Oral Anticoagulation in Special Population and Conditions

Introduction

Thromboembolic diseases bring about great impact on mortality and are a heavy burden to public health. There are certain groups of population at a high risk of thromboembolic disorders and thus need anticoagulation therapy. These patients are also at a high risk of experiencing side effects (such as teratogenicity and bleeding complications) of anticoagulation therapy. Management of anticoagulant therapy in these patients is thus very crucial. These patient groups include elderly population, pregnant women, cancer patients, and the patients with renal impairment.

Anticoagulant Therapy in Elderly

The main indications of anticoagulation therapy include prophylaxis and treatment of venous thromboembolism (VTE) in medical and surgical settings, atrial fibrillation (AF), and valvular heart disease. Elderly population is at high risk for thromboembolism, as well as haemorrhage. Atrial fibrillation is the most common cardiac arrhythmia observed in elderly population. Anticoagulants are often underutilised in elderly population because of underestimation of the thromboembolic risk, and overestimation of the bleeding risk. Although heparin congeners are effective anticoagulants, vitamin K antagonists (VKAs) are the first choice for long-term anticoagulation therapy.

There are certain issues with the use of anticoagulants in elderly population, which should be addressed to ensure the safety of anticoagulation therapy. Such issues include:

- High risk of bleeding
- Decreased renal function
- Comorbidities
- Risk of falls
- Altered pharmacodynamics and pharmacokinetics of anticoagulants
- Concomitant use of antiplatelet agents

Risk of Bleeding

Bleeding risk depends largely on the intensity of anticoagulation and patient’s intrinsic characteristics. Patients with international normalised ratio (INR) > 3.0 are at a higher risk of major bleeding complications, than those with INR maintained between 2.0 and 3.0. Oral anticoagulation (OAC), if well controlled, is safer and does not impose high risk of major bleeding.

Decreased Renal Function

Renal function is known to decrease with age. Heparin congeners and other direct coagulation factor inhibitors (such as fondaparinux, dabigatran, and rivaroxaban) are eliminated largely through urine. Thus, the assessment of renal function before prescribing these anticoagulants is suggested, so that accumulation can be avoided. Anti-factor Xa monitoring should be conducted periodically.

Comorbidities

Comorbidities such as hypertension, cerebrovascular diseases, ischaemic stroke, serious heart disease, diabetes, alcoholism, and liver disease predispose to bleeding complications.

Risk of Fall

Patients with AF, who are at high risk of falls, are at an increased risk of intracranial bleeding. Such patients are at higher risk of ischaemic stroke associated with AF, and thus benefit from anticoagulation therapy.

Altered Pharmacokinetics and Pharmacodynamics

Drug interactions are often observed in elderly population, because of concomitant medications for comorbidities, and frequent changes due to acute illnesses. An increased pharmacodynamics of VKAs may also be observed in elderly population due to several factors such as decreased synthesis of clotting factors.
in liver disease, less intake of dietary vitamin K, decreased intestinal production of vitamin K, concomitant use of interacting drugs such as aspirin, and hypermetabolic states such as fever. A low-dose regimen of VKAs has been recommended in elderly population.

Concomitant use of antiplatelet agents: Elderly patients with AF associated with ischaemic heart disease are often prescribed antiplatelet agents as well as anticoagulants. The risk of bleeding with such a combination is substantial.

The extent of renal impairment largely affects the choice of anticoagulants in elderly population. Vitamin K antagonists are metabolised in the liver while other anticoagulants depend on renal excretion. Thus, VKAs do not require dosage adjustments in renal impairment patients, and offer convenience in elderly population.

In a study conducted in the outpatients in a rural community, patients with VTE were treated with acenocoumarol for > 6 months. The study noted no thromboembolic event recurrence of death. However, there was about 3% incidence of major bleeding events in a 13-month follow-up. Majority of the included patients were elderly, who are considered to be at high risk of bleeding. The other risk factors that predispose to risk of bleeding, such as cancer, chronic renal failure, were minimal in the study population. Thus, for the treatment of VTE, anticoagulation with acenocoumarol may be safely prolonged for 6 months.

Novel anticoagulants such as dabigatran depend largely on renal excretion for their elimination. Renal impairment is common in elderly population, which predisposes them to accumulate such anticoagulants and thus develops overcoagulation. Dosage adjustments are thus necessary. The information regarding recommended dosage regimen of the novel anticoagulants, on the basis of levels of renal function, has been provided in ‘Renal Impairment’ section. Also, dabigatran is contraindicated in patients with active pathological bleeding and mechanical prosthetic heart valves. A lower dose of dabigatran (110 mg) has been approved in the European Union, Canada, Japan and Australia, to be used in elderly population.

### Anticoagulant Therapy in Pregnancy

Haemostatic changes during pregnancy, along with increased concentration of coagulation factors, coupled with decreased fibrinolysis, result in hypercoagulability, and hence increased risk of thromboembolic disorders. Anticoagulation is recommended in patients with paroxysmal, or permanent AF, left atrial thrombosis, or prior embolism. Women with moderate-to-severe mitral stenosis and spontaneous echocardiographic contrast in the left atrium, large left atrium, or congestive heart failure should also be prescribed anticoagulation therapy.

Congenital heart disease, pulmonary hypertension and other disorders predispose to maternal, and the offspring risk. Anticoagulation treatment should be considered in such patients. The recommendations for the management of congenital heart disease during pregnancy are summarised in Table 1.

The management of valvular heart disease is often challenging during pregnancy due to adverse maternal and foetal outcomes. Some of the key factors which can optimise the pregnancy outcomes include accurate diagnosis of the severity and aetiology of valve disease and preconception evaluation and counselling. Also, patients who are at the highest risk should be referred to the centres expertised in the management of such conditions. The recommendations for the management of valvular heart disease are summarised in Table 2.

Patients with valvular atrial fibrillation are at a high-risk of thromboembolic disease. Use of oral anticoagulants throughout pregnancy is reported to be beneficial. Immediate anticoagulation with unfractionated heparin (UFH), followed by low-molecular-weight heparin (LMWH) in the first and last trimester, and oral anticoagulants or LMWH during the second trimester is recommended. In mothers with a lower incidence of valve thrombosis, coumarin derivatives are reported to be relatively safer than unfractionated heparin (UFH) and LMWH.

Although teratogenic, the risk of embryopathy is probably lower with VKAs when used at a dose < 5 mg (for warfarin) daily. However, no definite conclusions can be drawn. Similarly, acenocoumarol at a dose < 2.0 mg may be considered safe in such population. The risk of embryopathy with coumarin derivatives can be eliminated by substituting coumarin derivatives with UFH or LMWH from the 6-12th week of pregnancy.

A case study reported that use of acenocoumarol throughout the second and third trimester in a pregnant woman with a mechanical heart valve caused no embryopathy in the newborn. Use of VKAs, such as acenocoumarol, is considered to be safe in breastfeeding mothers, as it is not secreted in the milk in active form. Postpartum anticoagulation with VKAs (for 4-6 weeks; with a target INR of 2.0-3.0) is recommended by some of the treatment guidelines.

There are no adequate and well-controlled studies in pregnant women for the use of new oral anticoagulants (NOACs) (Pregnancy Category C-dabigatran, Category C-Rivaroxaban, Category B-Apixaban). New oral anticoagulants may only be used if the potential benefit justifies the potential risk
to the mother and foetus. There is a need for reporting on new oral anticoagulation use in pregnancy to provide more information about the safety and risks to the foetus in utero.\textsuperscript{19}

\textbf{Cancer}

Malignancy is a major predisposing factor for the development and recurrence of VTE.\textsuperscript{20} Clinically manifested VTE has been reported in approximately 15\% of cancer patients. The risk varies with the type of cancer, stage of cancer, chemotherapy, surgical intervention, and generalised debility. In addition to the altered coagulation mechanisms, two extrinsic causes of hypercoagulability are cancer surgery and chemotherapy.\textsuperscript{21} Approximately, 60\% of cancer patients undergo surgery for one or another purpose. The risk of VTE increases to about 6.7-fold in patients receiving chemotherapy, such as cisplatin, etoposide, medroxyprogesterone, and tamoxifen.\textsuperscript{20} While on anticoagulant therapy, cancer patients with VTE are at 2-fold higher risk of recurrence than noncancer patients. Longer hospitalisation, difficulty in maintenance of anticoagulation, and poor prognosis intensify the challenge. For these reasons, cancer patients are considered to be at high risk for VTE complications and need more intense anticoagulation monitoring.\textsuperscript{22}

A population-based observational cohort study was conducted to assess the impact of long-term VKA use on the development of newly-diagnosed malignancies, and on cancer-related and overall mortality. The study included 89,787 individuals; VKA exposure was assessed on the basis of anatomical therapeutic chemical (ATC) codes on the drug prescription. It was noted that the patients in the VKA-exposed group were significantly older (76.4 ± 6.8 years vs 74.8 ± 7.2 years) and followed up for a longer duration (9.1 ± 2.4 years vs 8.8 ± 2.6 years). Further, the number of females was higher than males in both the groups (VKA-exposed: 50.4\% and control group: 59.9\%). After adjustments were done for age and sex, it was noted that patients exposed to VKA had lower incidence of cancer (hazard ratio 0.88, p < 0.015). Further, the incidence of prostate cancer was significantly reduced (hazard ratio 0.69, p = 0.008) among the specific tumours.\textsuperscript{23}

The study results support the hypothesis that long-term treatment with VKAs has a protective effect on the development of cancer, especially prostate cancer in elderly patients. The mechanism of this anticaner effect is proposed to involve thrombin in relation to protease-activated receptors GAS6 and AXL. This GAS6/AXL axis is believed to regulate the invasion, proliferation, and survival of prostate cancer. Animal studies supporting this hypothesis have been conducted. The hypothesis has been positively demonstrated in human studies though less number of events raises a concern about the validity of such studies. With the finding that VKAs exhibit reduced risk of cancer after years of exposure, it has been suggested that the protective effect of VKAs is exhibited at the stage of tumour initiation or promotion rather than an effect on established tumour.\textsuperscript{23}

A study conducted in cancer patients analysed the efficacy and safety of early and short-term thromboprophylaxis with acenocoumarol and dalteparin in the prevention of non-occlusive and occlusive central vein catheter-related thrombosis.
**Table 2 : Recommendations for the management of valvular heart disease during pregnancy**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral stenosis</strong></td>
<td></td>
<td></td>
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<tr>
<td>In patients with symptoms of pulmonary hypertension, restricted activities and β-selective blockers are recommended.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics are recommended when congestive symptoms persist despite β-blockers.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Patients with severe MS should undergo intervention before pregnancy.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Therapeutic anticoagulation is recommended in the case of atrial fibrillation, left atrial thrombosis, or prior embolism.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Percutaneous mitral commissurotomy should be considered in pregnant patients with severe symptoms or systolic pulmonary artery pressure &gt; 50 mmHg despite medical therapy.</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td><strong>Aortic stenosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with severe AS should undergo intervention pre-pregnancy if:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• they are symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• or LV dysfunction (LVEF &lt; 50%) is present</td>
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<td></td>
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<tr>
<td>Asymptomatic patients with severe AS should undergo intervention pre-pregnancy when they develop symptoms during exercise testing.</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td><strong>Regurgitant lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with severe mitral regurgitation and symptoms of impaired ventricular function or ventricular dilatation should be treated surgically pre-pregnancy.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Medical therapy is recommended in pregnant women with regurgitant, lesion when symptoms occur.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><strong>Mechanical valves</strong></td>
<td></td>
<td></td>
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<tr>
<td>OACs are recommended during the second and third trimesters until the 36th week.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Change of anticoagulation regimen during pregnancy should be implemented in hospital.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>If delivery starts while on OACs, caesarean delivery is indicated.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>OAC should be discontinued and dose-adjusted UFH (a PTT &gt; 2× control) or adjusted-dose LMWH (target anti-Xa level 4–6 hours before planned delivery and restarted 4–6 hours after delivery if there are no bleeding complications.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Immediate echocardiography is indicated in women with mechanical valves presenting with dyspnoea and/or an embolic event.</td>
<td></td>
<td></td>
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<tr>
<td>Continuation of OACs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is &lt; 5 mg/day (or phenprocoumon &lt; 3 mg/day or acenocoumarol &lt; 2 mg/day), after patient information and consent.</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>Discontinuation of OAC between weeks 6 and 12 and replacement by adjusted-dose UFH (a PTT ≥ 2× control in high risk patients applied as intravenous infusion) or LMWH twice daily (with dose adjustment according to weight and target and-Xa level 4–6 hours post-dose 0.8–1.2 U/mL) should be considered in patients with a warfarin dose required of &gt;5 mg/day (or phenprocoumon &gt; 3 mg/day or acenocoumarol &gt; 2 mg/day).</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>Discontinuation of OACs between weeks 6 and 12 and replacement by UFH or LMWH under strict dose control (as described above) may be considered on an individual basis in patients with warfarin dose required for therapeutic anticoagulation &gt;5 mg/day (or phenprocoumon &lt; 3 mg/day or acenocoumarol &gt; 2 mg/day).</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>Continuation of OACs may be considered between weeks 6 and 12 in patients with a warfarin dose required for therapeutic anticoagulation &gt; 5 mg/day (or phenprocoumon &gt; 3 mg/day or acenocoumarol &gt; 2 mg/day).</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>LMWH should be avoided, unless anti-Xa levels are monitored.</td>
<td></td>
<td>III</td>
</tr>
</tbody>
</table>

*aClass of recommendation. bLevel of evidence.*

aPtt: activated partial thromboplastin time; As: aortic stenosis; LMWH: low-molecular-weight heparin; LVEF: left ventricular ejection fraction; MS: mitral stenosis; OACs: oral anticoagulants; UFH: unfractionated heparin

The study reported that acenocoumarol was better than dalteparin in the prevention of CVCRT. 24

It has been recommended that in cancer patients, LMWH should be initiated and continued for the first 3-6 months, followed by either LMWH or VKA up to indefinite duration or until the cancer is treated. 25

### Renal Impairment

Dosing and monitoring of anticoagulants are especially important considerations in patients with renal insufficiency. 21 Pharmacokinetic studies have shown that anti-Xa activity is prolonged in patients with severe renal impairment (creatinine clearance < 30 ml/min) and, to a lesser extent, in patients with moderate dysfunction (30-50 ml/minute). Drug clearance may be reduced by about 40% in patients with severe renal impairment. Clinicians have raised concerns about bleeding complications in patients with kidney failure. 26

The prevalence of AF is reported to be higher in patients with renal impairment. Also, the risk of AF development increases with worsening of renal function. In patients with mild-to-moderate chronic kidney disease (CKD) and AF, use of VKA is shown to reduce ischaemic complications without significant bleeding risk. 27

As VKAs are metabolised in the liver, no dosage adjustments are required in patients with chronic renal impairment. However, a careful monitoring of therapy is recommended. Contrary to VKAs, heparin congeners as well as newer anticoagulants depend largely on renal excretion. Thus, the patients with renal impairment are at risk of accumulation and hence
over anticoagulation therefore dosage adjustments are necessary. All NOACs require dose reductions depending on renal function. In January 2012, in response to the reports of bleeding episodes, the Food and Drug Administration (FDA) revised the label of dabigatran to include detailed information about assessment of renal function and dosage adjustments to be done in patients with renal impairment. The dosage adjustments of newer OACs are summarised in Table 3.

While no dosage adjustments are required with VKAs, the doses of newer anticoagulants need to be reduced to prevent their accumulation and hence adverse events. Apart from increase in bleeding episodes with overdose, dabigatran overdose is associated with gastrointestinal symptoms. Further, their levels need to be monitored at regular intervals to avoid overcoagulation. This is particularly important in the elderly population. Clinicians have to assess the renal function before prescribing newer anticoagulants.

Vitamin K anticoagulants thus offer convenience in patients with renal impairment.

**Usage Protocol of Anticoagulation in Patients Undergoing Major and Minor Surgeries**

Very often, the patients presenting for elective surgical procedures have co-morbid conditions for which anticoagulants have been prescribed. The risk of procedure-associated bleeding depends on the organ, pathology, and surgical methodology. Antithrombotic medications may affect the risk of bleeding, where patients undergoing major/minor, cardiac/noncardiac surgeries need adjustments in their anticoagulation regimens, according to the risk of thromboembolism and the risk of bleeding (Table 4). A risk-benefit evaluation of antithrombotic drugs to assess the likelihood of operation-associated bleeding with/without antithrombotic use, and morbidity or mortality linked with this complication is suggested.

**Different strategies for management of anticoagulation have been suggested, including:**
- Discontinuation of OAC until INR is normal, without heparin replacement;
- Discontinuation of OAC until INR is normal, with heparin replacement as soon as the INR is < 2.0;
- Lowering the intensity of anticoagulation while OAC is maintained;
- Continuing a therapeutic level of anticoagulation.

Several factors influence the time interval before surgery for which anticoagulants need to be discontinued, such as half-life of the OAC used, the actual INR, the desired INR for the specific procedure, and the individual vitamin K pool. The American College of Cardiologists (ACC)/American Heart Association (AHA), and the British Society of Haematology suggest discontinuing VKAs 72 hours before routine noncardiac surgical procedures. Close monitoring of INR is suggested since the INR levels may vary greatly among different patients.

**Dental Surgery**

Dental surgery is one of the procedures with the lowest risk for thromboembolic complications. As such, dental surgical procedures do not require major changes in the anticoagulation intensity. The safest approach in dental surgery is to continue anticoagulation to maintain INR in the range of 2.0-2.5.

**Interventional Cardiac Procedures**

For left heart catheterisation by the brachial route, the INR should be < 2.5, radial route INR < 2 and by the femoral route it should be < 1.8.

**Minor Surgeries**

Minor surgical procedures can be performed with INR < 2 and OAC can be resumed on the day of surgery. Studies have reported that discontinuing OAC before cataract extractions and other ocularplastic

**Table 3: Dosage Adjustments of Anticoagulants in Patients with Renal Impairment**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Recommended dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td>CrCl: &gt; 30 ml/minute</td>
<td>150 mg b.d.</td>
</tr>
<tr>
<td>CrCl: 15–30 ml/minute</td>
<td>75 mg b.d.</td>
</tr>
<tr>
<td>CrCl &lt; 15 ml/minute</td>
<td>Avoid</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>CrCl: &gt;50 ml/minute</td>
<td>20 mg q.d.</td>
</tr>
<tr>
<td>CrCl: 30–50 ml/minute</td>
<td>15 mg q.d.</td>
</tr>
<tr>
<td>CrCl: &lt; 30 ml/minute</td>
<td>Avoid</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
</tr>
<tr>
<td>Mild-to-moderate renal impairment</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>CrCl: &gt; 15 ml/minute</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td></td>
</tr>
<tr>
<td>CrCl: &lt; 30 ml/minute</td>
<td>Dosage adjustment to anti-Xa range 0.5–1.5 IU/ml</td>
</tr>
<tr>
<td>Dalteparin</td>
<td></td>
</tr>
<tr>
<td>CrCl: &gt; 30 ml/minute</td>
<td>Dosage adjustment to anti-Xa range 0.5–1.5 IU/ml</td>
</tr>
</tbody>
</table>

CrCl: creatinine clearance.
surgical procedures is not necessary, provided the INR is not above the therapeutic range. In such cases anticoagulation needs to be maintained with heparin. Heparin should be started when the INR is < 2.5 in high-risk patients (such as those with mitral mechanical valves) and < 2.0 in patients with aortic mechanical valves. Heparin should be continued until 6 hours before surgery and resumed 6-12 hours after surgery, when surgically feasible. It should be continued until INR is > 2. Oral anticoagulation can be resumed 1-2 days after surgery.

**Major Surgeries**

Major surgical procedures require lowering of the INR to < 1.5. In such cases anticoagulation needs to be maintained with heparin. Heparin should be started when the INR is < 2.5 in high-risk patients (such as those with mitral mechanical valves) and < 2.0 in patients with aortic mechanical valves. Heparin should be continued until 6 hours before surgery and resumed 6-12 hours after surgery, when surgically feasible. It should be continued until INR is > 2. Oral anticoagulation can be resumed 1-2 days after surgery.

**Postprocedural Anticoagulation**

Patients with coronary artery bypass grafting (CABG) are at associated with high risk of AF and postoperative stroke. Thus, anticoagulation with VKA is indicated for 4 weeks. Among the patients who had a recent myocardial infarction (MI), left ventricular (LV) mural thrombus and are at risk of stroke after CABG, long-term (3-6 months) anticoagulation is probably indicated for the patient with recent anteroapical infarct and persistent wall-motion abnormality.

Optimal thromboprophylaxis following bioprosthetic aortic valve replacement (AVR) remains controversial. Despite the overall lower thrombogenic state of bioprostheses, there remains an increased risk of thromboembolic events in the first 3 months following surgery. The ACC/AHA, the European Society of Cardiology (ESC), and the American College of Chest
**Conclusion**

Elderly population is at high risk of thromboembolism as well as risk of bleeding. Comorbidities and concomitant medications make the use of anticoagulants difficult. Vitamin K antagonists play an important role in OAC, as no dosage adjustment is required in renal impairment, which is common in elderly.

Pregnancy predisposes to the risk of developing thromboembolism with the raised concentration of clotting factors and other stimuli. Anticoagulants are required in valvular heart disease, congenital heart disease, AF, and certain other disorders. Vitamin K antagonists at low dose are considered safe during pregnancy. Use of VKA such as acenocoumarol is considered to be safe in breastfeeding mothers, as it is minimally secreted into the breast milk.

The risk of thromboembolism is higher in cancer patients. In addition to malignancy, the chemotherapy and surgery further increase the risk of VTE. Long-term VKA use has a protective role toward the development of cancer, particularly prostate cancer. In cancer patients, LMWH should be initiated and continued for the first 3-6 months, followed by either LMWH or VKA up to indefinite duration or until the cancer is treated.

Patients with renal impairment tend to accumulate the anticoagulants excreted through kidneys. Such patients are thus at an increased risk of bleeding. Dosage adjustment of novel anticoagulants is necessary in such conditions. As VKAs are metabolised in the liver and do not depend on renal excretion, these can be used conveniently in patients with renal impairment, without any dosage modifications. Vitamin K antagonists are shown to reduce ischaemic complications in CKD patients without significant bleeding risk.

**References**

3. Grand’Maison A, Charest AF, Geerts WH. Anticoagulant use in patients...


