Journal of Applied Hematology, Saudi Medical Journal, Oman Medical Journal, and Dubai Medical Journal. There was no language, year of publications, or country-specific restrictions on the literature search. Data were retrieved only from level 1 quality of evidence, as classified by Wright et al.[21]

Based on the findings of the literature review, an initial set of draft statements was developed for the first round of voting. These statements addressed key aspects of managing major bleeding events associated with NOACs, including the increased use of NOAC in clinical practice, clinical care pathways, and treatment options.

Delphi Process and Consensus Development. The Delphi process consisted of two rounds of voting and an advisory meeting. In the first round, the initial set of statements was distributed to the panel of experts. Experts were asked to vote on each statement (agree/disagree) and were encouraged to provide comments and additional insights. A consensus was defined as an agreement level ≥ 75%.[22] After the first round, the responses were collated and analyzed. A summary of the results, along with anonymized comments from the experts, was distributed to the panel during an advisory meeting. Based on the feedback received during the meeting, the statements that did not reach the consensus levels were restructured for the second round of voting. The revised statements and questions were redistributed to the experts in this round. They were asked to review the changes and rate their level of agreement with the revised statements.

All panel members reviewed and approved the final consensus statements and manuscript.

Results and Discussion. Initially, 29 statements were developed by the survey development committee and were emailed to the experts for the first voting round. Of them, ten statements reached the consensus level, eight were rephrased without second-round voting, and one was removed. The remaining ten statements were rephrased during the expert meeting and reached the consensus level after the second round of voting. Thus, the present consensus was composed of 28 statements.

I. *Trends of NOAC utilization and incidence of major bleeding:*

Three statements about the trend of NOAC use in the GCC countries reached the consensus level (**Table 1**).

The last decade has witnessed a significant shift in the OACs landscape, characterized by a growing preference for NOACs over traditional VKAs. The experts agreed that the utilization of NOACs over VKAs has significantly increased in the GCC over the last decade (*Statement 1*). This decision runs in line with global statistics showing a significant increase in NOAC utilization rate from 5% to nearly 30-48% over the past 15 years.[23,24] In the GCC region, published data indicated a dramatic increase in NOAC utilization since 2013 (**Figure 1**).[17–19,25–28]

Several reasons can explain the trends of increased NOAC use in the GCC region. One of the primary drivers of this shift has been the pharmacological advantages that NOACs offer over VKAs. In addition, the increasing prevalence of conditions such as AF and VTE, which are key indications for OACs, has also likely contributed to the growing use of NOACs.[14,29] The patient population in the GCC countries is diverse, with varying comorbidities, age groups, and risk factors,[30,31] which increase the probability of receiving prophylactic OACs.

As the use of NOACs continues to rise in the GCC

Table 1. Experts' Consensus Statements on NOACs Use and Risk of Major Bleeding.

No.	Statements	%
1	There has been increasing use of NOACs over VKAs in Saudi Arabia and the UAE in the last decade	100%
2	The risk of major bleeding varies for different types of NOACs.	100%
3	NOAC-induced bleeding is considered major in patients who present with one or more of the following: a) Bleeding in a critical site b) Bleeding causes hemodynamic instability. c) Bleeding causes hemoglobin drop ≥ 2g/dL or transfusion of ≥ 2 units of packed RBCs.	100%

GCC, Gulf Cooperation Council; NOACs, Nonvitamin K Oral Anticoagulants; VKAs, Vitamin K Antagonists; UAE, United Arab Emirates; RBCs, Red Blood Cells; EMS, Emergency Medical Services; ED, Emergency Department; CT, Computed Tomography.

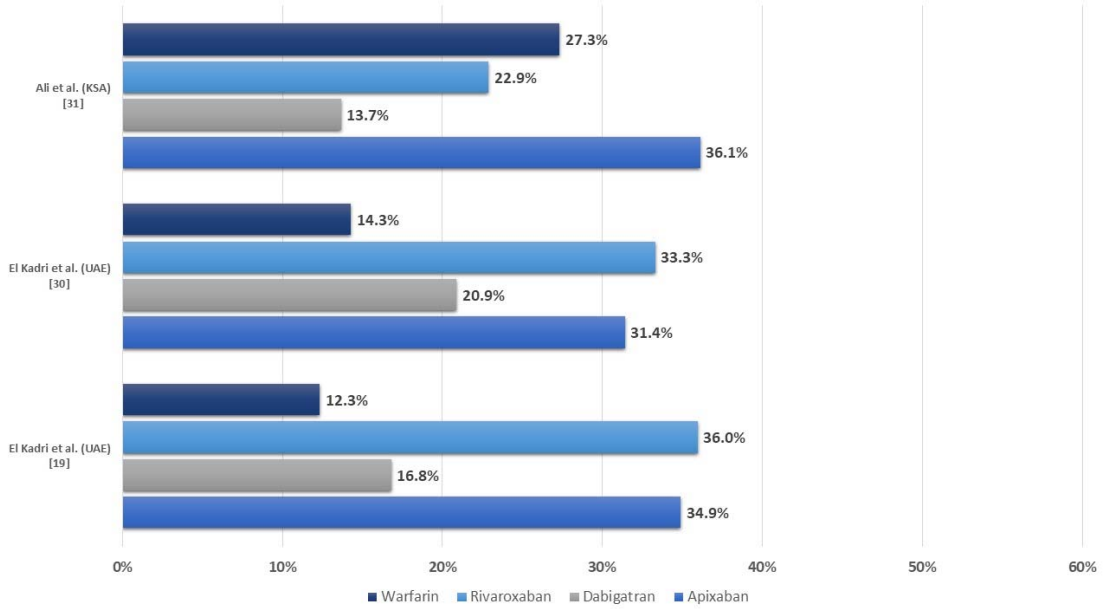

Figure 1. Rates of OACs Utilization in Real-world Practice in the GCC Countries.

Table 2. Experts' consensus statements on recommendations for clinical care pathway for major bleeding.

No.	Statements	%
4	All patients on NOAC therapy and their caregivers should be aware of major bleeding symptoms according to the site and extent of bleeding	91%
5	Emergency Medical Services (EMS) should be aware of the BEFAST stroke assessment criteria. EMS should have a clear identification of the available referral centers and follow a standardized protocol to determine the symptom onset, duration, site, and severity.	100%
6	EMS should be trained to activate pre-hospital notifications and transfer patients with suspected life-threatening bleeding to the nearest qualified hospital.	100%
7	The initial assessment of bleeding severity, medication history, and clinical presentation in patients treated with NOACs is essential for treatment decisions	100%
8	ED personnel should be aware of the approved NOACs, their complications, side effects, and antidotes	100%
9	The ED should be well-equipped to manage patients with major NOAC-induced bleeding using standardized protocols for bleeding management.	100%
10	All patients receiving NOAC therapy with any neurological manifestation should perform a CT scan	91%
11	For patients with life-threatening bleeding, NOACs should be stopped	100%

GCC, Gulf Cooperation Council; NOACs, Non-Vitamin K Oral Anticoagulants; VKAs, Vitamin K Antagonists; UAE, United Arab Emirates; RBCs, Red Blood Cells; EMS, Emergency Medical Services; ED, Emergency Department; CT, Computed Tomography.

countries, emergency departments (EDs) are anticipated to encounter cases of NOAC-associated major bleeding increasingly. In previous retrospective studies from Saudi Arabia, the overall rate of major bleeding ranged from 1.1% to 3.9% in NVAF and VTE patients receiving rivaroxaban or apixaban, while the rate of fatal bleeding was 0.2%.[20,32,33] Another study showed that the rate of intracranial hemorrhage (ICH) in patients receiving rivaroxaban in Saudi Arabia was 0.58%.[34] Therefore, the healthcare system must anticipate and prepare for the increased encounters of NOAC-associated major bleeding in the GCC region by adopting local recommendations and guidelines for clinical care pathways and management of NOAC-associated major bleeding.

The type and indication of NOACs, as well as patient-specific factors, appear to play a role in the risk of bleeding.[35] The experts agreed that the risk of major bleeding varies for different types of NOACs in clinical practice (*Statement 2*). Thus, clinicians must consider these differences, along with patient-specific factors (e.g., renal function, concomitant medications, and bleeding history), when selecting the most appropriate anticoagulant for each patient.

Despite the growing number of published guidelines,[36–39] there is no universal agreement on the definition of major bleeding. The experts agreed on adopting the definition of the 2020 American College of Cardiology (ACC) consensus.[12] The ACC consensus defines NOAC-associated major bleeding as bleeding that fulfills one or more of the following*:* bleeding in a critical site; bleeding causes hemodynamic instability; and/or bleeding that causes hemoglobin drop ≥ 2g/dL or transfusion of ≥ 2 units of packed red blood cells (*Statement 3*).

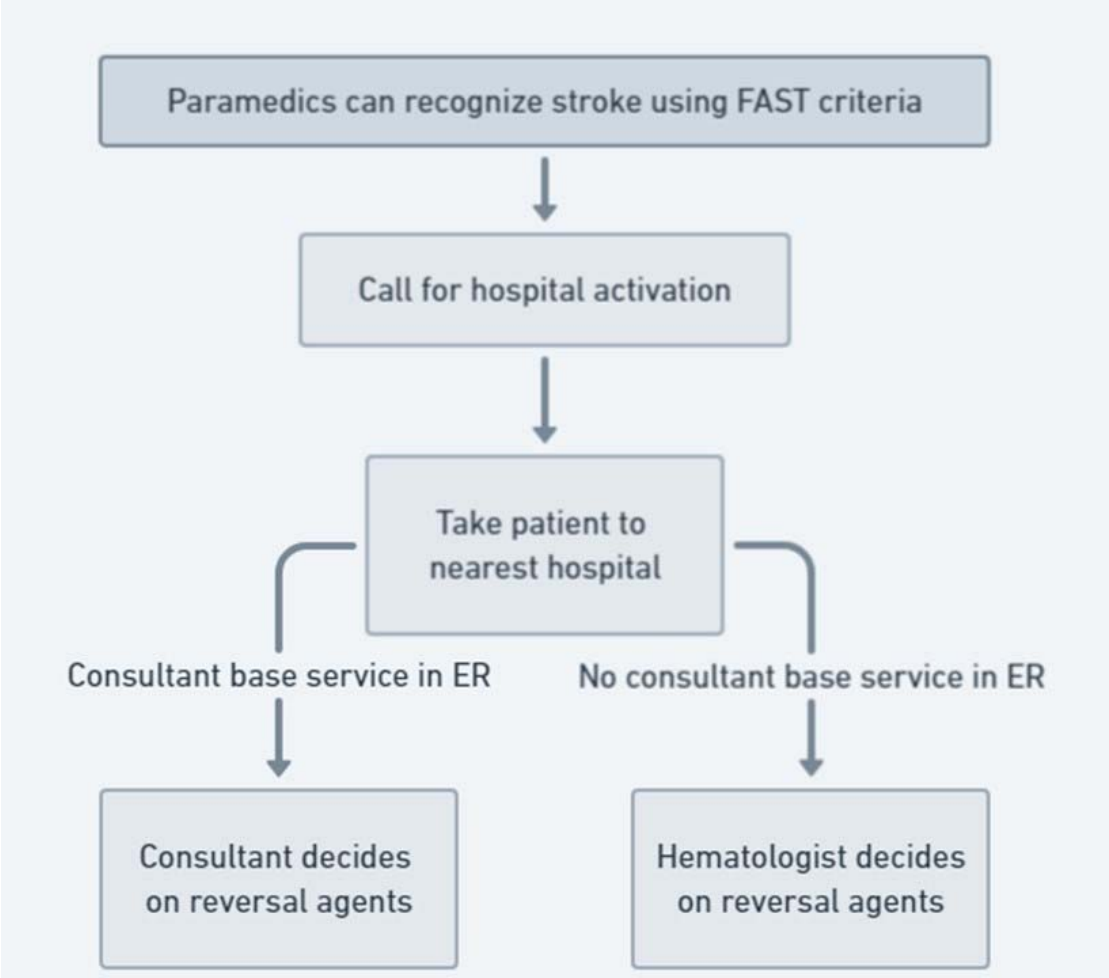

Figure 2. Patient Journey of NOAC-associated Major Bleeding in the GCC Countries.

II. Clinical Care Pathway:

Eight statements about the clinical care pathway for the management of NOAC-associated bleeding reached the consensus level (**Table 2**).

The identification of early signs of major bleeding can positively impact the clinical care pathway and patient outcome.[40,41] Thus, educating patients and their caregivers about the signs and symptoms of major bleeding can empower them to recognize potentially life-threatening events early and seek timely medical intervention (*Statement 4*).

Several simple and easy-to-use scores have been developed to identify early signs of stroke and ensure rapid access to medical care.[42] The BEFAST (Balance, Eyes, Face, Arm, Speech, Time) criteria were developed to improve the diagnostic accuracy of the original FAST tool in patients with signs of a stroke.[43] In the GCC setting, when paramedics recognize stroke or major bleeding using BEFAST criteria, they are required to activate pre-hospital notifications and transfer patients to the nearest qualified hospital. The decision to use the specific reversal agents then depends on the presence of an emergency medicine consultant or a hematologist (**Figure 2**).

Thus, the experts agreed that the Emergency Medical Services (EMS) staff should be aware of the BEFAST stroke assessment criteria. The EMS should Identify the available referral centers clearly and follow a standardized protocol to determine the symptom onset, duration, site, and severity (*Statement 5*). The EMS staff should be trained to activate pre-hospital notifications and transfer patients with suspected life-threatening bleeding to the nearest qualified hospital (*Statement 6*).

The initial assessment of bleeding severity, medication history, and clinical presentation in patients treated with NOACs is essential for treatment decisions (*Statement 7*). The current international guidelines indicate that the management of bleeding complications depends primarily on the severity and location of the bleeding.[12,13] Thus, the ED personnel should be aware of the approved NOACs, their complications, side effects, and antidotes (*Statement 8*).

Alongside the initial assessment, several laboratory measures have been recommended to assess patients with suspected NOAC-associated bleeding, mainly the coagulation profile, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level.[44] However, the PT and aPTT are limited when used for qualitative assessment of NOAC activities.[45] Previous reports suggested that PT and aPPT

prolongation is not exclusively associated with NOAC over-dosage and may lead to misleading results.46–48 In contrast, certain conditions may be associated with normal limits despite elevated NOAC concentrations.[49] Thus, it has been previously advocated that PT and aPTT should not be used alone.[50]

Quantitative assessment of NOAC levels is crucial to determine the serum concentration of the NOAC. Specialized assays, such as the anti-factor Xa assay (for rivaroxaban and apixaban) and the diluted thrombin time (dTT) or ecarin clotting time (ECT) for dabigatran, can be used to measure the specific NOAC levels.[51–53] One of the critical advantages of measuring NOAC plasma concentrations is the ability to ascertain whether bleeding events are attributable to over-dosage, and that is particularly relevant in acute settings where rapid decision-making is crucial. Establishing the presence of excessive anticoagulation can guide the administration of specific reversal agents, ensuring targeted and efficient management of bleeding complications.[49,54] Moreover, patients experiencing recurrent thrombosis while on NOAC therapy may benefit from plasma concentration testing to evaluate under-dosage or inadequate anticoagulation.[55] While not routinely recommended, adjusting the dosage based on plasma levels could be considered in such cases to optimize anticoagulation and prevent further thrombotic events. Additional clinical scenarios where NOAC plasma concentration testing is valuable include before initiating treatment, in preparation for surgical or invasive procedures, and before thrombolytic therapy for acute ischemic stroke.[50] Qualitative assays can also provide information on the NOAC activity in the case of normal PT or aPTT.[56] Plasma NOAC assays are also commercially available and easy to operate, with comparable results between laboratories.[50]

Despite the benefits and availability of NOAC plasma concentration testing, a notable barrier to its widespread adoption is physician reluctance. This hesitance may stem from a lack of familiarity with the tests, uncertainty about interpreting results, or concerns over the impact of testing on clinical workflow.[12] Addressing these concerns through education and evidence-based guidelines could enhance the utilization of NOAC testing in appropriate clinical scenarios.

Currently, there is significant variability in the laboratory assessment of patients with NOAC-associated major bleeding. Different institutions may have different protocols, and not all laboratories have the capacity to perform specialized NOAC assays. This lack of standardization can lead to variability in patient care and may affect outcomes. Therefore, the ED should be well-equipped with standardized protocols to manage patients with major NOAC-induced bleeding (*Statement 9*).

All patients receiving NOAC therapy with any neurological manifestation should perform a computed tomography (CT) scan (*Statement 10*). For patients with life-threatening bleeding, NOACs should be stopped (*Statement 11*).

III. Management of NOAC-associated Major Bleeding:

In the present consensus, 13 recommendations were developed regarding management approaches for patients with NOAC-associated major bleeding (**Table 3**).

The current guidelines emphasize the importance of a structured and systematic approach to the management of NOAC-associated bleeding. The initial management step is to stabilize the patient's hemodynamics in case of hemodynamic instability.[57–60] The experts agreed that patients with NOAC-associated bleeding should be continuously monitored in the intensive care unit (ICU) with special consideration to the bleeding extent/size, hemodynamic stability, airway management, and consciousness level (*Statement 12*).

For patients with severe or life-threatening bleeding, activation of a massive transfusion protocol may be necessary.[61] However, previous trials demonstrated better survival and lower risk of recurrent bleeding with restrictive rather than massive transfusion.[62] Additionally, massive transfusion can be associated with life-threatening consequences, such as coagulopathy, transfusion-related acute lung injury, and transfusion-associated circulatory overload.[63] The decision for massive transfusion in NOAC-associated major bleeding should be individualized in patients on NOACs who require a massive blood transfusion with a 1:1:1 ratio of packed RBCs, platelets, and fresh frozen plasma (FFP) (*Statements 13 and 14*).

In the setting of NOAC-associated bleeding, a comprehensive understanding of concomitant medications and comorbidities is essential. Concurrent use of antiplatelet medications with DOACs can significantly increase the risk of bleeding events.[64] Renal impairment is another critical consideration, as most NOACs, particularly dabigatran, are partially excreted by the kidneys; thus, renal dysfunction can lead to longer half-lives and an increased risk of bleeding.[65] In case of renal impairment, desmopressin acetate or cryoprecipitate may be beneficial in correcting uremia-associated platelet dysfunction.[66,67] Liver disorders, often associated with coagulopathy due to decreased synthesis of clotting factors, can further complicate the bleeding risk and the approach to reversal and hemostasis.[12] Therefore, intensive care specialists must thoroughly know the patient's medication profile and comorbid conditions (*Statement 15*).

The introduction of specific reversal agents has significantly improved the outcomes of bleeding complications of NOACs and provided a new horizon for better utilization of NOACs in clinical practice. Idarucizumab is a humanized monoclonal antibody

Table 3: Experts' consensus statements on the management of NOAC-associated major bleeding.

No.	Statement	%
12	Patients should be continuously monitored in the ICU with special consideration to the bleeding extent/size, hemodynamic stability, airway management, and consciousness levels.	**100%**
13	The decision for massive transfusion in non-trauma patients should be individualized, goal-driven, and taken by a senior specialist or an emergency medicine consultant due to its potentially life-threatening consequences	**91%**
14	In patients on NOACs who require a massive blood transfusion, transfuse with a 1:1:1 ratio of packed RBCs, platelets, and fresh frozen plasma	**82%**
15	Intensive care specialists should be aware of all concomitant medications and comorbidities that might impact major bleeding and its management, including antiplatelet medications, renal impairment, or liver disorders	**100%**
16	ER personnel should have rapid access to bleeding reversal agents in coordination with the attending hematologist to facilitate quick management decisions and ensure administration within the accepted window of opportunity	**100%**
17	If not received in the ED, consider the administration of reversal agents in the intensive care department as soon as possible	**100%**
18	In case of factor IIa inhibitor (dabigatran) induced bleeding, the following actions are recommended: ➢ Administer idarucizumab. ➢ If idarucizumab is not available, administer PCC. ➢ Hemodialysis could be considered.	**91%**
19	In case of factor Xa inhibitor (Apixaban and Rivaroxaban) induced bleeding, the following actions are recommended: ➢ Administer andexanet alfa. ➢ If not available, administer PCC.	**91%**
20	The accepted window to administer andexanet alfa depends on the received NOAC dosage and pharmacokinetics and can be up to 18 hours after the last dose of FXa inhibitor	**100%**
21	In case the major bleeding etiology [spontaneous versus traumatic bleeding] could not be assessed, immediate reversal of anticoagulation is indicated regardless of the bleeding site unless there is an absolute contraindication.	**91%**
22	Activated charcoal could be considered with known recent ingestion of NOACs [within 2 – 4 hours of ingestion].	**82%**
23	Fresh frozen plasma is not recommended in managing NOAC-induced major bleeding.	**100%**
24	Restarting anticoagulants in patients with NOAC-induced major bleeding is a multidisciplinary team decision to weigh the risks versus benefits of anticoagulation reintroduction.	**100%**

GCC, Gulf Cooperation Council; NOACs, Nonvitamin K Oral Anticoagulants; ER, Emergency Room; ED, Emergency Department; ICU, Intensive Care Unit; RBCs, Red Blood Cells; PCC, Prothrombin Complex Concentrate; PCC, Prothrombin Complex Concentrate.

fragment (Fab) that binds specifically and with high affinity to dabigatran, neutralizing its anticoagulant effect.[68,69] The pivotal REVERSE AD trial showed that idarucizumab effectively restored normal hemostatic activity in 88 to 98% of the patients with life-threatening/uncontrolled bleeding due to dabigatran. Similar findings were in patients who needed urgent surgery.[70] In 2018, the FDA fully approved idarucizumab as the first reversal agent for restoring hemostasis in dabigatran users with life-threatening/uncontrolled bleeding or needing urgent surgery.[71]

Andexanet alfa is a recombinant modified human factor Xa protein that acts as a decoy receptor for factor Xa inhibitors. It binds to these drugs, reducing their ability to inhibit endogenous factor Xa and reversing their anticoagulant effects.[72] In the ANNEXA-A and ANNEXA-R studies, which evaluated and examined alfa in healthy volunteers, anti-factor Xa activity was reduced by 92-94%, and the thrombin generation was restored in 100% of the patients.[73] In the pivotal phase III/IV ANNEXA-4 trial, which recruited patients with acute major bleeding due to apixaban or rivaroxaban, Overall, 82% of the patients had adequate restoration of homeostasis within 12 hours, while the median reduction in the anti-factor Xa activity was 92% within 18 hours. Within 30 days of follow-up, 10% of the patients had thromboembolic events. The overall mortality rate was 14%.[11] Based on these findings, andexanet alfa was granted accelerated approval by the FDA in 2018 as the first specific reversal agent for apixaban and rivaroxaban-treated patients.[74]

The experts agreed that, in the case of NOAC-induced life-threatening bleeding, specific reversal agents are recommended. Thus, ER personnel should have rapid access to these agents in coordination with the attending hematologist to facilitate quick management decisions and ensure administration within the accepted window of opportunity. If not received in the ED, reversal agents should be administered in the ICU as soon as possible (*Statements 16 and 17*). Idarucizumab and andexanet alfa are recommended in patients with life-threatening bleeding due to factor IIa and Xa inhibitors, respectively (*Statements 18 and 19*). The accepted window to administer and examine alfa depends on the NOAC dosage received and pharmacokinetics and can be up to 18 hours after the last dose of the FXa inhibitor (*Statement 20*). Patients on dabigatran, especially those with renal insufficiency, may benefit from hemodialysis;[12] thus, hemodialysis could be considered (*Statement 18*). In case the major bleeding etiology [spontaneous versus traumatic bleeding] could not be assessed, immediate reversal of anticoagulation is indicated regardless of the bleeding site unless there is an

absolute contraindication (*Statement 21*).

Measuring plasma concentrations of NOAC before the administration of a specific reversal agent should be considered whenever possible.[50] Although the pivotal clinical trials evaluating the reversal agents did not include the measurement of NOAC concentrations before administrating the reversal agents, post-hoc analyses of registration trials for idarucizumab and andexanet alfa revealed that approximately 30% of patients treated had relatively low NOAC concentrations at the time of antidote administration.[70,75] These findings raise important questions about the necessity and efficacy of administering antidotes without significant NOAC levels, suggesting that some patients may receive treatment without a clear pharmacological need. Measuring NOAC levels before administering antidotes could help identify patients who would most benefit from reversal agents, thereby enhancing the clinical value of antidote administration and preventing unnecessary use.[50] However, in the case of life-threatening bleeding, point-of-care NOAC assessment can be used. The NOAC assays require standardization and calibration for specific NOACs, and the performance and interpretation of these tests require a specialist.[76] Hence, most of the guidelines highlighted the importance of the clinical history of the patient and only using the test of NOACs if the test is available and the results will be ready within less than 20 minutes.[77]

When specific reversal agents are not available, 4-factor PCC, which contains the vitamin K-dependent coagulation factors II, VII, IX, and X, can be used to reverse the effects of NOACs (*Statements 18 and 19*). Observation studies showed that 4-factor PCC restored the hemostatic efficacy in nearly two-thirds of the patients with major bleeding due to apixaban or rivaroxaban.[78,79] In a recent meta-analysis, it was concluded that it is difficult to determine whether 4F-PCC, in addition to cessation of direct oral FXa inhibitor, is more effective than cessation of direct oral FXa inhibitor alone in patients with direct FXa inhibitor-related major bleeding.[80]

Activated charcoal is a highly porous substance with a large surface area that can bind to various drugs and toxins, thereby reducing systemic absorption. In the context of NOAC-associated bleeding, activated charcoal is considered a potential intervention to limit further drug absorption, especially when the NOAC has been recently ingested.[81] Activated charcoal could be considered with known recent (2-4 hours) ingestion of NOACs (*Statement 22*). On the other hand, FFP is not recommended due to the lack of supporting evidence and the potential risk of transfusion (*Statement 23*).

A growing number of studies indicated that NOAC stoppage increased the risk of ischemic events in NVAF patients who experienced major bleeding.[82] Restarting NOAC demonstrated safety and feasibility without increasing the risk of future bleeding.[83] Notably, restarting NOAC was found to be associated with a reduced risk of long-term disability.[84] Nonetheless, limited evidence is available regarding the factors that guide NOAC restarting decision. For instance, conflicting results exist regarding the impact of ICH location (lobar versus subarachnoid), the presence of aneurysm or hematoma, and patient-specific factors (e.g., age, history of thromboembolic events) on the recurrence risk after resuming NOACs.[85–88] The experts agreed that restarting anticoagulants in patients with NOAC-induced major bleeding requires a multidisciplinary team to weigh the risks versus benefits of anticoagulation reintroduction (*Statement 24*).

IV. Unmet Medical Needs in the GCC Countries:

Four statements about the recommendations to address the current gaps in NOAC-associated bleeding reached the consensus level (**Table 4**).

The experts agreed on the importance of conducting real-world studies in the GCC to understand the characteristics and outcomes of NOAC-associated major bleeding in the region (*Statement 25*). Local real-world evidence is vital in the GCC countries, where healthcare systems and patient demographics may differ significantly from those in Western countries.[43] Such evidence can provide insights into patient adherence to NOACs, the incidence and management of major bleeding events, and patient outcomes following such events. It can also help identify potential gaps in healthcare services, such as the need for more widespread availability of reversal agents or more extensive education on NOAC use and bleeding management.[89,90]

Table 4. Experts' consensus statements on the unmet needs for the management of NOAC-associated major bleeding.

No.	Statement	%
25	Real-world evidence in the GCC is essential to understand further the patient journey and outcomes of managing NOAC-induced major bleeding.	**100%**
26	Standardized definitions for major and life-threatening bleeding are recommended to allow proper assessment and standardized treatment plans	**100%**
27	National and institutional guidelines should be developed to aid all stakeholders involved in NOAC-induced bleeding management.	**100%**
28	Cross-specialty collaboration would improve communication, decisions, and outcomes of patients with NOAC-induced bleeding	**100%**

GCC, Gulf Cooperation Council; NOACs, Nonvitamin K Oral Anticoagulants.

The experts agreed on the need for standardized definitions of major and life-threatening bleeding in the GCC setting to allow proper assessment and standardized treatment plans (*Statement 26*). The lack of standardized definitions for major and life-threatening bleeding can lead to variability in clinical practice, making it challenging to compare data across different studies or healthcare settings.[91] A standardized definition would enable clinicians in the GCC countries to assess the severity of bleeding events uniformly, guide treatment decisions, and allow for more meaningful datacomparisons across different healthcare institutions. This standardization could, in turn, lead to more standardized and evidence-based treatment plans for patients experiencing NOAC-associated major bleeding.[92]

In addition, national and institutional guidelines are needed to aid all stakeholders involved in NOAC-associated bleeding management (*Statement 27*). The development of national and institutional guidelines in the GCC countries can provide an evidence-based and standardized approach to managing NOAC-associated bleeding.

The experts also agreed that cross-specialty collaboration can improve communication, decisions, and outcomes of patients with NOAC-associated bleeding (*Statement 28*). The management of NOAC-associated major bleeding is complex and often requires the involvement of multiple healthcare professionals, including emergency physicians, hematologists, intensivists, and pharmacists. In the GCC context, fostering cross-specialty collaboration is essential. Such collaboration can facilitate more effective communication among healthcare professionals, leading to quicker and more informed decision-making. It can also promote a more holistic approach to patient care, considering all aspects of a patient's condition and treatment needs.[93,94]

Conclusions. In conclusion, the use of NOACs continues to rise in the GCC countries, and EDs are anticipated to encounter cases of NOAC-associated major bleeding increasingly. Therefore, it is imperative for the healthcare system to anticipate and prepare for the increased encounters of NOAC-associated major bleeding in the GCC region by adopting local recommendations and guidelines for clinical care pathways and management of NOAC-associated major bleeding. The present Delphi consensus provided evidence-based recommendations and protocols for the management of NOAC-associated bleeding in the region. Patients with major DOAC-induced bleeding should be referred to well-equipped EDs with standardized management protocols. A multidisciplinary approach is recommended for establishing the association between NOAC use and major bleeding. Treating physicians should have rapid access to specific reversal agents to optimize patient outcomes. Real-world evidence and national guidelines are needed to aid all stakeholders involved in NOAC-associated bleeding management.

References:

1. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018;362:k2505. https://doi.org/10.1136/bmj.k2505 PMid:29973392
2. Paul C, Baby M, Anthraper AR, K K. NOACs: an emerging class of oral anticoagulants-a review article. Futur J Pharm Sci 2020 61 [Internet]. 2020 Nov 24 [cited 2022 Dec 4];6(1):1-7. Available from: https://fjps.springeropen.com/articles/10.1186/s43094-020-00114-1 https://doi.org/10.1186/s43094-020-00114-1
3. Laslo CL, Bacalbasa N, Stanescu AMA, Carsote M, Bungau S, Rus M, et al. New oral anticoagulants - possible extension to other indications (Review). Exp Ther Med [Internet]. 2020 Sep 1 [cited 2022 Dec 4];20(3):2401-5. Available from: http://www.spandidos-publications.com/10.3892/etm.2020.8713/abstract
4. Niessner A, Tamargo J, Morais J, Koller L, Wassmann S, Husted SE, et al. Reversal strategies for nonvitamin K antagonist oral anticoagulants: a critical appraisal of available evidence and recommendations for clinical management-a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis. Eur Heart J [Internet]. 2017 Jun 7 [cited 2022 Dec 5];38(22):1710-6. Available from: https://pubmed.ncbi.nlm.nih.gov/26705385/
5. Undas A, Drabik L, Potpara T. Bleeding in anticoagulated patients with atrial fibrillation: Practical considerations. Vol. 130, Polish Archives of Internal Medicine. 2020. p. 47-58. https://doi.org/10.20452/pamw.15136
6. Kawada T. Vitamin K and direct oral anticoagulants in patients with major bleeding: Risk assessment. Vol. 235, International Journal of Cardiology. 2017. p. 199. https://doi.org/10.1016/j.ijcard.2017.01.029 PMid:28342498
7. Deitelzweig SB, Lovelace B, Christoph M, Lingohr-Smith M, Lin J, Fermann GJ. Evaluation of the Incremental Healthcare Economic Burden of Patients with Atrial Fibrillation Treated with Direct-Acting Oral Anticoagulants and Hospitalized for Major Bleeds in the USA. Adv Ther [Internet]. 2020 Sep 1 [cited 2022 Dec 5];37(9):3942-53. Available from: https://pubmed.ncbi.nlm.nih.gov/32699994/ https://doi.org/10.1007/s12325-020-01440-9 PMid:32699994
8. Deitelzweig S, Neuman WR, Lingohr-Smith M, Menges B, Lin J. Incremental economic burden associated with major bleeding among atrial fibrillation patients treated with factor Xa inhibitors. J Med Econ [Internet]. 2017 Dec 2 [cited 2022 Dec 5];20(12):1217-23. Available from: https://pubmed.ncbi.nlm.nih.gov/28760063/ https://doi.org/10.1080/13696998.2017.1362412 PMid:28760063
9. Escobar A, Salem AM, Dickson K, Johnson TN, Burk KJ, Bashoura L, et al. Anticoagulation and bleeding in the cancer patient. Support Care Cancer. 2022;30(10):8547-57. https://doi.org/10.1007/s00520-022-07136-w PMid:35579752 PMCid:PMC9529787
10. Pollack C V., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med [Internet]. 2017 Aug 3 [cited 2023 Jan 23];377(5):431-41. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1707278 https://doi.org/10.1056/NEJMoa1707278 PMid:28693366
11. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2019;380(14):1326-35. https://doi.org/10.1056/NEJMoa1814051 PMid:30730782

12. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020;76(5):594-622. https://doi.org/10.1016/j.jacc.2020.04.053 PMid:32680646
13. Singh B, Pai P, Kumar H, George S, Mahapatra S, Garg V, et al. Expert Recommendations on the Usage of Nonvitamin K Antagonist Oral Anticoagulants (NOACs) from India: Current Perspective and Future Direction. Vol. 11, Cardiology and Therapy. 2022. p. 49-79. https://doi.org/10.1007/s40119-022-00254-w PMid:35137335
14. Al-Shamkhani W, Ayetey H, Lip GYH. Atrial fibrillation in the Middle East: unmapped, underdiagnosed, undertreated. https://doi.org/101080/1477907220181457953 [Internet]. 2018 May 4 [cited 2022 Dec 4];16(5):341-8. Available from: https://www.tandfonline.com/doi/abs/10.1080/14779072.2018.1457953 https://doi.org/10.1080/14779072.2018.1457953 PMid:29575965
15. Aljefree N, Ahmed F. Prevalence of Cardiovascular Disease and Associated Risk Factors among Adult Population in the Gulf Region: A Systematic Review. Adv Public Heal. 2015;2015:1-23. https://doi.org/10.1155/2015/235101
16. Hersi A, Abdul-Moneim M, Almous'ad A, Al-Samadi F, AlFagih A, Sweidan R. Saudi Atrial Fibrillation Survey: national, observational, cross-sectional survey evaluating atrial fibrillation management and the cardiovascular risk profile of patients with atrial fibrillation. Angiology [Internet]. 2015 Mar 1 [cited 2022 Dec 4];66(3):244-8. Available from: https://pubmed.ncbi.nlm.nih.gov/24687415/ https://doi.org/10.1177/0003319714529180 PMid:24687415
17. Kadri M El, Ghorab A, Joury J, Farghaly M, Awad N, Ramachandrachar BC, et al. Patient characteristics, adherence, and costs of oral anticoagulation therapy in non-valvular atrial fibrillation using the Dubai Real-World Claims Database. Avicenna J Med [Internet]. 2021 Apr [cited 2022 Dec 4];11(2):93. Available from: /PMC/articles/PMC8101642/ https://doi.org/10.4103/ajm.ajm_228_20 PMid:33996647
18. Alajami HN, Alshammari SA, Al-Dossari DS, Alajmi AN, Alsaikhan AS, Alessa MS, et al. Knowledge of Anticoagulation Among Saudi Patients With Atrial Fibrillation: A Cross-Sectional Study. Cureus [Internet]. 2021 Nov 3 [cited 2022 Dec 4];13(11). Available from: https://www.cureus.com/articles/75572-knowledge-of-anticoagulation-among-saudi-patients-with-atrial-fibrillation-a-cross-sectional-study https://doi.org/10.7759/cureus.19237
19. AlRuthia Y, AlOtaibi BQ, AlOtaibi RM, AlOtaibi NQ, Alanazi M, Asaad Assiri G. Cost effectiveness of rivaroxaban versus warfarin among nonvalvular atrial fibrillation patients in Saudi Arabia: A Single-Center retrospective cohort study. Saudi Pharm J [Internet]. 2022 Nov 18 [cited 2022 Dec 4]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1319016422002791
20. Al Sulaiman K, Badreldin HA, Korayem GB, Alenazi AA, Alsuwayyid F, Alrashidi A, et al. Evaluation of Apixaban safety and effectiveness in morbidly obese patients with atrial fibrillation: a retrospective cohort study. Thromb J [Internet]. 2022 Dec 1 [cited 2022 Dec 4];20(1):1-9. Available from: https://thrombosisjournal.biomedcentral.com/articles/10.1186/s12959-022-00379-x https://doi.org/10.1186/s12959-022-00379-x PMid:35501916
21. Wright JG, Swiontkowski MF, Heckman JD. Introducing levels of evidence to the journal. Vol. 85, Journal of Bone and Joint Surgery - Series A. 2003. p. 1-3. https://doi.org/10.2106/00004623-200301000-00001
22. Lynn MR. Determination and quantification of content validity. Nurs Res. 1986;35(6):382-6. https://doi.org/10.1097/00006199-198611000-00017 PMid:3640358
23. Bezabhe WM, Bereznicki LR, Radford J, Wimmer BC, Curtain C, Salahudeen MS, et al. Ten-Year Trends in the Use of Oral Anticoagulants in Australian General Practice Patients With Atrial Fibrillation. Front Pharmacol. 2021 Mar 23;12:441. https://doi.org/10.3389/fphar.2021.586370 PMid:33867975
24. Navar AM, Kolkailah AA, Overton R, Shah NP, Rousseau JF, Flaker GC, et al. Trends in Oral Anticoagulant Use Among 436 864 Patients With Atrial Fibrillation in Community Practice, 2011 to 2020. J Am Heart Assoc [Internet]. 2022 Nov 15 [cited 2022 Dec 4];11:26723. Available from: https://www.ahajournals.org/doi/abs/10.1161/JAHA.122.026723 https://doi.org/10.1161/JAHA.122.026723 PMid:36346063
25. Johnston KM, Osenenko KM, Qatami L, Donato BMK, Alsheikh-ali AA, Binbrek AS, et al. Health Care Resource Utilization and Costs in Individuals with Atrial Fibrillation in United Arab Emirates and Kingdom of Saudi Arabia : A Retrospective Cohort Study. Int J Intern Med. 2015;4(2):17-25. https://doi.org/10.1016/j.jval.2014.08.1527 PMid:27201532
26. El Kadri M, Bazargani N, Farghaly M, Mohamed R, Awad N, Natarajan A, et al. Profiling Clinical Characteristics and Treatment Patterns Among Non-Valvular Atrial Fibrillation Patients: A Real-World Analysis in Dubai, United Arab Emirates. Open Med J. 2019 Jun 11;6(1):33-41. https://doi.org/10.2174/1874220301906010033
27. Ali MD, Ahmad A, Banu N, Patel M, Ghosn SA, Eltrafi Z. Anticoagulant drug utilization pattern and their cost analysis: a retrospective study from Saudi Arabia. J Pharm Heal Serv Res [Internet]. 2020 Nov 9 [cited 2022 Dec 4];11(4):411-4. Available from: https://academic.oup.com/jphsr/article/11/4/411/6133277 https://doi.org/10.1111/jphs.12382
28. Elewa H, Alhaddad A, Al-Rawi S, Nounou A, Mahmoud H, Singh R. Trends in oral anticoagulant use in Qatar: a 5-year experience. J Thromb Thrombolysis 2017 433 [Internet]. 2017 Jan 30 [cited 2022 Dec 4];43(3):411-6. Available from: https://link.springer.com/article/10.1007/s11239-017-1474-4 https://doi.org/10.1007/s11239-017-1474-4 PMid:28138812
29. AlAmri A, AlShehri A, AlShammari R, AlAmri R, AlMulhim L, AlGhamdi M. Prevalence of atrial fibrillation among Saudi patients who had stroke: a retrospective cross-sectional study at a university hospital. Int J Med Dev Ctries. 2022;333-9. https://doi.org/10.24911/IJMDC.51-1639698513
30. Zubaid M, Rashed WA, Alsheikh-Ali AA, AlMahmeed W, Shehab A, Sulaiman K, et al. Gulf survey of atrial fibrillation events (Gulf SAFE) design and baseline characteristics of patients with atrial fibrillation in the arab middle East. Circ Cardiovasc Qual Outcomes. 2011;4(4):477-82. https://doi.org/10.1161/CIRCOUTCOMES.110.959700 PMid:21772004
31. Ajlan M, Almazroa L, AlHabib KF, Elasfar AA, Alfaleh H, Albackr H, et al. Atrial Fibrillation in Patients Hospitalized With Heart Failure: Patient Characteristics and Outcomes From the HEARTS Registry. Angiology [Internet]. 2018 Feb 1 [cited 2022 Dec 4];69(2):151-7. Available from: https://pubmed.ncbi.nlm.nih.gov/28592150/ https://doi.org/10.1177/0003319717711764 PMid:28592150
32. Alosaimi HM, Alqahtani S, Balkhi B, Alqahtani M, Alzamil F, Alhossan A, et al. A retrospective study of real-world effectiveness and safety of rivaroxaban in patients with non-valvular atrial fibrillation and venous thromboembolism in Saudi Arabia. PeerJ [Internet]. 2022 Sep 9 [cited 2022 Dec 5];10. Available from: /PMC/articles/PMC9466595/ https://doi.org/10.7717/peerj.13974 PMCid:PMC9466595
33. Riazuddin M, Mpharm MA, Butt MI, Abufarhaneh M, Khan SM, Emadi O, et al. Rivaroxaban Experience at Tertiary Care Centre in Saudi Arabia:A Retrospective Observational Study. Galen Med J [Internet]. 2020 Dec 26 [cited 2022 Dec 5];9:e1882. Available from: /PMC/articles/PMC8343821/ https://doi.org/10.31661/gmj.v9i0.1882 PMCid:PMC8343821
34. Alkhotani A, Alrishi N, Alharthi M, Alzahrani W. Rivaroxaban-associated intracranial hemorrhage in Saudi atrial fibrillation patients. Medicine (Baltimore) [Internet]. 2020 Nov 25 [cited 2022 Dec 5];99(48):e23316. Available from: https://journals.lww.com/md-journal/Fulltext/2020/11250/Rivaroxaban_associated_intracranial_hemorrhage_in.39.aspx https://doi.org/10.1097/MD.0000000000023316 PMCid:PMC7710243
35. Gieling EM, van den Ham HA, van Onzenoort H, Bos J, Kramers C, de Boer A, et al. Risk of major bleeding and stroke associated with the use of vitamin K antagonists, nonvitamin K antagonist oral anticoagulants and aspirin in patients with atrial fibrillation: a cohort study. Br J Clin Pharmacol [Internet]. 2017 [cited 2022 Dec 5];83(8):1844-59. Available from: https://pubmed.ncbi.nlm.nih.gov/28205318/ https://doi.org/10.1111/bcp.13265

36. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis. 2016;41(1):206-32. https://doi.org/10.1007/s11239-015-1310-7 PMCid:PMC4715848
37. Frontera JA, Lewin JJ, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care [Internet]. 2016 Feb 1 [cited 2023 Jan 23];24(1):6-46. Available from: https://pubmed.ncbi.nlm.nih.gov/26714677/ https://doi.org/10.1007/s12028-015-0222-x
38. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. Eur Heart J. 2017;38(27):2137-49. https://doi.org/10.1093/eurheartj/ehw058 PMCid:PMC5837231
39. Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol [Internet]. 2019 Jun 1 [cited 2023 Jan 23];94(6):697-709. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.25475 https://doi.org/10.1002/ajh.25475
40. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. 2019;23(1):98. https://doi.org/10.1186/s13054-019-2347-3 PMCid:PMC6436241
41. Witt DM, Nieuwlaat R, Clark NP, Ansell J, Holbrook A, Skov J, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Optimal management of anticoagulation therapy. Vol. 2, Blood Advances. 2018. p. 3257-91. https://doi.org/10.1182/bloodadvances.2018024893 PMCid:PMC6258922
42. Huwez F, Casswell EJ. FAST-AV or FAST-AB tool improves the sensitivity of FAST screening for detection of posterior circulation strokes. Vol. 8, International Journal of Stroke. 2013. https://doi.org/10.1111/ijs.12008
43. Chen X, Zhao X, Xu F, Guo M, Yang Y, Zhong L, et al. A Systematic Review and Meta-Analysis Comparing FAST and BEFAST in Acute Stroke Patients. Vol. 12, Frontiers in Neurology. 2022. https://doi.org/10.3389/fneur.2021.765069 PMCid:PMC8837419
44. Dager W, Hellwig T. Current knowledge on assessing the effects of and managing bleeding and urgent procedures with direct oral anticoagulants. Am J Heal Pharm. 2016;73(10):S14-26. https://doi.org/10.2146/ajhp150960
45. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: a systematic review. Chest. 2017;151(1):127-38. https://doi.org/10.1016/j.chest.2016.08.1462 PMCid:PMC5310120
46. Lindahl TL, Baghaei F, Blixter IF, Gustafsson KM, Stigendal L, Sten-Linder M, et al. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. Thromb Haemost. 2011;105(2):371-8. https://doi.org/10.1160/TH10-06-0342
47. Tripodi A, Chantarangkul V, Guinet C, Samama MM. The International Normalized Ratio calibrated for rivaroxaban has the potential to normalize prothrombin time results for rivaroxaban-treated patients: Results of an in vitro study. Vol. 9, Journal of Thrombosis and Haemostasis. 2011. p. 226-8. https://doi.org/10.1111/j.1538-7836.2010.04106.x
48. Samama MM, Martinoli JL, LeFlem L, Guinet C, Plu-Bureau G, Depasse F, et al. Assessment of laboratory assays to measure rivaroxaban - An oral, direct factor Xa inhibitor. Thromb Haemost. 2010;103(4):815-25. https://doi.org/10.1160/TH09-03-0176
49. Testa S, Legnani C, Tripodi A, Paoletti O, Pengo V, Abbate R, et al. Poor comparability of coagulation screening test with specific measurement in patients receiving direct oral anticoagulants: results from a multicenter/multiplatform study. J Thromb Haemost. 2016;14(11):2194-201. https://doi.org/10.1111/jth.13486
50. Tripodi A, Ageno W, Ciaccio M, Legnani C, Lippi G, Manotti C, et al. Position paper on laboratory testing for patients on direct oral anticoagulants. A Consensus Document from the SISET, FCSA, SIBioC and SIPMeL. Blood Transfus. 2018;16(5):462-70.
51. Nowak G. The ecarin clotting time, a universal method to quantify direct thrombin inhibitors. Vol. 33, Pathophysiology of Haemostasis and Thrombosis. 2003. p. 173-83. https://doi.org/10.1159/000081505
52. Samama MM, Contant G, Spiro TE, Perzborn E, Guinet C, Gourmelin Y, et al. Evaluation of the anti-factor Xa chromogenic assay for the measurement of rivaroxaban plasma concentrations using calibrators and controls. Thromb Haemost. 2012;107(2):379-87. https://doi.org/10.1160/TH11-06-0391
53. Gosselin RC, Adcock DM, Bates SM, Douxfils J, Favaloro EJ, Gouin-Thibault I, et al. International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. Thromb Haemost. 2018;118(3):437-50. https://doi.org/10.1055/s-0038-1627480
54. Bauer KA. Targeted Anti-Anticoagulants. N Engl J Med. 2015;373(6):569-71. https://doi.org/10.1056/NEJMe1506600
55. Mazahreh F, Habash F, López-Candales A. Venous Thromboembolism While on Anticoagulation With Apixaban. Cureus. 2021; https://doi.org/10.7759/cureus.15189 PMCid:PMC8218250
56. Kaide CG, Gulseth MP. Current Strategies for the Management of Bleeding Associated with Direct Oral Anticoagulants and a Review of Investigational Reversal Agents. J Emerg Med [Internet]. 2020 Feb 1 [cited 2023 Jan 23];58(2):217-33. Available from: https://pubmed.ncbi.nlm.nih.gov/31831187/ https://doi.org/10.1016/j.jemermed.2019.10.011
57. HEUBNER L, VICENT O, BEYER-WESTENDORF J, SPIETH PM. Bleeding management in patients with direct oral anticoagulants. Minerva Anestesiol. 2023;89(7-8). https://doi.org/10.23736/S0375-9393.23.17230-0
58. Baradarian R, Ramdhaney S, Chapalamadugu R, Skoczylas L, Wang K, Rivilis S, et al. Early Intensive Resuscitation of Patients with Upper Gastrointestinal Bleeding Decreases Mortality. Am J Gastroenterol. 2004;99(4):619-22. https://doi.org/10.1111/j.1572-0241.2004.04073.x
59. Spoerke N, Michalek J, Schreiber M. Crystalloid resuscitation improves survival in trauma patients receiving low ratios of fresh frozen plasma to packed red blood cells. Vol. 71, Journal of Trauma - Injury, Infection and Critical Care. 2011. https://doi.org/10.1097/TA.0b013e318227f1c5
60. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Vol. 2013, Cochrane Database of Systematic Reviews. 2013. https://doi.org/10.1002/14651858.CD000567.pub6 PMCid:PMC8925276
61. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR randomized clinical trial. JAMA - J Am Med Assoc. 2015;313(5):471-82. https://doi.org/10.1001/jama.2015.12 PMCid:PMC4374744
62. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. N Engl J Med. 2013;368(1):11-21. https://doi.org/10.1056/NEJMoa1211801
63. Pham HP, Shaz BH. Update on massive transfusion. Br J Anaesth. 2013;111(SUPPL.1). https://doi.org/10.1093/bja/aet376
64. Zhang Y, Souverein PC, Gardarsdottir H, van den Ham HA, Maitland-van der Zee AH, de Boer A. Risk of major bleeding among users of direct oral anticoagulants combined with interacting drugs: A population-based nested case-control study. Br J Clin Pharmacol. 2020;86(6):1150-64. https://doi.org/10.1111/bcp.14227 PMCid:PMC7256117
65. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart R. Vol. 140, Circulation. 2019. p. e125-51. https://doi.org/10.1161/CIR.0000000000000665
66. Janson PA, Jubelirer SJ, Weinstein MJ, Deykin D. Treatment of the Bleeding Tendency in Uremia with Cryoprecipitate. N Engl J Med. 1980;303(23):1318-22. https://doi.org/10.1056/NEJM198012043032302

67. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ. Evidence-based treatment recommendations for uremic bleeding. Vol. 3, Nature Clinical Practice Nephrology. 2007. p. 138-53. https://doi.org/10.1038/ncpneph0421
68. Schiele F, Van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, et al. A specific antidote for dabigatran: functional and structural characterization. Blood [Internet]. 2013 May 2 [cited 2022 Dec 6];121(18):3554-62. Available from: https://pubmed.ncbi.nlm.nih.gov/23476049/ https://doi.org/10.1182/blood-2012-11-468207
69. Pollack C V., Reilly PA, Bernstein R, Dubiel R, Eikelboom J, Glund S, et al. Design and rationale for REVERSE AD: A phase 3 study of idarucizumab, a specific reversal agent for dabigatran. Thromb Haemost. 2015;114(1):198-205. https://doi.org/10.1160/TH15-03-0192
70. Garrett AD. Idarucizumab for dabigatran reversal. Drug Topics [Internet]. 2015 Aug 1 [cited 2022 Dec 6];159(8). Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1502000
71. Idarucizumab receives full FDA approval | MDedge Hematology and Oncology [Internet]. [cited 2022 Dec 6]. Available from: https://www.mdedge.com/hematology-oncology/article/185007/thrombosis/idarucizumab-receives-full-fda-approval
72. Kaatz S, Bhansali H, Gibbs J, Lavender R, Mahan CE, Paje DG. Reversing factor Xa inhibitors - Clinical utility of andexanet alfa [Internet]. Vol. 8, Journal of Blood Medicine. Dove Press; 2017 [cited 2022 Dec 6]. p. 141-9. Available from: https://www.dovepress.com/reversing-factor-xa-inhibitors-clinical-utility-of-andexanet-alfa-peer-reviewed-fulltext-article-JBM https://doi.org/10.2147/JBM.S121550 PMCid:PMC5602457
73. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med [Internet]. 2015 Dec 17 [cited 2022 Dec 6];373(25):2413-24. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1510991 https://doi.org/10.1056/NEJMoa1510991
74. Andexanet Becomes First FDA-Approved Antidote for Factor Xa Inhibitors. 2021.
75. Connolly SJ, Milling TJ, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016;375(12):1131-41. https://doi.org/10.1056/NEJMoa1607887 PMCid:PMC5568772
76. Walenga JM. Can We Improve on the Rapid Assessment of Clinically Relevant Levels of Direct Acting Oral Anticoagulants (DOAC)? Vol. 28, Clinical and Applied Thrombosis/Hemostasis. 2022. https://doi.org/10.1177/10760296221096422 PMCid:PMC9099059
77. Christensen H, Cordonnier C, Kõrv J, Lal A, Ovesen C, Purrucker JC, et al. European Stroke Organisation Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage. Eur Stroke J. 2019;4(4):294-306. https://doi.org/10.1177/2396987319849763 PMCid:PMC6921939
78. Majeed A, Ågren A, Holmström M, Bruzelius M, Chaireti R, Odeberg J, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood [Internet]. 2017 Oct 12 [cited 2023 Jan 23];130(15):1706-12. Available from: https://pubmed.ncbi.nlm.nih.gov/28835439/ https://doi.org/10.1182/blood-2017-05-782060
79. Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L, et al. Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thromb Haemost [Internet]. 2018 May 1 [cited 2023 Jan 23];118(5):842-51. Available from: https://pubmed.ncbi.nlm.nih.gov/29564837/ https://doi.org/10.1055/s-0038-1636541
80. Piran S, Khatib R, Schulman S, Majeed A, Holbrook A, Witt DM, et al. Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: A meta-analysis. Blood Adv. 2019;3(2):158-67. https://doi.org/10.1182/bloodadvances.2018024133 PMCid:PMC6341194
81. Van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate - A novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Vol. 103, Thrombosis and Haemostasis. 2010. p. 1116-27. https://doi.org/10.1160/TH09-11-0758
82. Nielsen PB, Larsen TB, Gorst-Rasmussen A, Skjøth F, Rasmussen LH, Lip GYH. Intracranial hemorrhage and subsequent ischemic stroke in patients with atrial fibrillation: a nationwide cohort study. Chest [Internet]. 2015 Jun 1 [cited 2023 Jan 24];147(6):1651-8. Available from: https://pubmed.ncbi.nlm.nih.gov/25412369/ https://doi.org/10.1378/chest.14-2099
83. Li Y guang, Lip GYH. Anticoagulation Resumption After Intracerebral Hemorrhage. Curr Atheroscler Rep [Internet]. 2018 Jul 1 [cited 2023 Jan 24];20(7). Available from: /PMC/articles/PMC5960649/ https://doi.org/10.1007/s11883-018-0733-y PMCid:PMC5960649
84. Murphy MP, Kuramatsu JB, Leasure A, Falcone GJ, Kamel H, Sansing LH, et al. Cardioembolic Stroke Risk and Recovery after Anticoagulation-Related Intracerebral Hemorrhage. Stroke [Internet]. 2018 [cited 2023 Jan 24];49(11):2652. Available from: /PMC/articles/PMC6211810/ https://doi.org/10.1161/STROKEAHA.118.021799 PMCid:PMC6211810
85. Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke [Internet]. 2015 Jul 4 [cited 2023 Jan 24];46(7):2032-60. Available from: https://pubmed.ncbi.nlm.nih.gov/26022637/ https://doi.org/10.1161/STR.0000000000000069
86. Biffi A, Kuramatsu JB, Leasure A, Kamel H, Kourkoulis C, Schwab K, et al. Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage. Ann Neurol [Internet]. 2017 Nov 1 [cited 2023 Jan 24];82(5):755. Available from: /PMC/articles/PMC5730065/ https://doi.org/10.1002/ana.25079 PMCid:PMC5730065
87. Mujer MTP, Rai MP, Atti V, Dimaandal IL, Chan AS, Shrotriya S, et al. An Update on the Reversal of Nonvitamin K Antagonist Oral Anticoagulants. Adv Hematol [Internet]. 2020 [cited 2023 Jan 24];2020. Available from: /PMC/articles/PMC7097770/ https://doi.org/10.1155/2020/7636104 PMCid:PMC7097770
88. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J [Internet]. 2018 Apr 21 [cited 2023 Jan 24];39(16):1330-93. Available from: https://pubmed.ncbi.nlm.nih.gov/29562325/
89. Liu F, Demosthenes P. Real-world data: a brief review of the methods, applications, challenges and opportunities. Vol. 22, BMC Medical Research Methodology. 2022. https://doi.org/10.1186/s12874-022-01768-6 PMCid:PMC9636688
90. Roberti R, Iannone LF, Palleria C, Curcio A, Rossi M, Sciacqua A, et al. Direct Oral Anticoagulants: From Randomized Clinical Trials to Real-World Clinical Practice. Vol. 12, Frontiers in Pharmacology. 2021. https://doi.org/10.3389/fphar.2021.684638 PMCid:PMC8188985
91. Mehran R, Rao S V, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011 Jun;123(23):2736-47. https://doi.org/10.1161/CIRCULATIONAHA.110.009449
92. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: Communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(11):2119-26. https://doi.org/10.1111/jth.13140
93. Von Heymann C, Rosenthal C, Kaufner L, Sander M. Management of direct oral anticoagulants-associated bleeding in the trauma patient. Curr Opin Anaesthesiol [Internet]. 2016 Mar 23 [cited 2023 Apr 2];29(2):220-8. Available from: https://pubmed.ncbi.nlm.nih.gov/26934279/ https://doi.org/10.1097/ACO.0000000000000294
94. Moia M, Squizzato A. Reversal agents for oral anticoagulant-associated major or life-threatening bleeding. Vol. 14, Internal and Emergency Medicine. 2019. p. 1233-9. https://doi.org/10.1007/s11739-019-02177-2 PMCid:PMC6881427