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The Role of Anticoagulant Therapy During Prostate Biopsy

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1. Introduction

Since the advent of PSA (prostate specific antigen) in the early 1980s there has been a dramatic increase in the diagnosis of prostate cancer and transrectal ultrasound-guided biopsy (TRUS) has emerged as one of the most frequently performed urological procedures. The most common complications are haemorrhagic. Haematuria (12.5 to 80%), haematospermia (5.1 to 89%), and rectal bleeding (1.3 to 58.6%) have been reported to occur [1-3]. However, these bleeding symptoms generally resolve without treatment. Factors other than biopsy can influence the bleeding complication rate like anticoagulant medication and some medical conditions.

Older patients constitute the main target group for prostate cancer screening and subsequently undergo prostate biopsy. At the same time cardiovascular disease most commonly affects the elderly who require low dose acetylsalicylic acid (ASA, 75 mg, once daily), clopidogrel or warfarin as the mainstay of primary and secondary prophylaxis for coronary and peripheral vascular disease. The optimal management of patients who receive low doses (up to 100 mg) of acetylsalicylic acid (ASA) / clopidogrel / warfarin and who are scheduled to undergo prostatic biopsy is still controversial. The approaches being implemented in every day clinical practice vary and include discontinuation of anticoagulation therapy, replacement with low-molecular weight heparin and continuing ASA during peri-procedural period.

Little evidence is available and standardized comprehensive guidelines have not been developed to determine how to manage antiplatelet therapy or warfarin in surgical patients.

2. Literature review

To our knowledge there has not been a comprehensive review of this topic for evaluating haemostatic status before interventions. Here we shall provide a summation of literature regarding the patients coagulation status, detail patient conditions that can affect coagulation, and review common medications used to modify the haemostatic system to prevent complications.

2.1 Antiplatelet medication – ASA (acetylsalicylic acid, aspirin)

The mechanism of aspirin's antiplatelet action was first described in 1971 by the British pharmacologist John Vane. It inhibits the enzyme cyclooxygenase (COX), thereby

preventing the production of prostaglandins. Subsequently, researchers identified two COX isoenzymes, COX-1, and COX-2. Cyclooxygenase is required for prostaglandin and thromboxane synthesis. Prostaglandins produced by COX-2 primarily trigger pain and inflammation, while those produced by COX-1 perform maintenance functions such as promoting normal platelet activity.

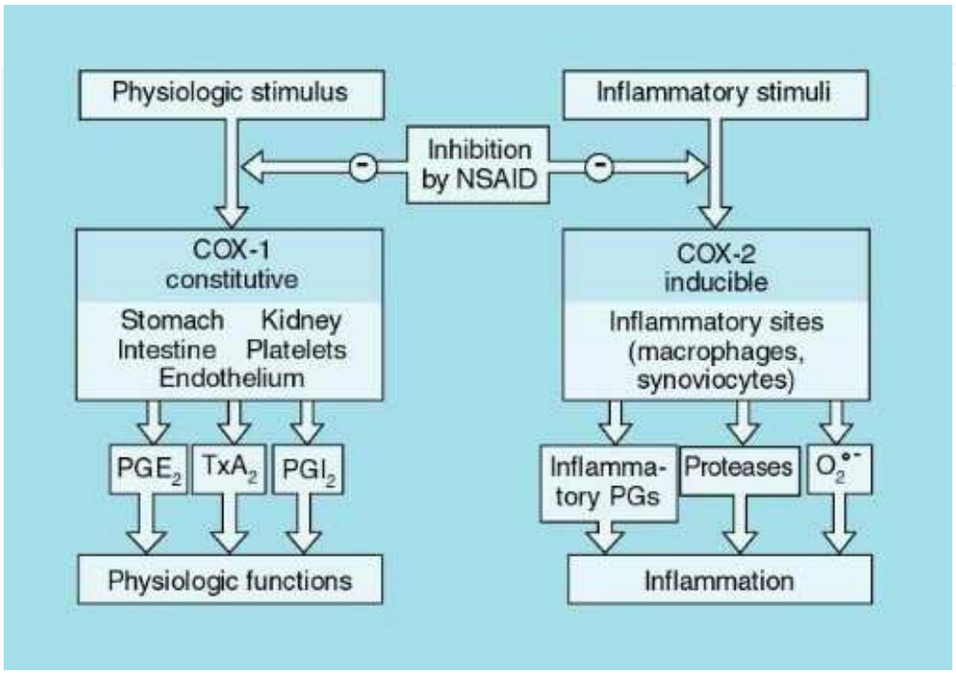


Fig. 1. Showing action of COX-1 and COX-2 enzyme - the products of COX-1 tend to have so-called housekeeping functions. This enzyme is constitutively present in cells. In contrast, the COX-2 enzyme is induced in cells in response to inflammatory stimuli. The products of both enzymes tend to cause inflammation.

In platelets, the COX-1 enzyme produces thromboxane A_2, which causes platelets to aggregate. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the COX enzyme. Aspirin, by inhibiting the COX-1 enzyme and therefore the production of thromboxane A_2, derives a potential antiplatelet effect which lasts for the life of the platelet (7-10 days). Because platelets do not have a nucleus and therefore contain no DNA, no new cyclo-oxygenase can be produced, so the effect of aspirin on platelets persists until enough new platelets have been formed to replace affected ones. This takes approximately seven to ten days, i.e. the lifespan of a platelet as we mentioned earlier. Therefore, the risk of increased bleeding, caused by aspirin, persists for some days after aspirin treatment has been stopped. COX-1 catalyzes the synthesis of thromboxane A_2 (Tx-A_2), which causes platelet activation, vasoconstriction, and smooth muscle proliferation. Tx-A_2 levels are elevated in conditions associated with platelet activation, including unstable angina and cerebral ischemia. Conversely, COX-2 controls the synthesis of prostacyclin (PGI_2), a local platelet regulator with an effect opposite to that of Tx-A_2. PGI_2 is produced as a compensatory response to increases in Tx-A_2 during ischemic events.

Aspirin at low doses selectively inhibits the formation of Tx-A_2 without inhibiting the basal biosynthesis of cardioprotective PGI_2. This effect is irreversible because platelets are

enucleate and, thus, unable to resynthesize COX-1. This makes aspirin different from other NSAIDs (such as diclofenac and ibuprofen), which are reversible.

2.1.1 Mechanism of action of aspirin (C9H8O4)

Aspirin is rapidly absorbed in the stomach and upper small intestine, primarily by passive diffusion of nondissociated acetylsalicylic acid across gastrointestinal membranes. It takes 30-40 minutes to reach plasma peak level for an uncoated aspirin whereas three to four hours for enteric coated formulations. Aspirin first comes into contact with platelets in the portal circulation, and as a consequence, platelets are exposed to substantially higher drug level than are present in the systemic circulation. Aspirin has a half life of 15-20 minutes in the plasma. Despite rapid clearance of aspirin from the circulation, its antiplatelet effect lasts for the life of platelet owing to the permanent inactivation of a key platelet enzyme, an effect that can only be reversed through the generation of new platelets. Thus there is a complete dissociation between pharmacokinetics and pharmacodynamics of aspirin, allowing the use of a once-a-day regimen for antiplatelet therapy despite the very short half-life of the drug.

By diffusing through the cell membranes, aspirin enters the COX channel, a narrow hydrophobic channel connecting the cell membrane to the catalytic pocket of the enzyme. Aspirin first binds to an arginine-120 residue, a common docking site for all non-steroidal anti-inflammatory drugs. It then acetylates a serine residue (serine 529 in human COX-1 and serine 516 in human COX-2) located in the narrowest section of the channel, thereby preventing arachidonic acid from gaining access to the COX catalytic site of the enzyme [4]. This is an esterification reaction, so the linkage that is formed is covalent. It means that the inhibition is irreversible.

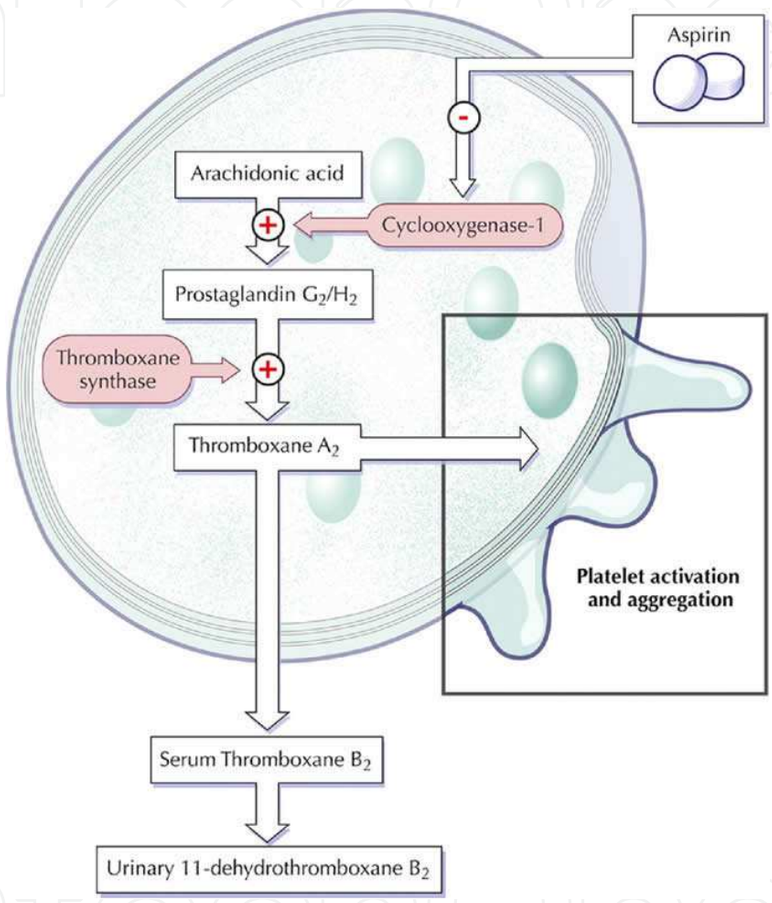
Higher levels of aspirin are needed to inhibit COX-2 than to inhibit COX-1 [5] These differences may account, at least in part, for the need to use considerably higher dose of aspirin to achieve analgesic and anti-inflammatory effects, whereas antiplatelet effects can be obtained with daily doses as low as 30 mg [6].

$$\text{Protein-Serine-}CH_2\text{-OH} + \text{Aspirin} \rightarrow \text{Protein-Serine-}CH_2\text{-O-CO-}CH_3$$

Antiplatelet agents are principally aspirin and clopidogrel, used alone or in combination – have been shown to reduce the formation of fibrin clots by irreversibly inhibiting platelet. Patients who have cardiovascular events like myocardial infarction (MI), ischaemic heart disease, stroke, and unstable angina, non-ST-elevation (NSTE)-acute coronary symdromes (ACS) and ST-elevation MI (STEMI), take aspirin for secondary prevention – that is, to prevent a recurrence. Aspirin also often prescribed for primary prevention, that is, to prevent cardiovascular events in patients with risk factors and is recommended as life-long therapy. Clopidogrel is recommended for periods ranging from 1 to 12 months or as life-long substitute for aspirin in patients in whom aspirin is contraindicated. We shall discuss clopidogrel later in the article. As a result, antiplatelet agents have become essential components of the treatment of these conditions.

The exact time to stop or discontinue antiplatetet therapy prior to surgery or invasive procedure is still controversial. Discontinuation of antiplatelet agents results in recovery of platelet function which contributes to the occurrence of ischaemic events. Unfortunately, neither good evidence from clinical trials nor authoritative guidelines are available to guide physicians faced with this dilemma.

A meta-analysis determined that patients taking aspirin had twice the risk of moderate to severe post-operative complications, although this increase translated only to an increased absolute risk of 2% (1). Most of the centres in the UK recommend discontinuation of aspirin for 7 days prior to the scheduled prostate biopsy. Zhu et al [7] from Denmark also recommended stopping aspirin 1 week prior to all invasive urological procedures. However, there are some published data suggest that aspirin in standard doses do not increase the risk of significant bleeding after prostate biopsy (Table 1 and 2).



Source: Gasparyan, A. Y. et al. J Am Coll Cardiol 2008;51:1829-1843

Fig. 2. Aspirin inhibition of COX-1 decreases TXA2 production.

In all of the above studies, regarding haemorrhagic complication rates, there were no statistically significant differences between the two groups. Haematuria, rectal bleeding and haemospermia rates between the groups were also comparable. No severe bleeding complications occurred. Some studies showed that an increasing number of cores might increase haemorrhagic events, but it does not affect the duration of bleeding [2,3]. Interestingly, one study showed [9] that aspirin users were significantly older than non-users and haematuria became less likely with increasing age.

There is no guideline on the management of aspirin before taking prostate biopsy. A National Survey performed by Masood et al [12] showed, that only 44% of urology departments have protocols in place relating to aspirin use before prostate biopsy. Of those who replied 65% do

not routinely stop aspirin before biopsy. 35% stop aspirin and of these, 52% 1 week before, 41% 2 weeks and 6% >2 weeks before the biopsy. A third of the urologists felt that aspirin increases bleeding complications and 59% stated that the cerebrovascular risks of stopping aspirin outweigh the benefit of stopping aspirin for bleeding.

	Kariotis I et al 2010 [8]	Halliwell OT et al 2008 [9]	Giannarini G et al 2007 [10]	Maan Z 2003 [11]
Study Design	Prospective Questionnaire	Prospective Questionnaire	Prospective Randomized Questionnaire	Prospective cohort Questionnaires
Study Period	Feb 2007 to Sept 2008	2 year	Jan 2005 to Aug 2006	NA
Number of patients/ accessible	530/434	1520/1512	200/196	200/177
aspirin group / non-aspirin /heparin group	152/282/NA	387/1125/NA	67/66/67	36/141/
Number of Biopsy taken	12 cores	NA	10 cores	6 cores
Biopsy needle	18G	NA	18 G	18G
Evaluation time (Questionnaire)	30 day from the date of biopsy	10-14 day from the date of biopsy	14 day post-biopsy	7 day post-biopsy

ASA – acetylsalicylic acid, NA – Not Available

Table 1.

Haemorrhagic Events	Kariotis I et al 2010		Halliwell OT et al 2008		Giannarini G et al 2007			Maan Z 2003	
	ASA	NASA	ASA	NASA	ASA	Hep	NASA	ASA	NASA
Haematuria	64.5%	60.65	72%	61%	78.5%	69.7%	81.5%	56%	59%
Duration of haematuria	4.45 ±2.7	2.4 ± 2.6	4.05	2.85	6	4	2	NA	NA
Rectal Bleeding	33.5%	25.9%	21%	13%	31.3%	29.9%	NA	0%	22%
Duration of rectal bleeding	3.3 ± 1.3	1.9 ± 0.7	2.41	2.03	3	2	1	NA	NA
Haemospermia	90.1%	86.9%	17%	21%	21.4%	18.5%	9.3%	11%	28%
Duration of Haemospermia	21.2 ± 11.9	22.4 ± 10.4	6.8	4.0	NA	NA	NA	NA	NA

Table 2.

A meta-analysis incorporating almost 50,000 patients (14,981 of these on aspirin) found that although aspirin increased the rate of bleeding complications by 1.5 times, it did not lead to greater severity of bleeding complications except for intracranial surgery and possibly TURP [13]

2.1.2 Risk of antiplatelet withdrawal and bridging therapy

There is no doubt that cessation of antiplatelet therapy in patients with a recent coronary stent carries a significant risk [14]. In addition, one French study suggests that recent withdrawal of this therapy may be harmful in patients with coronary artery disease. Half of the withdrawers underwent substitution therapy in the form of non-selective NSAIDS or low molecular weight heparin, which did not protect the patients [15].

2.1.3 Evidences from other specialties

Multiple studies from other specialties have shown the safety of aspirin during a wide array of interventions. Peritoneal dialysis catheter insertion and removal [16], 9-14 gauge core needle breast biopsy [17] and dental extraction [18] all have been shown to be safe with aspirin. Aspirin does not increase the risk for haematoma with spinal or epidural anaesthesia [19], or bleeding with spinal surgery [20].

There are certain clinical instances in which continued aspirin coverage is critical: Aspirin should never be stopped in patients with coronary stents because they face a 45% complication rate and a 20% mortality rate with the highest risk for those with a stent placed in the previous 35 days [21].

2.1.4 Restarting aspirin

A UK National survey [12] reported that the urologists who routinely stop aspirin, the medium (range) time for restarting aspirin after biopsy was 2 (0-10) days.

2.2 Antiplatelet medication – Clopidogrel bisulphate (Plavix, Bristol-Myers Squibb)

Clopidogrel is a thienopyridine that inhibits platelet aggregation by selectively blocking the binding of adenosine diphosphate (ADP) to its platelet receptor, and subsequently ADP-mediated activation of the GP IIb/IIIa complex. ADP stimulates expression of the GP IIb/IIIa receptor and may mediate release of other aggregation agonists and enhance platelet binding of von Willebrand factor. Hence, the end result of ADP inhibition is impairment of platelet aggregation and fibrinogen-mediated platelet crosslinking. Because it irreversibly modifies the platelet ADP receptor, platelets exposed to clopidogrel are affected for the remainder of their life span (7-10 days). After stopping clopidogrel, platelet aggregation and the bleeding times gradually return to baseline value, usually within 5 days.

Clopidogrel has a mixed safety record depending on which intervention is studied. It does not increase the risk of haematoma with spinal anaesthesia [22]. The maintenance of clopidogrel during surgery or invasive procedures has not been extensively studied. Patients taking clopidogrel after coronary artery intervention have a high risk of late stent thrombosis if they interrupt their medications (usually clopidogrel & aspirin). Of patients who stopped medications prematurely, 29% suffered stent thrombosis and 45% of those patients died [23]. There have been several non-urological studies assessing the risk of bleeding in patients on clopidogrel undergoing cardiothoracic surgery [24], plastic surgery [25], ophthalmology [26] and vascular surgery [27]. However, conclusions regarding the risk of bleeding are contradictory. To date, there have been very few reports

in the urological literature regarding the risks associated with clopidogrel continuation and urological surgery.

A UK survey [28] on the peri-operative management of Urological patients with clopidogrel showed that majority of the urologists stop clopidogrel prior to TUR surgery (96.6%), major urological surgery (91.7%), TRUS Biopsy (90.6%), ESWL (81.8%), and Cystoscopy & Biopsy (70.1%). Almost half of the respondents (total 570 respondents) would stop aspirin irrespective of its indication and 40.7% never consulted a cardiologist/haematologist before stopping clopidogrel. Over half (55%) reported bleeding complications in patients who continued clopidogrel during interventions and 7.4% responders reported an adverse thrombotic event after discontinuing the drug.

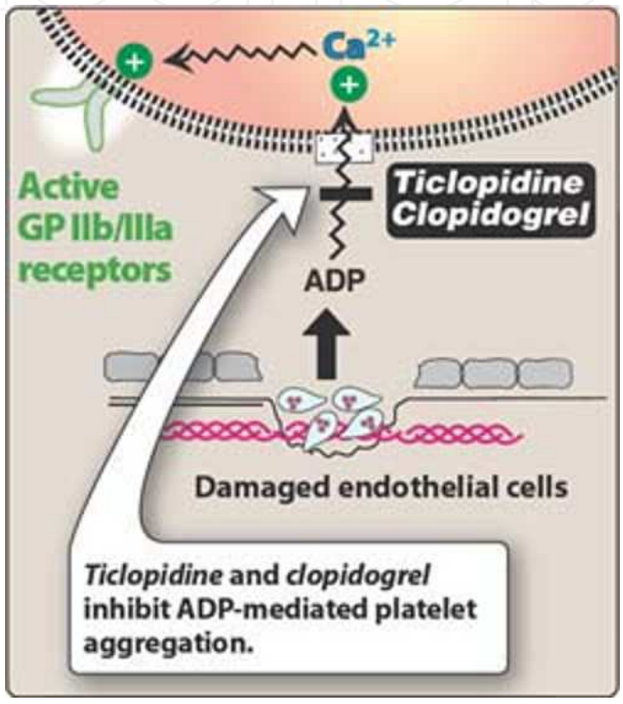


Fig. 3. Pathway of blockage of ADP receptors by clopidogrel. Source: Harvey, R; Champe, P "Lippincott illustrated reviews: Pharmacology", 4th edition. LWW: 2009.

2.2.1 Bridging therapy

If patients take aspirin in addition to clopidogrel because of a coronary artery stent, the aspirin should be continued to mitigate the risk of late stent thrombosis [29] and clopidogrel should be restarted following TRUS biopsy as soon as possible using a loading dose. Bridging anticoagulation for patients who must interrupt clopidogrel is controvertial. Anticoagulation with warfarin or heparin has not proven useful [30] and is questionable [31]. In general, antiplatelet therapy should not be interrupted until patients are beyond the safety window. If an intervention cannot be delayed, the risks of drug interruption should be weighed carefully against the risk of bleeding. As a practical matter, the surgeon, cardiologist, haematologist and anaesthesiologist should consult on each case regarding the risk of peri-operative bleeding if antiplatelet therapy is continued and the risk of ischaemic events if therapy is discontinued. If the course is not acceptable, postponement of the surgery should be considered if possible.

2.2.2 Re-starting clopidogrel

The decision of each patient should be individualised based on the clinical situation. An attempt should be made to restart the clopidogrel as soon as possible after the procedure, when the risk of bleeding is minimal, to minimise the risk of thrombo-embolic phenomena. It should be restarted using a loading dose.

2.3 Warfarin (4-hydroxycoumarins)

Warfarin inhibits the formation of vitamin K-dependent coagulation proteins, i.e., factor II, VII, IX, X and protein C and S. These are proteins of the extrinsic pathway and thus would be monitored by INR. These diminished factors lead to decreased fibrin clot formation and, to a lesser extent, primary haemostasis by platelets (because thrombin is an important activator of platelets).

2.3.1 Mechanism of action of warfarin

Warfarin is a vitamin K antagonist. It produces its anticoagulant effect by interfering with the vitamin K cycle. Specifically, it interacts with the KO reductase enzyme so that vitamin KO cannot be recycled back to vitamin K. This leads to a depletion of vitamin KH_2, thereby limiting the γ- carboxylation of the coagulation factors mentioned above. Factors like prothrombin are not carboxylated, and cannot effectively bind to phospholipid membranes. Its activation by Factor Xa is not affected. Thus blood coagulation is limited. Therapeutic doses of warfarin decrease the effects of Vitamin K-dependant clotting factors by approximately 30 to 40%.

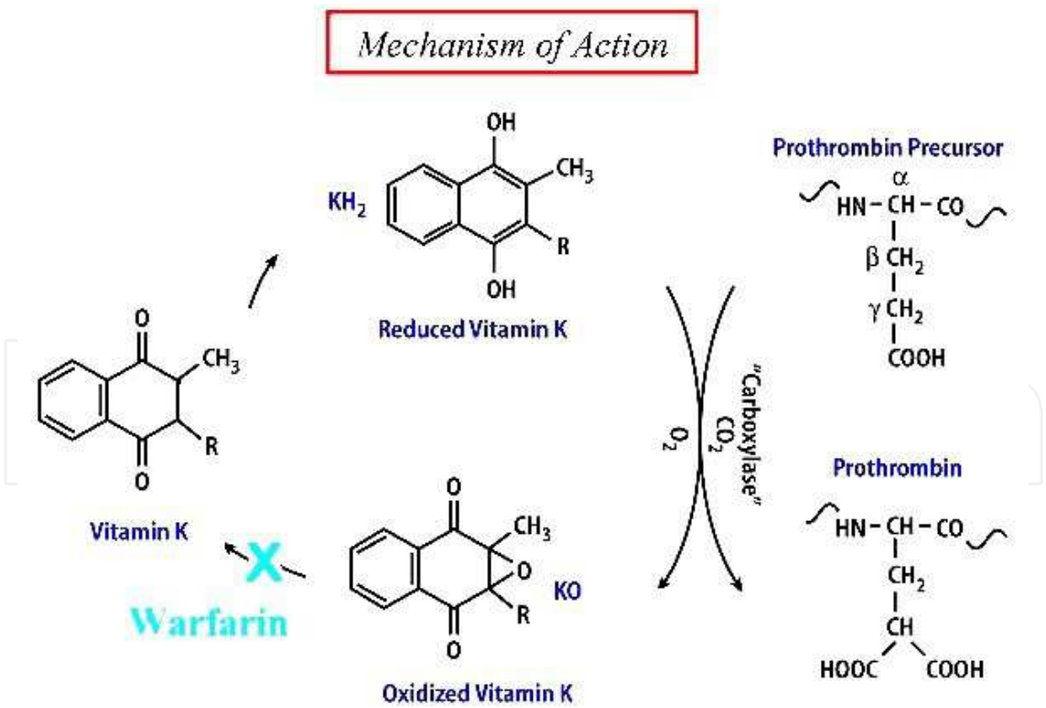


Fig. 4. The carboxylation process is associated with the vitamin K cycle. In this cycle, vitamin K is reduced by enzyme Vitamin K reductase to its hydroquinone form, vitamin KH_2, which then catalyses the carboxylation process and is converted to its epoxide (vitamin KO). This is then converted back to vitamin K by the enzyme Vitamin KO reductase.

2.3.2 Bleeding risks during invasive procedures

Bleeding is the obvious risk when continuing warfarin during surgical interventions. One study found a seven fold increase in moderate to severe post-operative complications in patients taking the medication [32].

The relation between warfarin use and the frequency of bleeding complications after TRUS biopsy was reported in a prospective study of 1000 patients. Forty nine patients continuously used warfarin before and after the biopsy. The prevalence and severity of bleeding complications were assessed by a questionnaire 10 days after the biopsy. There were no significant difference in the severity of bleeding between patients taking warfarin and controls [28]. However, limitations of this study include non-randomized design, patients had either 4 or 6 core biopsies and complications were entered retrospectively 10 days after biopsy.

Some studies showed that maintaining a therapeutic level of warfarin anticoagulation is safe for many interventions. Ihezu et al [33] showed less bleeding in patient taking warfarin with an average INR of 2.2, than in control subject. Similar evidences are found in some non-urological invasive interventions – trans-femoral coronary angiography using 5 or 6 French sheaths [INR 2.0-3.0] [34], cataract surgery [35], dental surgery [INR upto 4.2] [36], and dermatologic surgery [INR upto 4.5] [37].

A survey among urologists and radiologists found that 84% of urologists stopped it 4 days before TRUS biopsy and 95% of radiologists stopped it 5 days before TRUS biopsy. An international normalized ratio below 1.5 is accepted for most elective procedures [38].

2.3.3 Bridging therapy and risk of warfarin withdrawal

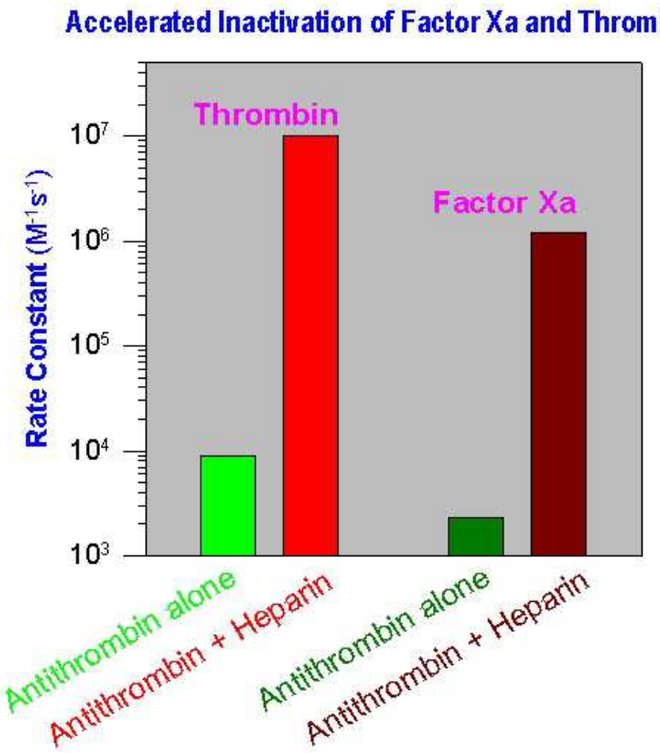
The decision whether to stop anticoagulants depends on the indications for anticoagulation and the risk of thrombosis in a particular patient. The decision should be discussed with the patient and the primary physician managing the anticoagulant. Several regimens have been developed to increase the safety of warfarin interruption. The simplest involves stopping the medication 3-5 days before the intervention and restarting it immediately afterwards [38]. An anticoagulation effect generally occurs within 24 hours after the drug administration, though peak anticoagulant effect may be delayed 72 to 96 hours. The action of a single dose of warfarin lasts 2 to 5 days, & the effects of warfarin may become more pronounced as effects of daily doses overlap.

An alternative regimen is to reduce the warfarin dose to achieve an INR of 1.5-2.0 for surgery or interventions [38]. Bridging anticoagulation with unfractionated heparin or low-molecular weight heparin (LMWH) should be considered for patients at the highest risk of thromboembolism, such as those with prosthetic metallic heart valves. This involves stopping warfarin 3-5 days before the surgery and administering unfractionated heparin or LMWH until 6-24 hours before the procedure [38].

Heparin, containing the unique five-residue sequence, forms a high-affinity complex with antithrombin. The formation of antithrombin - heparin complex greatly increases the rate of inhibition of two principle procoagulant proteases, factor Xa and thrombin. The normally slow rate of inhibition of both these enzymes (~ 10^3 - 10^4 $M^{-1}s^{-1}$) by antithrombin alone (see graph below) is increased about a 1,000-fold by heparin. Accelerated inactivation of both the active forms of proteases prevents the subsequent conversion of fibrinogen to fibrin that is crucial for clot formation.

On the other hand, compared with the unfractionated heparin, low-molecular weight heparin has a greater ratio of anti-factor Xa / anti-factor IIa activity, greater bioavailabity,

and longer duration of action. It is also suitable as outpatient treatment and requires less monitoring [39]. It does not cross placenta, therefore it can be used during pregnancy.



Graph: Effect of action of heparin

Patients with an acute venous thromboembolism in the previous 3 months or an arterial embolism in the previous month should receive unfractionated heparin or LMWH. The risk for recurrent venous thromboembolism is high [40] if anticoagulation is stopped in the first month after an acute event (40%), and decreases if the anticoagulants are not stopped until the second or third month (10%). The bridging anticoagulant is usually restarted as soon after the procedure as is considered safe to do so and continued until a therapeutic INR has been established with warfarin.

3. Other inherent bleeding risks

Identification of patients at high risk for bleeding is the first step in managing those on antiplatelet agents or warfarin who require invasive procedures. Demographic factors that increase the likelihood of bleeding are advanced age, previous history of bleeding events, haemorrhagic peptic ulcer or haemorrhagic stroke [31]. Medical conditions that increase the risks of bleeding include obesity, diabetes, hypertension, renal impairment, heart failure, other major organ dysfunction and haemostatic disorders [31, 41]. Patients with these conditions present a particularly difficult dilemma for clinicians. Data on patients with these conditions are not found in the medical literature. A unified validated method of sorting patients in terms of their bleeding risk and weighing it against their risk of ischaemic events is sorely needed but is yet unavailable.

4. Comment

There is insufficient clinical evidence to establish comprehensive guidelines regarding continuation of aspirin during TRUS biopsy. However, data are emerging and from some level 2 evidence it appears that patients on ASA should have this maintained during TRUS biopsy. In clearly identified cases, where bleeding might threaten the patient's life e.g. after acute cardiac events, the discontinuation protocol must be established in conjunction with cardiologist and the ASA therapy resumed as soon as possible. Bridging with LMWH is not recommended in the aspirin or clopidogrel group. Consideration should be given to postponing TRUS biopsy in high risk individuals. Patients with combination of aspirin and clopidogrel should at least continue aspirin during the procedure. Evidence on discontinuation of warfarin is sparse but emerging. However, bridging therapy with heparin in this situation could be an effective replacement of warfarin. There is an urgent need for research in order to change the practice of stopping anticoagulants and to establish a comprehensive set of recommendation before the TRUS biopsy.

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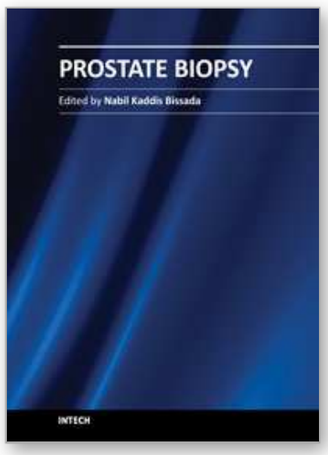

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Prostate Biopsy represents the standard procedure for diagnosing Prostate Cancer. This procedure can be performed transrectally, through perineum or occasionally through the urethra. Although the procedures of Prostate Biopsy are covered in numerous publications, there is still a need for gathering different aspects and methods in one source. Hopefully, this book will help physicians in their effort to provide the best treatment for their patients.

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