Review Article

Anticoagulation therapy in Iran

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Abstract: Thromboembolic disorders are among the leading causes of morbidity and mortality in Iran. Anticoagulation therapy of affected patients is achieved using a variety of agents, including vitamin K antagonists (VKAs), heparin, and direct oral anticoagulants (DOACs). Although DOACs have a growing role in the management of thromboembolic complications, warfarin has remained the most widely prescribed anticoagulant in Iran. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are other common anticoagulants prescribed in Iran. LMWH, particularly enoxaparin, is more commonly used than UFH. Among, DOACs, rivaroxaban is the most commonly used anticoagulant in Iran. Dabigatran, as a direct thrombin inhibitor (DTI), is another commonly used DOAC. It seems that in Iran, similar to most other parts of the world, with the advent of the new anticoagulants, the overall pattern of anticoagulation therapy is shifting toward DOACs.

Keywords: Anticoagulation therapy; thrombosis; warfarin; heparin; direct oral anticoagulants

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Introduction

Thrombosis and bleeding are two sides of the double-edged sword of hemostasis. Bleeding disorders are associated with a high rate of morbidity and mortality (1). Management of thrombosis and bleeding has improved significantly in recent years. Advancements in recombinant coagulation factors synthesis have made a breakthrough in the management of the bleeding disorders and has made significant changes in affected patients' life quality (2). On the other side, with the advent of new anticoagulants, prophylaxis, and management of thrombotic events, as a leading cause of morbidity and mortality, has both improved significantly (3,4). Vitamin K antagonists (VKAs) and heparin were, in the recent past, the only available drugs for anticoagulation therapy in thromboembolic disorders (5). Warfarin, the most well-known VKAs, is the commonly used anticoagulants for management of thrombosis and related complications (6). Although warfarin is cheap, and widely available, it has a narrow therapeutic window, several side effects, and requires regular and close laboratory monitoring (7). Heparin, including unfractionated heparin (UFH) and low molecular weight heparin (LMWH), is another commonly used anticoagulant worldwide, but regular monitoring and several potentially severe adverse effects, such as hemorrhage and heparin induced thrombocytopenia

Table 1 Characteristics of anticoagulation therapy in Iran

Type of anticoagulant	Anticoagulant	Clinical indication	Available monitoring tests	Reversal agents
VKA	Warfarin	AF, VTE	PT/INR	Vitamin K, FFP, PCC, rFVII
Heparin	UFH	VTE, AF, DIC	APTT, PLT, anti-FXa assay	Protamine sulfate
	LMWH (enoxaparin)	VTE, ACS	Anti-FXa assay	Protamine sulfate, FFP
DOAC	Rivaroxaban	VTE, HIT, AF	Anti-FXa assay	PCC, rFVII
	Dabigatran	VTE, ACS, AF	APTT, ECT, TT	FFP, PCC
	Apixaban	VTE, AF, HIT	Anti-FXa assay	PCC, rFVII

VKA, vitamin K agonist; UFH, unfractionated heparin; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; PLT, platelet; ECT, ecarin clotting time; TT, thrombin time; DIC, disseminated intravascular coagulation; ACS, acute coronary syndromes; AF, arterial fibrillation; VTE, venous thromboembolism; HIT, heparin induced thrombocytopenia; FFP, fresh frozen plasma; PCC, prothrombin complex; rFVII, recombinant factor VII.

Table 2 Main characteristics of unfractionated heparin and low molecular weight heparin

Anticoagulant	Unfractionated heparin (UFH)	Low molecular weight heparin (LMWH)
Function	AT-III activity > AT-FX_a activity	Anti-FX_a activity > AT-III activity
Indication	CPB,VTE, Thrombus prophylaxis in AF	Prophylaxis of DVT, treatment of DVT and PE, prophylaxis in high risk abdominal surgery, knee replacement, hip replacement, general surgery, neurosurgery, coronary angioplasty, AF, spinal cord injury
Monitoring	APTT; anti-FXa assay	Anti-FXa assay
Alternative monitoring	ACT, CTT, PiCT, HCV, ROTEM, AWBCT, ETP, HT	–

AT-III activity, anti-thrombin III activity; CPB, cardiopulmonary bypass; AF, atrial fibrillation; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; APTT, activated partial thromboplastin time; ACT, activated clotting time; CTT, concentrated thrombin time; PiCT, prothrombinase induced clotting time; HCV, heparin correlation value; AWBCT: activated whole blood clotting time; ETP, endogenous thrombin potential; HT, Howel time; ROTEM, rotational thromboelastometry.

(HIT), are the main disadvantages of such parenterally administered anticoagulants (8). Direct thrombin inhibitors (DTIs) and factor Xa inhibitors (FXIs), known as direct oral anticoagulants (DOACs), have a growing role in the management of thromboembolic disorders (9). In the present study, we report different aspects of anticoagulation therapy in Iran, including the type of anticoagulants which are prescribed, clinical indications, and available laboratory monitoring tests.

Anticoagulation therapy in Iran

Anticoagulant therapy is a common practice in Iran, mostly prescribed by cardiologists, hematologists, oncologists, internists, anesthesiologists, and gynecologists. All types of anticoagulants, including the VKAs (warfarin), heparin (UFH and LMWH), and DOACs are available in Iran. Although with the advent of new anticoagulants, the overall pattern of anticoagulant therapy has changed toward the use of DOACs, VKAs are still the most commonly used anticoagulants in Iran (*Table 1*).

The main reasons for high frequency of warfarin prescription in Iran are low cost, easy laboratory monitoring, good clinical experiences, and the wide availability of reversal agents. Prothrombin time/international normalized ratio (PT/INR) is used for warfarin therapy monitoring. In Iran, UFH is prescribed for various conditions such as management or prophylaxis of venous thromboembolism (VTE), atrial fibrillation (AF), and management of patients with disseminated intravascular coagulation (DIC) (*Table 2*).

Similar to other parts of the world, bleeding is the most common complication of UFH therapy in Iran. Protamine sulfate is used to reverse the anticoagulant effect of UFH. The dose of protamine sulfate is determined based on the

Table 3 Main advantages and disadvantages of unfractionated heparin and low molecular weight heparin

Anticoagulant agent	Unfractionated heparin (UFH)	Low molecular weight heparin (LMWH)
Advantages	Low cost, immediately action, long history of successful clinical use, rapidly reversed by protamine	No monitoring required except in selected cases, subcutaneous administration, lower risk of HIT, decreased platelet activation, lower risk of osteoporosis, longer half-life
Disadvantages	Iv administration, frequent blood tests are used for monitoring, risk of HIT, platelet activation	High cost, risk of bleeding, some risk of HIT, hypoaldosteronism, limited use in patients with renal insufficiency
Antidote	Yes (protamine sulfate)	Yes (protamine sulfate)*

*, less effective in LMWH than UFH. HIT, heparin induced thrombocytopenia; IV, intravenous.

Table 4 Characteristics of available direct oral anticoagulants in Iran

Drug	Commercial names	Function	Drug form	Antagonist	Recommended indication	FDA*
Dabigatran	Pradaxa	FIIa inhibitor	Capsule	Idarucizumab; Aripazine	Prophylaxis or treatment of NVAF, PE and DVT	Approved
Rivaroxaban	Xarelto	FXa inhibitor	Tablet	Andexanet alfa; Aripazine; Andexanet alfa	Prophylaxis or treatment of NVAF, PE , DVT and stroke	Approved
Apixaban	Eliquis	FXa inhibitor	Tablet	Andexanet alfa; Aripazine	Prophylaxis of SE in NVAF	Approved

*, Iran accepts FDA approval as permitted use in Iran. FIIa, activated factor II; FXa, activated factor X; CPB, cardiopulmonary bypass; AF, atrial fibrillation; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary Embolism; NVAF, non-valvular atrial fibrillation; SE, systemic embolism.

administrated dose of UFH. Due to several advantages, including a lower rate of heparin induced thrombocytopenia (HIT) and osteoporosis, and no need for close laboratory monitoring in most patients, LMWH is used more frequently in Iran than UFH (*Table 3*).

Among LMWHs, including enoxaparin, dalteparin, and tinzaparin, enoxaparin is the most commonly used agent in Iran. One of the main advantage of LMWH compared with UFH and VKAs, is a lower requirement for close laboratory monitoring. When required, the anti-factor Xa assay is routinely used for monitoring of enoxaparin therapy in Iran. Although LMWH therapeutic monitoring by anti-factor Xa assay is not usually necessary, it is recommended for selected patients such as those who require higher doses of the drug, overweight patients, and patients with renal failure. The major complication of enoxaparin therapy is bleeding, and protamine sulfate and fresh frozen plasma (FFP) are used to reverse the anticoagulant effect of the drug.

In recent years, due to more awareness of physicians, the use of DOACs is increasing, but the high cost of these drugs and lack of clinical experiences are the main obstacles to the widespread use of them (*Table 4*).

Rivaroxaban is the most widely used FXa inhibitor in Iran, while dabigatran is the most commonly used DTI. In fact, dabigatran is the only used DTI in Iran. Apixaban is the second most common FXa inhibitor prescribed in Iran.

Similar to other anticoagulants, bleeding is the most common complication of DOACs in Iran. There is no specific antidotes for DOACs in Iran, and in emergency situations, FFP, prothrombin complex (PCC), and recombinant factor VII are used to reverse their anticoagulant action (*Table 1*). Hepatic and renal function analysis is performed in regular intervals on Iranian patients under DOACs therapy.

The role of global hemostasis assays for the monitoring of anticoagulation therapy has increased in Iran, and rotational thromboelastometry (ROTEM) is used for monitoring of anticoagulation therapy, particularly in candidate patients for surgery.

Discussion

With the advent of new anticoagulants, management of thromboembolic complications has significantly improved

in recent years (9). Therapeutic options for management of thromboembolic disorders are variable in different countries, mostly due to economic issues (10). Like most countries worldwide, in Iran, as a Middle East country, all types of anticoagulants including VKAs, heparin, and DOACs are available for management of the patients with thromboembolic disorders. Although the use of DOACs has an increasing trend in Iran, warfarin is still the most widely used anticoagulant due to low cost, good clinical experiences, easy laboratory monitoring, and availability and the low cost of warfarin reversal agents. Although an increasing trend in use of DOACs has been reported in other countries like Italy, Finland, and Australia, warfarin remains the most popular anticoagulant worldwide. This popularity is not restricted to developing countries, but includes a considerable number of developed countries like USA, Australia, Italy, and Canada (10-15).

Both types of heparin including, UFH and LMWH are prescribed in Iran. The availability, low cost, easy laboratory monitoring, and good clinical experiences are the reasons for the high prescription of these anticoagulants in this country. LMWH is more commonly used than UFH, in Iran. Antidotes are also available for these anticoagulants in Iran. Similar to Iran, enoxaparin is the most widely used LMWH among US hospitals too. In a study on 224 acute-care hospitals in the USA, it was revealed that enoxaparin is prescribed in more than 80% of hospitals, while dalteparin and tinzaparin were used in 17.3% and 1.6% of hospitals, respectively (16). Based on the efficacy and safety of enoxaparin in different populations, it was revealed that enoxaparin has the widest food and drug administration (FDA) approved indication range. Although the use of DOACs has increased in the recent years, their prescription varies between different countries. For example, in England, it varies from 8% to >60% (17). The use of DOACs, notably rivaroxaban is increasing in recent years in Iran. Although rivaroxaban is the most commonly used DOACs in some countries such as Finland and Slovakia, Chania, and some South-American countries, it is the third most common anticoagulant in the world (10,11,15). Apixaban has been reported as the most common DOACs in North-European and Latin American countries, but is the second most common FXa inhibitor prescribed in Iran (10).

Routine use of DOACs, particularly rivaroxaban, can increase the prescription cost of anticoagulation therapy from 20 to 80 times in Iran. In England, the average cost of warfarin therapy per month is £0.83, while this cost is >£50 for DOACs. In addition, costs of specific antidotes of DOACs are extremely high for clinical use. For example, idarucizumab, as a specific antidote of dabigatran, has a cost of >£2,500 per use (18). Another example is andexanet alfa, an antidote of factor Xa inhibitor, which has a short half-life and high cost (>£1,500) (19). The relative cost for warfarin and heparin antidotes is comparably very low. Specific antidotes of DOACs are not available in Iran, and the physicians have to use alternative choices, including PCC and FFP. For factor Xa inhibitors, 4-factor PCC (4F-PCC) and recombinant activated factor VII are available (20). Further studies are required to confirm the best and most cost-effective approach to anticoagulant reversal. The American College of Cardiology Foundation/American Heart Association recommended FFP and packed red blood cells to control the bleeding in patients under DTI therapy (21). Others recommended hemodialysis to control severe bleeding in patients with renal failure under dabigatran therapy (22).

Further studies reveal that the risk of gastrointestinal bleeding is higher in older patients under DOACs therapy (23). DOACs generate greater risk in patients with renal failure. In such cases, most physicians empirically lower the dose of the drug. In a meta-analysis, it was identified that anti-factor Xa inhibitors may increase the risk of myocardial infarction. In another meta-analysis of randomized controlled trials, it was identified that DOACs are better than warfarin in preventing embolic and hemorrhagic stroke, but gastrointestinal bleeding is higher in patients under DOACs therapy (24). Several studies have also shown a decreased rate of malignancies in patients receiving warfarin therapy, which is an apparent advantage in compared to the newer anticoagulants, especially in the older patients. All of these issues emphasis on a more objective assessment of the current trend towards DOACs as the first-choice of anticoagulant therapy (25).

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