RCT

Potential PURL Review Form

PURL Jam Version

PURLs Surveillance System

Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL

[to be completed by PURLs Project Manager]

A. Citation: CRISTAL Study Group, Sidhu VS, Kelly TL, et al. Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial. JAMA. 2022;328(8):719-727. doi:10.1001/jama.2022.13416

B. Link to PubMed Abstract: https://pubmed.ncbi.nlm.nih.gov/35997730/

C. First date published study available to readers: 8/23/2022

D. PubMed ID: 35997730

E. Nominated By: Greg Castelli

F. Institutional Affiliation of Nominator: PA - UPMC

G. Date Nominated: 8/31/2022

H. Identified Through: JAMA

I. PURLs Editor Reviewing Nominated Potential PURL: Greg Castelli

J. Nomination Decision Date: 9/29/2022

K. Potential PURL Review Form (PPRF) Type: RCT

L. Abstract: **Importance**: There remains a lack of randomized trials investigating aspirin monotherapy for symptomatic venous thromboembolism (VTE) prophylaxis following total hip arthroplasty (THA) or total knee arthroplasty (TKA). **Objective**: To determine whether aspirin was noninferior to enoxaparin in preventing symptomatic VTE after THA or TKA. **Design, setting, and participants:** Cluster-randomized, crossover, registry-nested trial across 31 hospitals in Australia. Clusters were hospitals performing greater than 250 THA or TKA procedures annually. Patients (aged ≥18 years) undergoing hip or knee arthroplasty procedures were enrolled at each hospital. Patients receiving preoperative anticoagulation or who had a medical contraindication to either study drug were excluded. Patients receiving pre-operative antiplatelet medication were

allowed to continue during the study, resulting in a total of 884 patients in the aspirin group and 634 in the enoxaparin group, or approximately 16.5% for each group. A total of 9711 eligible patients were enrolled (5675 in the aspirin group and 4036 in the enoxaparin group) between April 20, 2019, and December 18, 2020. Final follow-up occurred on August 14, 2021. **Interventions:** Hospitals were randomized to administer either aspirin (100 mg/d) or enoxaparin (40 mg/d) for 35 days after THA and for 14 days after TKA. Crossover occurred after the patient enrollment target had been met for the first group. All 31 hospitals were initially randomized and 16 crossed over prior to trial cessation. Main outcomes and measures: The primary outcome was symptomatic VTE within 90 days, including pulmonary embolism and deep venous thrombosis (DVT) (above or below the knee). The noninferiority margin was 1%. Six secondary outcomes are reported, including death and major bleeding within 90 days. Analyses were performed by group randomization.

Results: Enrollment was stopped after an interim analysis determined the stopping rule was met, with 9711 patients (median age, 68 years; 56.8% female) of the prespecified 15 562 enrolled (62%). Of these, 9203 (95%) completed the trial. Within 90 days of surgery, symptomatic VTE occurred in 256 patients, including pulmonary embolism (79 cases), above-knee DVT (18 cases), and below-knee DVT (174 cases). The symptomatic VTE rate in the aspirin group was 3.45% and in the enoxaparin group was 1.82% (estimated difference, 1.97%; 95% CI, 0.54%-3.41%). This failed to meet the criterion for aspirin to be noninferior to enoxaparin, which was significantly better at preventing symptomatic VTE P = .007). Of 6 secondary outcomes measured, there was no significant difference between either group. **Conclusions and relevance**: Among patients undergoing hip or knee arthroplasty for osteoarthritis, aspirin is inferior when compared with enoxaparin when used as post-operative DVT prophylaxis, resulting in a significantly higher rate of symptomatic VTE within 90 days post-operatively, defined as below- or above-knee DVT or pulmonary embolism. These findings may be informed by a cost-effectiveness analysis.

M. Pending PURL Review Date: 1/1/2023

SECTION 2: Critical Appraisal of Validity

A. Number of patients starting each arm of the study?

Aspirin arm – 7238, enoxaparin arm - 5146

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)

Inclusions: >18 years old undergoing primary total hip arthroplasty or total knee arthroplasty for osteoarthritis at hospitals tin Australia performing >250 total knee or hip arthroplasties annually

Exclusions: Patients receiving preoperative anticoagulation (direct oral anticoagulant, warfarin, dual antiplatelet therapy), patients with medical contraindications to either study drug

C. Intervention(s) being investigated?

Aspirin 100mg daily for 35 days post total hip arthroplasty and 14 days post total knee arthroplasty

D. Comparison treatment(s), placebo, or nothing?

Enoxaparin (40mg daily subcutaneous, 20mg daily for patients weighing less than 50kg or GFR <30 ml/min/1.73m^2) for a duration of 35 days post total hip arthroplasty and 14 days post total knee arthroplasty

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)

Length of follow up was 6 months, patients were evaluated for any symptomatic venous thromboembolism within 90 days as the primary outcome. Secondary outcomes included major bleeding, readmission and reoperation within 90 days as well as reoperation within 6 months.

F. What outcome measures are used? List all that assess effectiveness.

Primary: Symptomatic VTE, PE, DVT (below or above knee);

Secondary: major bleeding event; joint related readmission within 90 days; joint-related re-operation within 90 days and 6 months; mortality within 90 days; medication adherence rates as assessed by audits

Patient reported

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.

Symptomatic venous thromboembolism within 90 days in 187 patients (3.45%) in the aspirin group and 69 patients (1.82%) in the enoxaparin group (estimated difference, 1.97%; 95% CI, 0.54%-3.41%, p=.007)

H. What are the adverse effects of intervention compared with no intervention?

More symptomatic venous thromboembolism occurred in the aspirin group compared to enoxaparin, the rates of major bleeding and mortality were not significantly different between the two groups.

I. The study addresses an appropriate and clearly focused question.

Well covered

Comments:

J. Random allocation to comparison groups:

Well covered

Updated 2/2021

K. Concealed allocation to comparison groups:

no

Comments: Hospitals were not blinded to treatment allocation

L. Subjects and investigators kept "blind" to comparison group allocation:

Not blinded

Comments:

M. Comparison groups are similar at the start of the trial:

adequately addressed

Comments: but no data regarding matching for comorbidities other than history of prior venous thromboembolism

N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.

yes

Comments: Differences in hospital characteristics and protocol may contribute to biases, such as location in different socioeconomic settings and access to resources.

O. Were all relevant outcomes measured in a standardized, valid, and reliable way?

a. Well covered

P. Are patient oriented outcomes included? If yes, what are they?

Reduction in symptomatic venous thromboembolism post hip and knee arthroplasty

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?

Aspirin group: 259/5675 = 4.6%

Enoxaparin group: 249/4036 = 6.2%

Aspirin may be easier to administer as it is PO, which may contribute to higher drop out rate in the enoxaparin group

R. Was there an intention-to-treat analysis? If not, could this bias the results? How?

yes

S. If a multi-site study, are results comparable for all sites?

This is unknown. The study did not divide results by site.

T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?

No, funding was by the Australian federal government 4 year Medical Research Futures Fund grant.

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.

Patients undergoing total knee and hip arthroplasty well as other orthopedic procedures.

V. In what care settings might the finding apply, or not apply?

Hospital and outpatient primary care, outpatient orthopedic clinics

W. To which clinicians or policy makers might the finding be relevant

Orthopedists, hospitalists, primary care

SECTION 3: Review of Secondary Literature

A. DynaMed excerpts

B. DynaMed citation

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

D. UpToDate excerpts

"The use of aspirin for thromboprophylaxis in patients undergoing major orthopedic surgery is best supported for **select** lower-risk patients (see 'Risk of thrombosis' above) as an extended-duration prophylactic agent following an initial 5- to 10-day course of anticoagulant prophylaxis (eg, LMW heparin or DOAC) [24,108]. We do **not** use aspirin as a sole initial agent during the early postoperative course.

"…**Patients undergoing knee or hip arthroplasty** – For most patients undergoing knee or hip arthroplasty, we suggest low molecular weight (LMW) heparin or a direct oral anticoagulant (DOAC) as the initial agent in the early perioperative period (Grade 2C) (ie, the immediate postoperative period and up to 14 days thereafter).

Enoxaparin or dalteparin are LMW heparin agents that are well studied and commonly used. Among the DOACs, we suggest rivaroxaban or apixaban rather than dabigatran or edoxaban (Grade 2C) since there are more data to support their use in this setting.

While we prefer **not** to use aspirin as the sole initial agent for VTE prophylaxis in the early postoperative period, many orthopedic surgeons have adopted this practice viewing it as an effective and safe agent. However, the typical dosing used varies in practice and further data are needed before we feel this approach should be routinely used. We are, however, proponents of switching to aspirin after a short course of anticoagulant therapy, which is discussed in the bullet "Duration of pharmacologic prophylaxis" below. Dosing and efficacy of these agents are provided above. (See 'Low molecular weight heparin' above and 'Direct oral anticoagulants' above and 'Aspirin' above.)

E. UpToDate citation

Douketis JD, Mithoowani S. *Prevention of Venous Thromboembolism in Adults Undergoing Hip Fracture Repair or Hip or Knee Replacement.* In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2023. Available at https://www.uptodate.com/login. Last updated: January 17, 2023. Accessed January 26, 2023.

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

Aspirin is not recommended as a sole initial agent during the early postoperative course following total knee or hip arthroplasty. Low molecular weight heparin or direct oral anticoagulants are preferred agents in the early postoperative period.

G. Other excerpts (USPSTF; other guidelines; etc.)

a) "There is currently a lack of high quality randomized controlled trials supporting the use of aspirin as VTE chemoprophylaxis in the initial postoperative period for both total hip and total knee arthroplasty. The results of this meta-analysis provide cautious endorsement for the position that aspirin is likely a safe alternative to enoxaparin for TKA patients as part of a multimodal enhanced recovery protocol, but care is advised for THA patients owing to a lack of data from trials. Current evidence from randomized

controlled trials is generally of low quality and does not estimate critical event data for VTE incidence or mortality, as well as major and minor bleeding events with sufficient certainty. “

b) American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients: Orthopedic Surgery Recommendations 9-15:

“For patients undergoing total hip arthroplasty or total knee arthroplasty, the ASH guideline panel *suggests* using aspirin (ASA) or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects). When anticoagulants are used, the panel *suggests* using direct oral anticoagulants (DOACs) over low-molecular-weight heparin (LMWH) (conditional recommendation based on moderate certainty in the evidence of effects); the panel *suggests* using any of the DOACs approved for use (conditional recommendation based on low certainty in the evidence of effects). If a DOAC is not used, the panel *suggests* using LMWH rather than warfarin (conditional recommendation based on very low certainty in the evidence of effects) and *recommends* LMWH rather than unfractionated heparin (UFH) (strong recommendation based on moderate certainty in the evidence of effects).
For patients undergoing hip fracture repair, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects) and *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects).”

c) American Academy of Orthopedic Surgeons Guideline on Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty, 2012:

“We suggest the use of pharmacologic agents and/or mechanical compressive devices for the prevention of venous thromboembolism in patients undergoing elective hip or knee arthroplasty, and who are not at elevated risk beyond that of the surgery itself for venous thromboembolism or bleeding. (Grade of Recommendation: Moderate) Current evidence is unclear about which prophylactic strategy (or strategies) is/are optimal or suboptimal. Therefore, we are unable to recommend for or against specific prophylactics in these patients. (Grade of Recommendation: Inconclusive) In the absence of reliable evidence about how long to employ these prophylactic strategies, it is the opinion of this work group that patients and physicians discuss the duration of prophylaxis. (Grade of Recommendation: Consensus)

In the absence of reliable evidence, it is the opinion of this work group that patients undergoing elective hip or knee arthroplasty, and who have also had a previous venous thromboembolism, receive pharmacologic prophylaxis and mechanical compressive devices. (Grade of Recommendation: Consensus)

In the absence of reliable evidence, it is the opinion of this work group that patients undergoing elective hip or knee arthroplasty, and who also have a known bleeding disorder (e.g., hemophilia) and/or active liver disease, use mechanical compressive devices for preventing venous thromboembolism. (Grade of Recommendation: Consensus)”

d) American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis

"2.0 Patients Undergoing Major Orthopedic Surgery: Total Hip Arthroplasty (THA), Total Knee Arthroplasty (TKA), Hip Fracture Surgery (HFS):

2.1.1. In patients undergoing THA or TKA, we recommend use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose VKA, aspirin (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C)

…2.3.1. In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted dose VKA, or aspirin (all Grade 2C)."

H. Citations for other excerpts

a) Farey JE, An VVG, Sidhu V, Karunaratne S, Harris IA. Aspirin versus enoxaparin for the initial prevention of venous thromboembolism following elective arthroplasty of the hip or knee: A systematic review and meta-analysis. Orthop Traumatol Surg Res. 2021 Feb;107(1):102606. doi: 10.1016/j.otsr.2020.04.002. Epub 2020 Jul 4. PMID: 32631716.

b) Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv*. 2019;3(23):3898-3944. doi:10.1182/bloodadvances.2019000975

c) Jacobs JJ, Mont MA, Bozic KJ, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Bone Joint Surg Am*. 2012;94(8):746-747. doi:10.2106/JBJS.9408.ebo746.

d) Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in Chest. 2012 Apr;141(4):1129. Dosage error in article text] [published correction appears in Chest. 2012 Dec;142(6):1698. Dosage error in article text]. *Chest*. 2012;141(2 Suppl):7S-47S. doi:10.1378/chest.1412S3.

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

Aspirin may be a safe option for venous thromboembolism prevention in select total hip arthroplasty patients; however, there is a lack of high quality evidence and should be used with caution. There is insufficient evidence to provide recommendations for aspirin use in venous thromboembolism prevention for total hip arthroplasty patients.

SECTION 4: Conclusions

A. Validity: Are the findings scientifically valid?

Yes

B. If A was coded "Other, explain or No", please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

n/a

C. Relevance: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?

Yes

D. If C was coded "Other, explain or No", please provide an explanation.

n/a

E. Practice changing potential: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?

Yes

F. If E was coded as "Yes", please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

There is no consensus among leading authorities regarding preferred treatment for venous thromboembolism prevention in post total hip and knee replacement patients. There have been studies suggesting aspirin as sufficient prophylaxis in this setting, however data is conflicting and of low quality. This study suggests aspirin is inferior to enoxaparin for symptomatic venous thromboembolism prevention and could change practices for those supporting aspirin as monotherapy in this setting.

G. Applicability to a Family Medical Care Setting:

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention?

Yes

H. Please explain your answer to G.

Family medicine doctors care for post total hip and knee arthroplasty patients both acutely in the hospital setting and in follow up care in the clinic and nursing home, this could guide treatment in these settings.

I. Immediacy of Implementation:

Is the service, device, drug, therapy, or other essentials readily available on the market? Additionally, does immediate implementation lack major barriers such as cost, challenges for reimbursement, or regulatory barriers? Choose an item.

Yes

J. If I was coded "Other, explain or No", please explain why.

K. Clinically meaningful outcomes or patient oriented outcomes:

Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?

Yes

L. If K was coded "Other, explain or No", please explain why.

M. In your opinion, is this a pending PURL?

1. Valid: Strong internal scientific validity; the findings appear to be true. **yes**

2. Relevant: Relevant to the practice of family medicine. **yes**

3. Practice Changing: There is a specific identifiable new practice recommendation that is

applicable to what family physicians do in medical care settings and seems different than

current practice. **yes**

4. Applicability in medical setting. **yes**

5. Immediacy of implementation. **yes**

N. Comments on your response for question M

The literature is inconclusive regarding the effectiveness of aspirin in venous thromboembolism prophylaxis in the post operative period for those undergoing total hip or knee arthroplasty with conflicting guidelines in this setting. There are guidelines cautiously suggesting consideration of aspirin for this use; however, this study demonstrated enoxaparin as superior to aspirin in preventing symptomatic venous thromboembolism and may help to inform guideline recommendations moving forward.