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New oral anti-coagulation drugs and prostate biopsy: a call for guidelines

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Abstract

Background: Prostate biopsy is a rather frequent procedure, mostly performed in outpatient settings. Bleeding complications following this procedure require precise and delicate management of pre-, peri- and post-procedure anti-coagulation treatments. New oral anti-coagulation drugs (NOACs) are increasingly used. However, the management of such treatments is feared and not yet well known to urologists. A protocol for prostate biopsy management of NOACs seems mandatory.

Materials and methods: A review of the literature, using Pubmed and Cochrane databases, together with analysis of several medical associations' recommendations in urology, anaesthesiology, cardiology, oncology and drug safety agency, was performed.

Results: There are no recommendations about NOAC management for prostate biopsy available from scientific societies. There is also a lack of specific urological studies. However, several panels of expert recommendations could be helpful in establishing standardized protocols adapted from surgery to prostate biopsy. With the growing use of NOACs, recommendations have shifted to continue anti-coagulant treatment without bridging NOACs for low bleeding risk procedures such as prostate biopsy, in carefully selected groups of patients.

Conclusion: Extensive indications coupled with the ease of use of NOACs contribute significantly to the widespread replacement of traditional vitamin K antagonist. Knowing that heparin bridging leads to more bleeding, and in the pursuit of more autonomy and safety, urologists should be able to propose dedicated anti-coagulant management using NOACs adapted to carefully selected patients before the prostate biopsy procedure. Further studies and guidelines specific to the concept of non-bridging for anti-coagulant-requiring patients are mandatory for this routine procedure.

Keywords: complications, new oral anti-coagulant (NOAC), prostate biopsy

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Introduction

Since the Food and Drug Administration (FDA) approved new oral anti-coagulation drugs (NOACs) use for atrial fibrillation in October 2010, there has been an exponential increase in the prescription of these medications. They are gradually replacing the traditional vitamin K antagonist (VKA) as the new standard in oral anti-coagulation.[1,2]

The estimated prevalence for oral anti-coagulation is increasing. In the next decade, it may affect 12–18 million people, just for atrial fibrillation in Europe and the United States. Specifically, patients over 65 years old are more impacted by this trend.[3] Around 15% of these patients will undergo an invasive procedure that may lead to dilemmas regarding anti-coagulant treatment.[4] Interestingly, this age group represents in urology an important part of the population targeted by prostate biopsies, making proper knowledge of NOACs management mandatory for urologists.

However, for such procedures, NOAC usage is still not well known to urologists, who are frequently

dealing with anti-coagulation drug management and its complications, during the pre-, peri- and post-biopsy periods. Prostate biopsy procedures are frequent and mostly performed on an outpatient basis in daily practice, in complete autonomy, without systemic anaesthesia. The management of NOAC treatment lacks specific guidelines and a clear reversal protocol for all of these new drugs.

The bleeding risk of the procedure is usually classified as low in many urological sources,[5–8] despite disagreement between experts.[9] Mild and self-limited bleeding including haematuria, rectal bleeding and haematospermia are the most common adverse events following prostate biopsies. Conversely, severe bleeding, mainly gross haematuria, requiring hospital admission is rare (less than 1% in the main series).[10–13] A few cases of pelvic vessel puncture leading to giant retroperitoneal haematoma have also been reported.[14]

The mechanism of action of NOACs is based on the inhibition of the transformation of fibrinogen to fibrin. This is achieved by direct inhibition of factor IIa (also called thrombin) for dabigatran,[1] or by direct inhibition of factor Xa for rivaroxaban,[15] edoxaban[16,17] and apixaban.[18] These drugs have several advantages that favour their use (fixed dosage, no need for dose adaptations, no need for blood test surveillance, and fewer drug–drug and drug–food interactions compared to VKA), with a clearly proven safety profile comparable to and even better than that of VKA.[8] These advantages could decrease iatrogenic hospital admissions, which are more common with the use of traditional anti-coagulants.[4,19] Finally, and because of their safety profiles, all NOACs appear to be cost-effective alternatives to warfarin for long-term treatment, leading to better healthcare at affordable costs.[20] All these reasons encouraged cardiologists to gradually replace the traditional anti-coagulants with NOACs, and this trend will continue with time to become the new standard of care. Urologists should adapt their practice to this reality. The contraindications for NOAC usage are those classically associated with anti-coagulant usage (active bleeding, homeostasis disorders and/or organic lesions likely to bleed, kidney or liver disease associated with coagulopathy and/or bleeding risk).

Therefore, performing prostate biopsies in patients on NOACs requires proper, balanced management, minimizing bleeding risks without increasing the risk of thromboembolism. The purpose of this review is to suggest recommendations dedicated to urologists for the management of NOACs adapted to prostate biopsies, based on the literature available in 2018.

Methodology

A review of the literature was performed using Pubmed and Cochrane databases, without time limits. English and French articles were included in our review using association of MESH [NEW ORAL ANTICOAGULANTS] AND [UROLOGY] or with [NEW ORAL ANTICOAGULANTS] AND [PROSTATE BIOPSY]. We have judged unnecessary the realization of a PRISMA flow diagram because of the scarcity of the results. Therefore, relevant additional studies or experts' opinions found during the analysis were added. These were mostly identified by reviewing the reference lists of included systemic reviews.

In addition, this review of the literature was completed using manual analysis of recommendations produced by several international associations of: urology – American Urological Association (AUA), European Association of Urology (EAU); of oncology – National Comprehensive Cancer Network (NCCN), National Institute for Health and Care Excellence (NICE); of anaesthesiology – American Society of Anesthesiologists (ASA), European Society of Anaesthesiology (ESA), of cardiology – American Heart Association (AHA), American College of Cardiology (ACC), European Heart Rhythm Association (EHRA), European Society of Cardiology (ESC); of drugs agencies – the FDA, European Medicines Agency (EMA); and from a panel of experts in haemostasis, the Groupe d'Intérêt en Hémostase Périopératoire (GIHP).

Relevant additional studies or experts' opinions identified by review during the research were added in the results data.

Results

There were very few results directly obtained using MESH in the databases. A total of 28 results were found by using [NEW ORAL ANTICOAGULANT] and [UROLOGY], and only 5 with [NEW ORAL ANTICOAGULANT] and [PROSTATE BIOPSY].

Some recommendations of good practice regarding urological care have been published by several

associations,[7,21–24] but none of them precisely mentioned the management of patients treated by NOACs during prostate biopsies or recent reviews about anti-coagulant management.[25,26] However, some non-specific good practice guidelines were identified for patient on NOACs undergoing surgical interventions, edited by several cardiology and anaesthesia societies.[8,27,28] That being said, none of these were specific to outpatient prostate biopsy.

Due to this situation and for more comfort and autonomy in their daily practice, urologists should know, on one hand, how to identify and weigh the risk of thrombosis related to stopping or continuing NOAC treatment, and on the other hand the bleeding risks related to the intended surgical procedure, especially when antidotes are not yet commercially available for all these new drugs,[28,29] with the exception for dabigatran.[30] It is also substantial to mention that there is no specific way to determine precisely the persistence of an effective anti-coagulative effect, such as international normalized ratio (INR) for VKA.[8]

Discussion

Prostate biopsy today

Recently, in order to avoid unnecessary biopsies and complications, EAU guidelines have been updated.[31] The authors stressed the need for further investigations for asymptomatic patients, with normal digital rectal examination (DRE) and PSA level between 2 and 10 ng/ml. Guidelines now recommend the use of a risk calculator, MRI or urine or blood test, depending of local availability [Prostate Health Index test (PHI test), four kallikrein score (4K score), Prostate cancer gene 3 (*PCA3*), *HOXC6*/*DLX1*]. Suspicious PSA level and/or suspicious DRE or suspicious lesion on imaging remain classical indications for prostate biopsies.[31]

Transrectal prostate biopsies are the most commonly used even if significantly fewer infections are reported with perineal access. However, bleeding complication rates remain the same for the two approaches.[32] None of these two techniques have shown a superior accuracy to detect cancer.[32]

The PRECISION study has recently shown a significant benefit of targeted biopsies using fusion of MRI and transrectal ultrasound (TRUS) targeted prostate biopsies. These results may lead to more precise procedures, reducing the number of cores needed for the diagnosis of significant prostate cancer.[33] Interestingly, it has never been proven that there is a direct correlation between the number of cores and the risk of bleeding.[13]

Continuing, discontinuing or bridging?

Nowadays, there are no specific studies assessing the bleeding risks for patients undergoing prostate biopsies without stopping NOACs. The evidence to help decision-making is limited.[27] Interestingly, two large studies have shown that groups continuing VKA during prostate biopsies did not experience significant clinically important bleeding complications.[34,35] Recently, this concept was evaluated for catheter ablation in atrial fibrillation in the RE-CIRCUIT study: uninterrupted dabigatran and warfarin were compared. The study showed significantly fewer bleeding complications for uninterrupted dabigatran.[36] It is worth mentioning that this procedure is considered, like prostate biopsy, a low-risk bleeding procedure.

Furthermore, according to secondary data analysis from the RE-LY study[37,38] or ROCKET-AF study[15] and ARISTOTLE study,[18] discontinuing NOACs without bridging is associated with fewer significant bleeding events and thromboembolic complications when performing scheduled or even urgent surgical procedures.

A bridging attitude was evaluated for low and high bleeding risk interventions with the same conclusion.[39,40] The BRIDGE study results clearly demonstrated that heparin bridging is significantly associated with an increased risk of bleeding,[41] without reducing the incidence of thromboembolic events. These findings were confirmed for TRUS biopsies by Hamano and colleagues in a large retrospective study.[42] Heparin bridging for VKA users significantly increases the risk of bleeding compared to discontinuation. Again, the authors emphasized the lack of clear data and recommendations.

NOAC prostate biopsy protocol

Nowadays, the majority of scientific societies and experts' opinion panels are converging to the same conclusion regarding operative management for low-risk bleeding procedures such as prostate biopsies to continue anti-coagulant treatment without bridging, regardless of the thrombotic risk.[6,8,43,44]

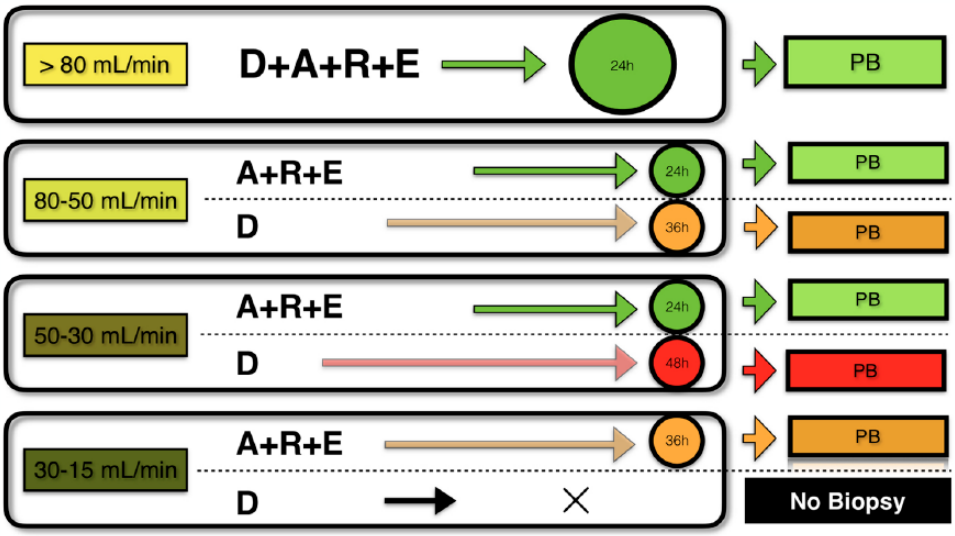

Figure 1. Last intake of NOAC before prostate biopsy.
A, apixaban; D, dabigatran; E, edoxaban; PB, prostate biopsy; R, rivaroxaban.

Given that NOAC concentration peaks 2 h after ingestion, the last dose of the NOAC must be taken 18–24 h before the procedure. There is no agreement regarding the need for haemostatic biological control before prostate biopsies. Due to its safety profile, coagulation tests are optional for most experts.[8,28,45] However, they could be useful even if they are not specified, especially in cases of patients with renal (maintenance of the anti-coagulant effect, especially when using dabigatran) or hepatic impairment, potential drug–drug interactions or suspected overdosing. An activated partial thromboplastin time (APTT) for the oral anti-IIa (dabigatran) and prothrombin time (PT) for the oral anti-Xa (apixaban, rivaroxaban and edoxaban) may provide useful information about coagulation.[8,28,43–45]

Renal insufficiency should always be carefully considered due to the increased half-life of NOACs, which will promote bleeding. Creatinine clearance must be tested shortly before the procedure. For oral anti-Xa, the last dose must be delayed and taken 36 h before the procedure if clearance is lower than 30 ml/min (which is usually a poor indication for that drug even if they are not contraindicated).[8]

It should be stressed that special precautions must be taken for patients with renal impairment using only the oral anti-IIa (dabigatran). Its management is more complicated due to a major renal excretion. Therefore, the last dose must be taken 36 h before the procedure for a creatinine clearance between 80 and 50 ml/min, and 48 h before the procedure for a creatinine clearance between 50 and 30 ml/min. Note that oral anti-IIa is contraindicated for clearance under 30 ml/min.[8] Association with non-steroidal anti-inflammatory drugs (NSAIDS) and antifungal (systemic ketoconazole, itraconazole, cyclosporine, tacrolimus) should be contraindicated.

The absence of the need to bridge the NOAC is also another benefit compared to VKA for post-biopsy management. Treatment can be restarted 6 h post-prostate biopsy after making sure that potential bleeding is well controlled.[8] However, in rare cases of major post-biopsy bleeding,[10,11] it is advisable not to release the patient and to continue with heparin if surgical haemostasis is required. The NOAC can be reinitiated 12 h after the last heparin administration.[46,47]

Even though urological associations have not yet published proper recommendations, a simple and standardized protocol could be proposed for patients undergoing prostate biopsies without heparin bridging, obviously requiring validation in large studies (Figure1).

Conclusion

Extensive indications coupled with the ease of use of NOACs contribute significantly to the widespread replacement of traditional VKA. Heparin

bridging leads to more bleeding events; for greater autonomy and safety, urologists should be able to propose dedicated anti-coagulant management using NOACs adapted to carefully selected patients before the prostate biopsy procedure. Further studies and guidelines specific to the concept of non-bridging for anti-coagulant-requiring patients are mandatory for this daily routine procedure.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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