REVIEW ARTICLE

Understanding the RECORDS 3 Trial and its impact on anticiagulation practice in resource poor countries

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Abstract

Venous thromboembolism is a significant cause of mortality and morbidity in patients following major orthopaedic surgeries. The RECORDS 3 trial revolutionised anticoagulation practice especially in patients with total knee arthroplasty and challenging the strong hold of warfarin and heparin in anticoagulation practice. With all these novel agents shifting the paradigm in anticoagulation management, Cost, in accessibility and lack of awareness of the availability of the agents amongst clinicians and surgeons alike are some factors militating against the use of these agents in patients in resource poor countries.

Key words: Anticoagulation practice, new anticoagulation therapy, Regulation of Coagulation in Orthopedic surgery to prevent Deep venous thrombosis and pulmonary embolism 3 trial, rivaroxaban

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Introduction

Venous thromboembolism (VTE) comprise two interdependent disease conditions that are part of the same pathological process; Deep venous thrombosis (DVT) and pulmonary embolism (PE).[1] The disease process ranges from clinically unsuspected to clinically unimportant to clinically significant fatal embolism. There is a 10-fold increase risk of VTE in hospitalised patients after trauma, surgery or immobilizing medical illness.[2] It is reported that 54% of hospital inpatients who had developed symptomaticVTE were general medical or nonsurgical oncology inpatients.[3] Meta-analysis of randomized trials estimates the risk of DVT in hospitalized medical patients receiving no thrombo-prophylaxis to be as high as 20%.[4]

VTE is a significant cause of morbidity and mortality following major orthopedic surgeries[5] such as total hip arthroplasty (THA) and total knee

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arthroplasty (TKA).[6] Studies have shown that symptomatic DVT occurs approximately in 15–30% of patients undergoing THA or TKA.[7] The current VTE regimen used for patients after THA is anything but ideal. It is advocated and recommended that the ideal anticoagulation agents should be selective, specific for the disorder, rapid onset of action, easily reversible and availability of antagonizing agents, hence an orally active drug with these features makes for easy applicability for both acute and chronic conditions.[8] Russell *et al*. showed that even with acceptable efficacy and safety profiles, the challenges with warfarin therapy range from its long onset of action, narrow therapeutic margins, unpredictable pharmacodynamics and pharmacokinetic properties that requires close and constant monitoring when compared to low molecular weight heparin (LMWH) parenteral administration with an appreciable risk of bleeding in both.[6] Reduced drug compliance study by Friedman *et al*. group showed only 75% of patients being compliant with medication after discharge with patients on warfarin having 33% compliance rate, frequently falling outside the target INR and leading to increased incidence of VTE and bleeding.[9] Anakwue *et al*. also showed in a 5-year retrospective study that effective use anticoagulation therapy in Nigeria is constrained by poor diagnostic capabilities, absence of anticoagulation monitoring clinics as well as the apprehension of adverse effects amongst clinicians.[10] A South African review by Jacobson *et al*. also implicated the lack of guidelines as one of the significant factors responsible for under prescription of anticoagulant agents in some African countries.[11]

It becomes imperative to administer anticoagulant agents with good safety, efficacy profile, better patient compliance and limited monitoring, especially in countries that lack the necessary protocol to ensure the safe and effective use of anticoagulation agents. There is a paradigm shift from the days of nonselective anticoagulants with unfavorable pharmacokinetics, pharmacodynamics, outdated and highly vulnerable manufacturing processes and predictably unpredictable off-target effects.[12] The new oral anticoagulation agents; dabigatran, apixaban, and rivaroxaban hold such a promise. Rivaroxaban is a direct factor Xa inhibitor currently approved in the United States for VTE prophylaxis after TKA and THA.[13] There have been two phase III trials (Regulation of Coagulation in Orthopedic surgery to prevent DVT and pulmonary embolism [RECORD] 1–4) evaluating its safety and efficacy in orthopedic patients by RECORD study group. This paper will review, critically analyze the RECORD 3 trial process and also evaluate its impact on anticoagulation practice in resource-poor countries.

Methodology

Online searches on the following database; Google Scholar, PubMed, Biomed Central and SciELO was done. Attempt was made to review articles with keywords RECORD 3 trial, new anticoagulation therapy anticoagulation practice and rivaroxaban online databases were searched; Google Scholar, PubMed SciELO. Articles published from the year 2000 till date was reviewed.

Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 3 Trial

Since the discovery of warfarin more than 50 years ago, the search for an ideal oral anticoagulant agents that would compare favorable in terms of efficacy and safety with warfarin and parenteral anticoagulant agents has been ongoing. The importance of new, safe and convenient oral anticoagulants in clinical practice cannot be over-emphasized because these agents offer hope for improved anticoagulation therapy free from the notable constraints of warfarin therapy (insert refrence).

The findings of RECORD 3 clinical trial were published in 2008 as an original article in the New England Journal of Medicine (NEJM) titled rivaroxaban versus enoxaparin for thromboprophylaxis after TKA. The title was apt and well suited for the report, highlighting the objectives and clinical relevance of the study.

The RECORD 3 study was sponsored by Bayer Health Care with members of Steering Committee, Independent Central Adjudication Committees, Bleeding Event Adjudication Committee and Data and Safety Monitoring Board. It was a mutinational and multicenter study that involved investigators from Belgium, Canada, China, Colombia, Czech Republic Denmark France Germany, Israel, Italy, Mexico, the Netherlands, Norway, Peru South Africa, Spain, and Sweden. The multi-nationality of the trial team is good example of partnership between the developed and developing nations and universality of clinical trials as a tool to provide evidence-based medicine for good clinical practice globally. The groups' choice to publish their findings in NEJM was appropriate, as NEJM is one of the oldest continuously published medical periodical and attaining its second century of publication in 2012.[14]

The objectives of the Regulation of Coagulation in Orthopedic surgery to prevent Deep venous thrombosis and pulmonary embolism 3 trial

The primary objective was to establish the efficacy and safety of rivaroxaban in the prevention of VTE in patient after TKA. Though the standard of care for thromboprophylaxis in TKA at the time of this study was enoxaparin, even with its acceptable safety and efficacy profile,[6] there was still need to improve patient compliance, the safety profile and mode of administration.[15] As stated by Pocock, one of the fundamental rules is that phase III trials are comparative.[16]

To achieve the objective, rivaroxaban (new anticoagulant) was compared with enoxaparin (standard care anticoagulant) and establish the safety and efficacy profile of the new agent. An earlier phase II trial by Eriksson *et al*. had already established daily dose of 10 mg of rivaroxaban as safe and efficacious to achieve thromboprophylaxis in patients with TKA[17] hence a phase III trial was needed with more study subjects not only to establish the efficacy and safety profile of this agent-rivaroxaban but evaluate how it compares in those terms with the known standard thromboprophylaxis agent in patients with TKA (in this case enoxaparin).

Study design and primary measures

RECORD 3, clinical trial was double-blind controlled study with investigators from across the world. It was conducted in accordance with the Helsinki Declaration, and the protocol was approved by the Ethics Committee or the Institutional Review Board of each participating center. In addition to double-blinding, the investigators also used the double dummy technique, to ensure the study was truly blinded.[18] The double dummy is a method for retaining the blind in a clinical trial when the two treatments are of different formulation, e.g., oral versus parenteral.[19] Each participant in each arm took both the test drug in its formulations and a placebo for the other drug at the same time. This study design was appropriately structured to answer the trials main objectives.

The study involved 2556 patients. They were enrolled from 147 centers in 19 countries between February 2006 and November 2006.[18] The South America countries Mexico and Peru had the lowest number of enrolled patients. The investigators did not state why this is so but one could infer that TKH being an expensive procedure will screen out patients in developing countries who can't afford it especially those with a background of inadequate health care and medical insurance systems. Another probable reason may be the wrong perception about clinical trials and lack of trust in the medical system amongst the populace a fallout of unethical clinical trials conducted in some resource-poor settings, e.g., the Tuskegee syphilis study[20] and the Kano Pfizer Trovan Trial.[21] On the other hand countries like Spain, Poland and Germany recorded the highest enrollees; these countries boast of well-structured health care and medical insurance systems.[22]

The exclusion criteria were similar for both arms of the trial and included, "individuals with increased bleeding risk contraindicated for the use of enoxaparin, any contraindications to enoxaparin or any contraindication to dose adjustment of enoxaparin. Other exclusion criteria include conditions preventing bilateral venography, clinical significant concomitant use of protease inhibitor of HIV and pregnancy or breastfeeding."[18]

The trial outcome measures were categorized into (1) safety and (2) efficacy measures. The primary efficacy outcome measure was the composite of any DVT, nonfatal PE or death within 13–17 days after surgery. The secondary and tertiary efficacy outcome measures included cases of major VTE, nonfatal PE or death related to VTE or any symptomatic DVT or PE occurring during the treatment or follow-up period. The primary safety outcome was incidence of significant bleeding occurring between intake of the first dose and 2 days after the last dose. Other outcomes included past surgical bleeds, other serious adverse effects and death. The Central Independent Adjudication Committee also blinded to the treatment assignments assessed these study outcomes.[18] Notably, absent was the assessment of the quality of life of patients in the two arms as an outcome measure. This would have provided valuable information to further support the findings of the trial.

Brief Overview of the Result

Of the 2556 patients enrolled for the study, 25 failed the initial screening. The remaining 2531 patients underwent randomization of which 1254 were assigned to receive 10 mg of rivaroxaban daily, and 1277 were assigned 40 mg enoxaparin once daily.[18]

The primary outcome measure was to establish the diagnosis of VTE. Thus, investigators reported that only 67% of enrolled patients who underwent randomization were included in the "modified" intention to treat population. To avoid affecting the power of the study the steering committee of the RECORD 3 group approved increased recruitment from 2300 to 2500 all in the bid to maintain the statistical power of more than 80% used for most clinical trials. In addition, several sensitivity analyses were also performed to ensure the missing data did not constitute bias for the study.

The clinical trial reported the primary efficacy outcome occurred in 79 out 824 patients (9.6%) in the rivaroxaban arm and in 166 out of 878 (18.9%) in the enoxaparin arm (absolute risk reduction, 9.2%; 95% confidence interval [95% CI], 5.9 to 12.4; $P < 0.001$). They also reported major VTE occurring in 9 of 908 (1.0%) given rivaroxaban and 24 of 925 (2.6%) given enoxaparin (absolute risk reduction, 1.6%; 95% CI, 0.4–2.8; $P = 0.1$). Symptomatic events occurred less frequently than with enoxaparin.[9]

These results support the main findings of the RECORD 3 trial; rivaroxaban showed a significant reduction in the incidence of the primary outcome when compared with enoxaparin. Noting the high patient attrition rate in the study, were these findings enough to warrant such a conclusion? The investigators took a conservative stance by assuming that all those with inadequate assessment of thromboembolism had an event. One could argue that this was quite ambitious, but knowing the high mortality and morbidity associated with VTE[1] it would be advisable

to err on the side of treatment than no treatment, their stance would then be considered the most appropriate for the situation.

Translating the results of Regulation of Coagulation in Orthopedic surgery to prevent Deep venous thrombosis and pulmonary embolism 3 to clinical practice

The enrollment and total care for patients in clinical trials is quite different from what happens in day to day clinical practice.[23] The RECORD 3 trial has established that the use of rivaroxaban for prophylaxix of VTE was not inferior compared with other new oral anticoagulants (NOACs) rivaroxaban was found to be safe, bioavailable (80–100%) when taken with food at 10 mg daily dose but fasting reduced the bioavailabilty to about 66%.[24] Rivaroxaban is excreted in urine and fecal pathways with no major active metabolites in circulation.[25] There was little need for dose adjustment for patients weighing >50 kg.[26] Thus, rivaroxaban at a dose of 10 mg is safe, well tolerated and laboratory monitoring is not strongly emphasised, this NOAC can be very effective in resource poor setting as the concerns of anticoagulation therapy monitoring and dose adjustments can be obviated by its use.

Impact on anticoagulation practice in resource poor settings

Anticoagulation practice in resource poor settings is still far from ideal. The traditional anticoagulation agents such as heparin (unfractionated and LMWH); are still mainstay for prophylactic and therapeutic anticoagulation by most clinicians whose main attraction to these agents remain their cost effectiveness, accessibility and relative rapid onset of action. However, these advantages are marred in the case of warfarin by its narrow therapeutic margin, frequent monitoring, bleeding and interaction with food and other medication, genetic heterogeneity of its metabolizing enzymes leading to variability of patient dosing.[2] Unfractionated heparin is associated with heparin-induced thrombocytopenia or with thrombosis while the cost of LMWH militates against prolonged administration. Undocumented report suggests that most physicians and surgeons in resource poor settings are constantly faced with the obvious clinical scenario requiring either anticoagulation prophylaxis or therapy may choose not to anticoagulate patients or give sub-optimal doses or for sub optimal duration because of the fear of the side effects of warfarin.

The RECORD 3 trial with rivaroxaban truly revolutionized anticoagulation therapy, but there is undocumented evidence that its use in resource poor setting is continuously being marred by its high cost, lack of universal coverage health insurance scheme, inaccessibility and unavailability even for surgeons and physicians familiar with its use the cumulative cost advantage documented for patients with atrial fibrillation over the traditional anticoagulation agents[27] are yet to be appreciated by patients with TKA as well as by their surgeons who administer or plan to use this agent as their stronghold to achieve anticoagulation as such its use has not been fully embraced in resource poor setting.

Conclusion

The RECORD 3 trial had established efficacy of rivaroxaban an orally active direct factor Xa inhibitor in preventing VTE after TKA. The trial demonstrated the superiority of rivaroxaban, an orally effective direct factor Xa inhibitor given in a fixed unmonitored daily dose over enoxaparin in prevention VTE. Thus, this study has revolutionized anticoagulation therapy worldwide yet cost prevents most patients in resource poor settings from feeling the impact of this study as anticoagulation therapy is still dominated by heparin and warfarin although their acceptable efficacy and safety profile froth with pharmacodynamics and pharmacokinetic challenges still makes VTE management problematic.

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Conflicts of interest

There are no conflicts of interest.

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