Development of Clinical Decision Support Tool for Management of Patients Taking Newer Oral Anticoagulants During Dental Procedures

By

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Abstract

Newer oral anticoagulants (NOAs) such as dabigatran etexilate, rivaroxaban, edoxaban, and apixaban are widely used these days as an alternative to warfarin for anticoagulation. Surgical procedures such as extraction are common during dental treatments and are often associated with bleeding. Hence, when treating patients taking anticoagulants clinicians must have a thorough knowledge of the pharmacology of these drugs for adequate management and prevention of any complications to their patients. Clinicians need to constantly update their knowledge as the NOA drugs have been newly introduced and studies regarding their use during dental procedures are only recently available in the literature and continue to evolve. The objective of this paper is to assist clinicians in providing dental care for patients taking these newer oral anticoagulants and are at risk of bleeding complications during dental procedures. In order to accomplish this, a Clinical Decision Support (CDS) system can be developed to allow clinicians to rely on, for any information on these drugs. Clinical decision rules and recommendations are provided to the clinicians in light of the most recently available knowledge.

Introduction

Anticoagulants are drugs that reduce the ability of blood to form clots and coagulate. These days, as patients using anticoagulants have widely increased, so are the number of newly discovered anticoagulants in the market [10]. Over the last 50 years, vitamin K antagonists such as warfarin were the most widely used anticoagulants and were considered as gold standard prophylaxis for reducing cerebrovascular strokes [9,11]. Recently, use of emerging newer alternatives such as dabigatran etexilate, rivaroxaban and apixaban, and edoxaban have been widely increased because of limitations of parentally administered heparin, no need for constant monitoring as for vitamin k antagonists like warfarin, few drug and food interactions, and a broader therapeutic margin [3,11,14]. While dabigatran etexilate is a direct thrombin inhibitor, rivaroxaban, edoxaban, and apixaban are factor Xa inhibitors [3]. They are widely used for anticoagulation in the management of diseases such as atrial fibrillation and venous thromboembolism [10,11]. Although few studies have documented the bleeding risk of these newer anticoagulants, there is no statistically significant evidence available on the risk of bleeding after dental procedures [1,9]. The mechanism of action, indications, interactions with other medications and food, safety profile, and management of adverse events, such as bleeding, of these newer anticoagulants continue to evolve. Dentists must be cautious while performing surgical procedures on patients taking these NOA medications [10]. Any alterations to the medication regimen must be carefully assessed and must be done after consulting the patient's physician [3].

Background and Theoretical framework

The newer orally administered anticoagulants are being used for prophylaxis and treatment of various diseases such as venous thrombosis and pulmonary embolism, thromboembolic complications associated with atrial fibrillation, prosthetic cardiac valve replacements, reduction of the risk of death, re-infarction, and thromboembolic events after myocardial infarction [3,10]. With the increased use of newer oral anticoagulants, dentists come across patients using these drugs almost on a daily basis. In dentistry and oral surgery, attention is required in the treatment of patients taking novel oral anticoagulants (NOAs) due to major concerns such as the risk of hemorrhage and the absence of a specific reversal agent (except for dabigatran etexilate) [1,10]. The patient's individual risk of bleeding, renal functionality, and complexity of surgical procedure is most important factors to be considered during surgical dental treatment of patients taking NOAs [10]. The patient's medical condition as well as other drugs taken by the patient that has significant anticoagulant or antiplatelet action influence the bleeding risk of a patient [11]. As enough data is still not available to establish an evidence base about ideal management of dental patients with NOA's, dentists have to deal with caution when performing procedures on patients using these newer anticoagulants [3,10]. According to the literature available now, for patients requiring simple dental extraction or minor oral surgery procedures, interruption of NOA is not generally necessary, while a higher control of bleeding and discontinuation of the drug (for at least 24 h) would be necessary before invasive surgical procedures, depending on renal functionality [3,10].

Factors that are considered as to be contributing factors for bleeding complications during and after a dental procedure are as follows [11]:

Medical condition	Chronic renal failure, Liver disease, advancing age, major heart problems, use of antiplatelet therapy, uncontrolled hypertension
Coagulation disorders	Hemophilia, Idiopathic thrombocytopenic purpura, Von Willebrand disease, Glanzmann disease, Factor V, VII, X, XI deficiency, Disseminated intravascular coagulation, Congenital platelet dysfunction
Drug usage	Oral anticoagulants and antiplatelet drugs, bone marrow suppressants, NSAIDs such as ibuprofen, aspirin, Drugs acting on nervous systems such as Carbamazepine, Selective serotonin reuptake inhibitors.

Table 1: Contributing factors for bleeding complications

The dental procedures that cause bleeding are classified in the following table as low risk and higher risk, based on the risk of bleeding complications during and after the procedure is performed [10,11].

Low to medium risk	High risk
Simple extractions (1-3 teeth)	Complex extractions involving more than 3 adjacent teeth
Incision and drainage of intraoral cysts	Procedures requiring Flap surgeries and ostectomy
Root surface instrumentation and subgingival scaling	Gingival recontouring
Direct or indirect restorations with subgingival margins	Osseous biopsy
Administration of local anesthesia	Surgery lasting for greater than 45min (head and neck cancer, extensive oral and maxillofacial surgery in patients with comorbidities)
Soft tissue biopsy 1-2.5 cm	Soft tissue biopsy >2.5cm
Ultrasonic scaling	Removal of torus
Placement of a single implant	Placement of multiple implants
One or two quadrants subgingival scaling	Full mouth disinfection with subgingival scaling

Localized periodontal surgery involving <5 teeth	Periodontal surgery>5 teeth

Table 2: Classification of dental procedures based on bleeding risk

Recent guidelines for management during dental procedures in patients taking the newer anticoagulants can be outlined as follows [2,3]:

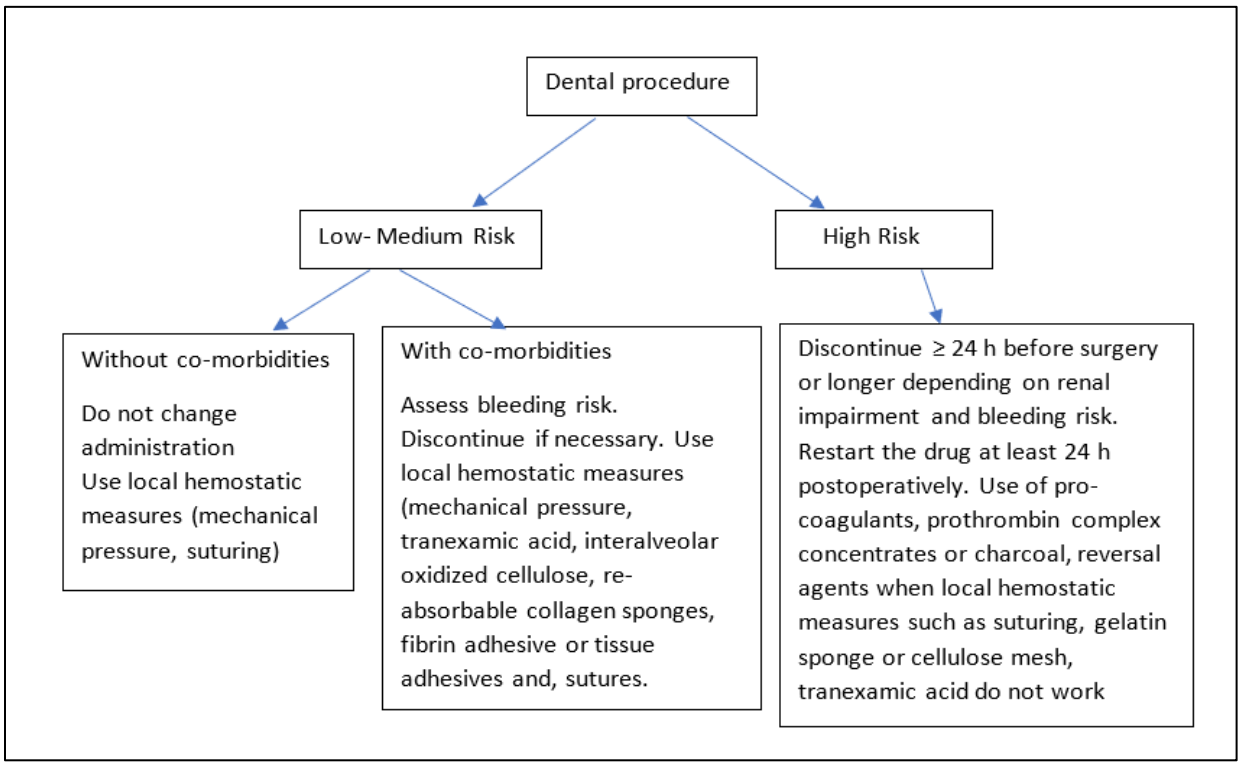

Figure 1: Guideline for management

Guide to discontinuation of dabigatran before elective surgery:

The half-life of dabigatran is about 12-14hrs in healthy patients, 14-17hrs in elderly and up to 27hrs in patients with severe renal impairment [10]. Depending on the pharmacokinetics of the drug, patients with liver disease or impaired renal function may have a higher risk of bleeding following invasive dental treatments as they may have an increased plasma concentration of the drug. As dabigatran is excreted from the kidneys, patients with renal impairment may

exhibit elevated concentrations of the drug, it may be beneficial to check serum creatinine prior to elective surgery and calculate the creatinine clearance [2]. The table below, provides guidance for discontinuation of dabigatran etexilate prior to elective surgery based on the risk of bleeding and degree of renal impairment. [10]

Creatinine clearance (ml/min)	Time of discontinuation before surgery for standard risk of bleeding	Time of discontinuation before surgery for high risk of bleeding
>80	24 h	2–4 days
>50 to ≤ 80	24 h	2–4 days
>30 to ≤ 50	≥48 h	4 days
≤30	2–5 days	5 days

Table 3: Guide to discontinue Dabigatran before surgery

Case scenarios

Low risk: For simple procedures with a minor bleeding risk such as scaling, restoration with use of a matrix band, endodontic treatment, or single tooth extraction, the NOA will likely not need to be stopped [11]. For uncomplicated low to medium risk procedures, local hemostatic measures such as mechanical pressure, suturing and topical hemostatic agents such as Gelfoam or Surgicel should be adequate to control the bleeding [11].

Figure 2: Low risk scenario

High risk: A patients undergoing multiple extractions greater than 3 teeth, alveoloplasty and tuberosity reduction, taking dabigatran 150 mg twice daily with a history of atrial fibrillation, coronary artery disease, hypertension, type 2 diabetes [2]. The dental surgeon will liaise with the patient's physician to consider temporary cessation of the oral anticoagulant drug at least 24 hours (two half-lives) before the procedure [2]. The activated partial thromboplastin time

(aPTT) or thrombin time (TT) should be checked preoperatively (6-12 hrs prior) to ensure the drug effect is reduced. [2,11]

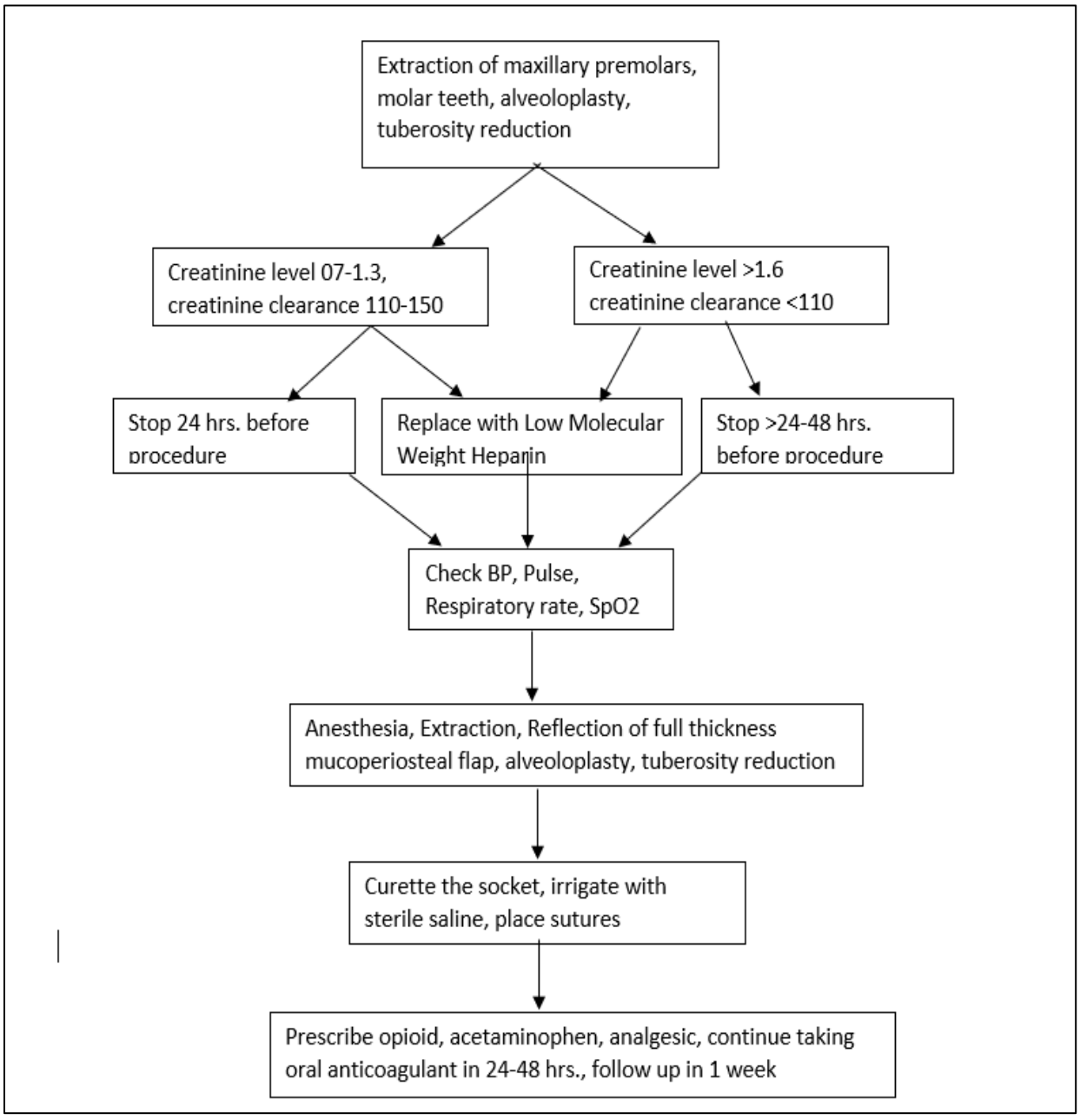

Figure 3: High risk scenario

Workflows

Dentist office workflow

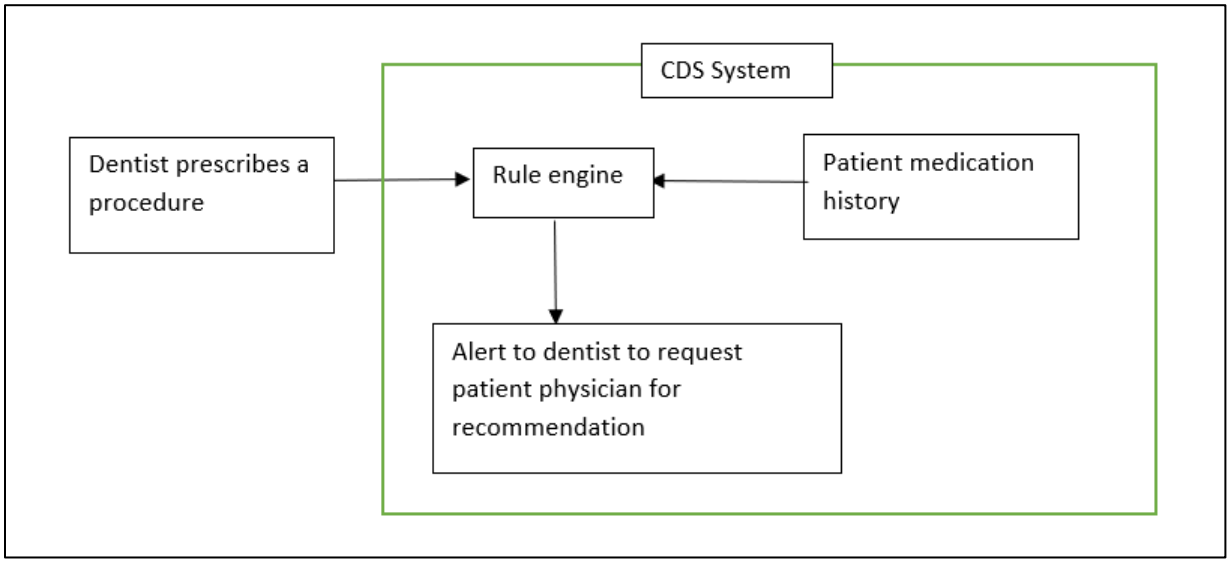

Figure 4: Dentist office workflow

Physician office rule execution workflow

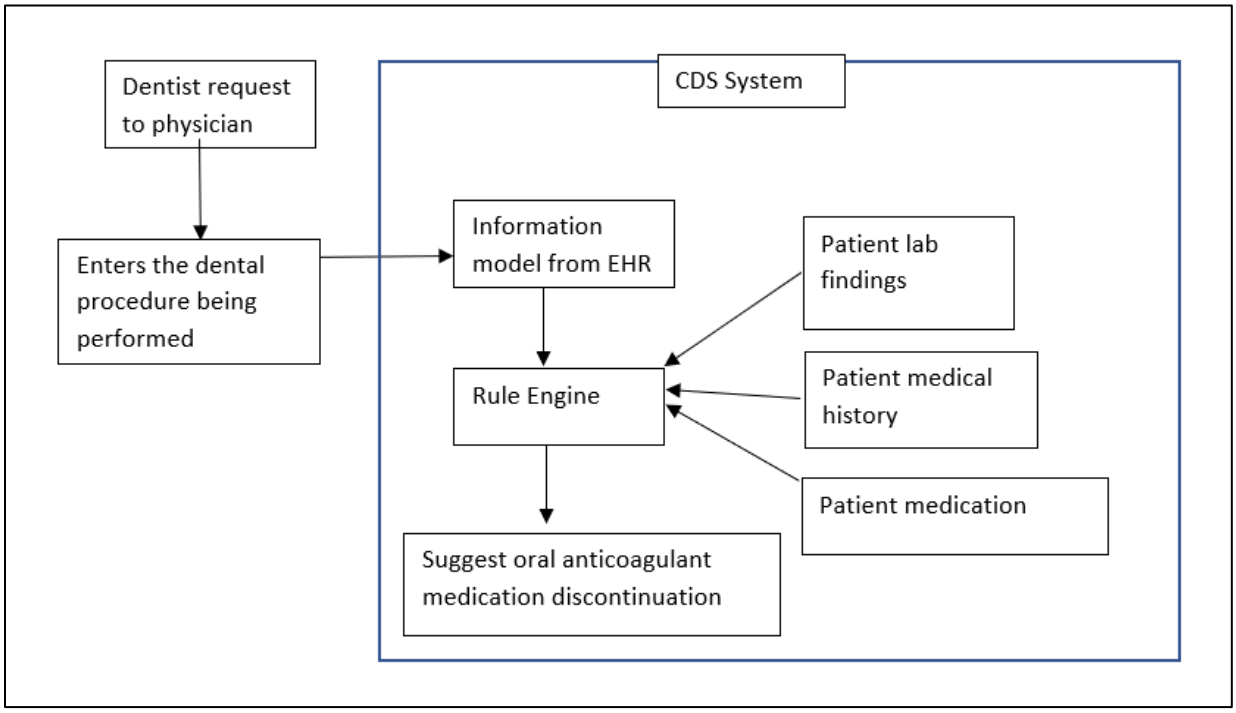

Figure 5: Physician office workflow

Method

A focused review of literature has been performed to identify articles that discussed possible effects and risk associated with bleeding events while taking newer oral anticoagulants, during oral and dental procedures. Articles were reviewed to identify the management protocols that are currently in practice. The concepts used in the search included oral surgery, tooth extraction, bleeding, hemostasis, newer oral anticoagulants, dabigatran, rivaroxaban, edoxaban and apixaban. The literature review was then extended to include case studies that evaluated the risks and benefits of withholding or continuing the novel oral anticoagulant drugs before an invasive dental procedure. It has been observed that very limited evidence is available from these case studies, as not many studies have been performed to identify implications of taking the anticoagulant drug for dental procedures [2]. From the limited evidence obtained from the literature reviews, a management protocol has been designed and implemented in the form of a Clinical Decision Support (CDS) tool in this project.

Clinical Decision Support tool

CDS Authoring tool has been used as an interface to create CDS logic. In order to build CDS logic in CDS authoring tool, 2 accounts were created. One in the CDS authoring tool, and second a UMLS Terminology Services (UTS) account.

UTS accounts are maintained by the National Library of Medicine (NLM) [16]. Once a profile is created, it generates an API key. The API Key generated from UTS account is used within the CDS authoring tool to access services provided by the Value Set Authority Center (VSAC) [16]. “The VSAC is a repository and authoring tool for public value sets created by external

programs" [15]. These services enable us to search for value sets, codes and other services provided by VSAC [16]. In order to use these services in the CDS authoring tool, the UMLS API key must be provided. The CDS Authoring tool provides the space to create and manage artifacts [16].

Create and Build CDS artifact: For this project, a new artifact named '001_CDS_Project' was created. It can be done using the '+Create new Artifact' option and it provides access to workspace. The workspace includes components such as Summary, Inclusions, Exclusions, Subpopulations, Base elements, Recommendations, Parameters and External CQL. The CDS artifact is built in the CDS Authoring tool by adding and joining elements in particular contexts [16]. These elements specify the criteria to determine the aspects the patient qualifies to be included for a recommendation [16].

Inclusions: Any person who has an active medication order for the newer oral anticoagulants such as Dabigatran etexilate, rivaroxaban, edoxaban and apixaban can be included in the CDS recommendation. In order to create this, a medication request is selected as the element type. When there exists a medication order which consists of codes of any of these four medications (Dabigatran etexilate, rivaroxaban, edoxaban and apixaban), the patient is included for the CDS recommendation. The code system used for medications for this tool is the RXNorm. The VSAC service enables to search for Value set and codes. In order to use this service, one must authenticate VSAC with the API key, and search for the required codes and value set.

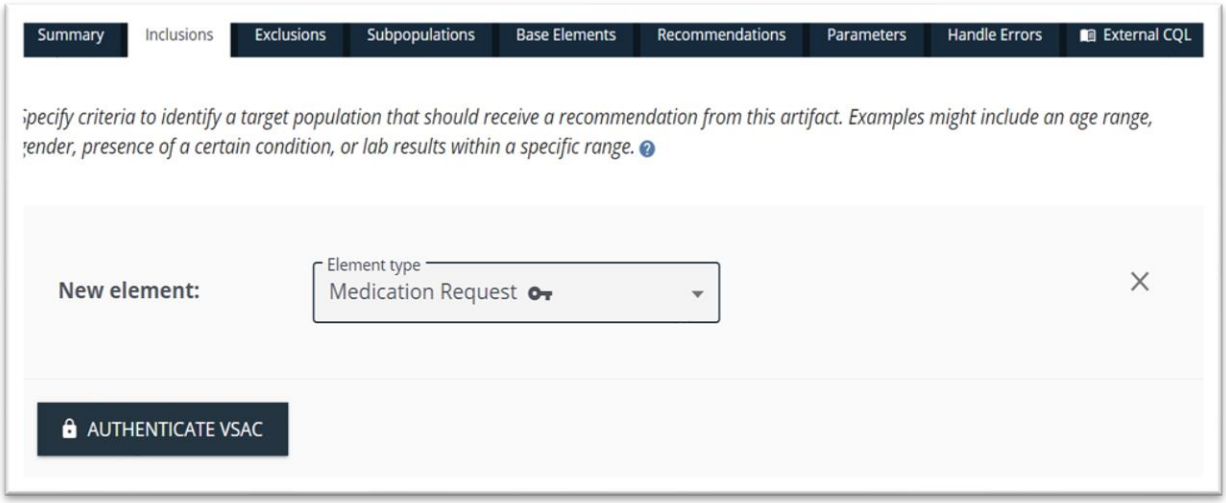

Figure 6: Inclusion Element-Medication request

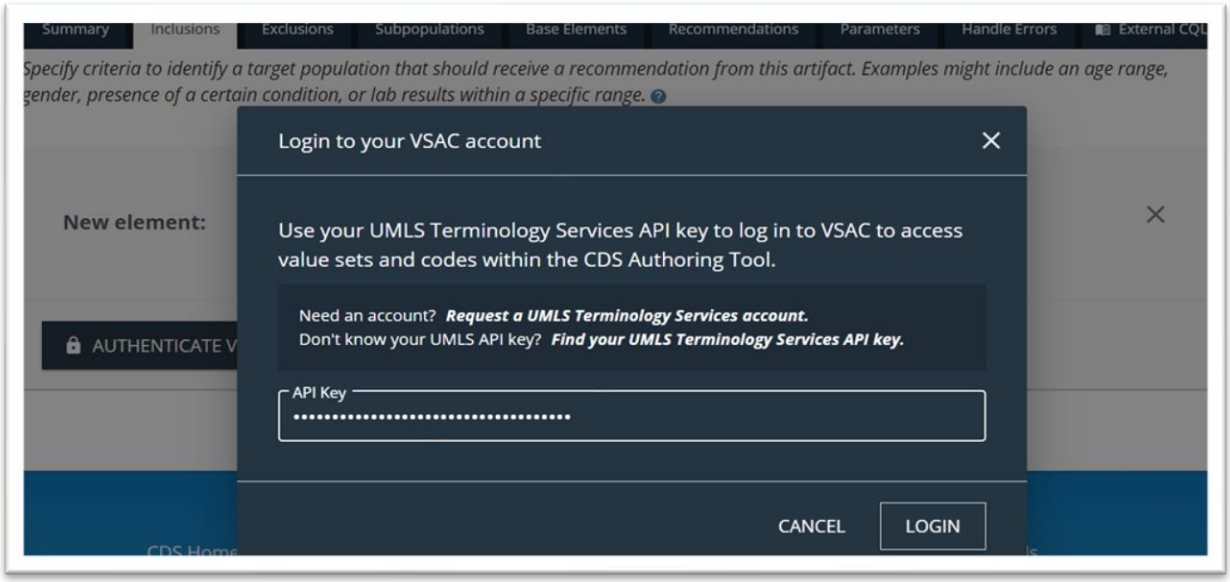

Figure 7: VSAC authentication

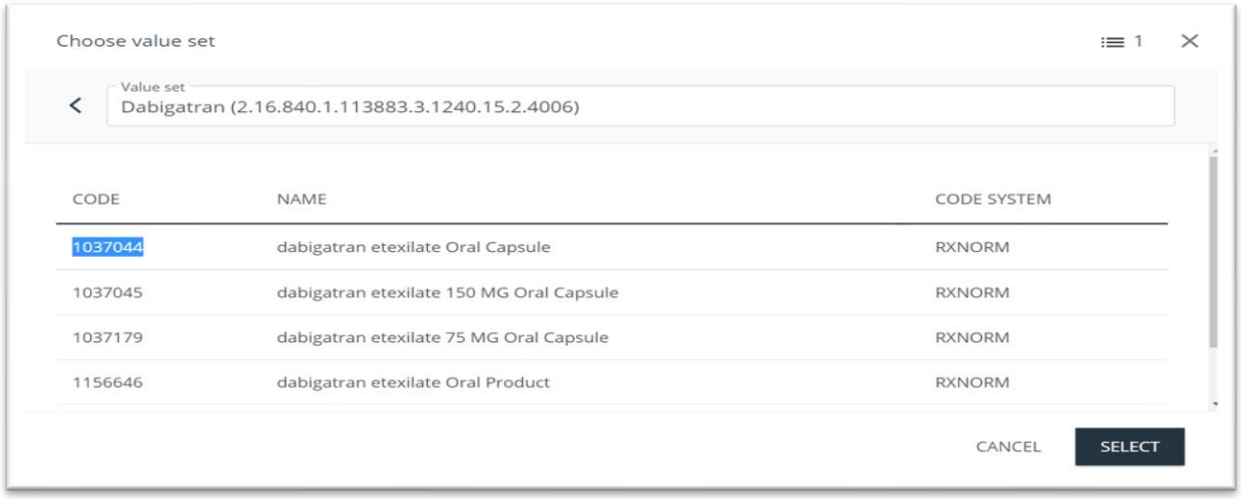

Figure 8: Value set for Medication

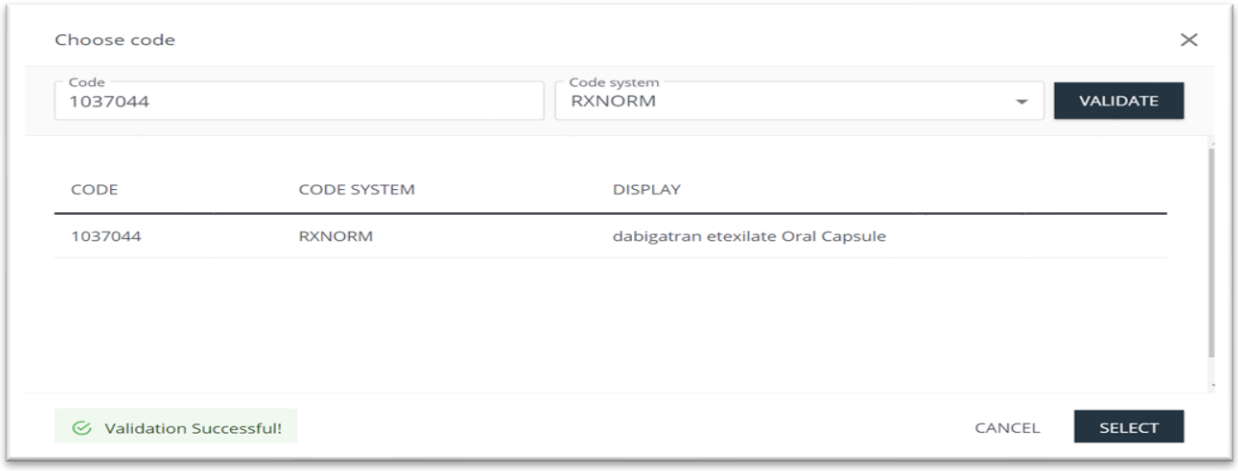

Figure 9: Code for Medication

Subpopulations: The patients are suggested more specific recommendations based on the elements which can be specified in the subpopulations [16]. In the CDS application, populations are grouped based on the following list of criteria:

- most recent value of creatinine clearance,
- the bleeding risk of dental procedure being performed which can be a
    - low to medium risk or
    - high-risk procedure,

- presence of chronic medical conditions such as chronic kidney disease or a liver disease, cardiac conditions, and valve replacement procedures.

For Observation elements such as creatinine clearance LOINC codes were used, and SNOMED codes were used for Condition element. For specifying dental procedures, CDT codes have been used and ICD 10 for medical procedures.

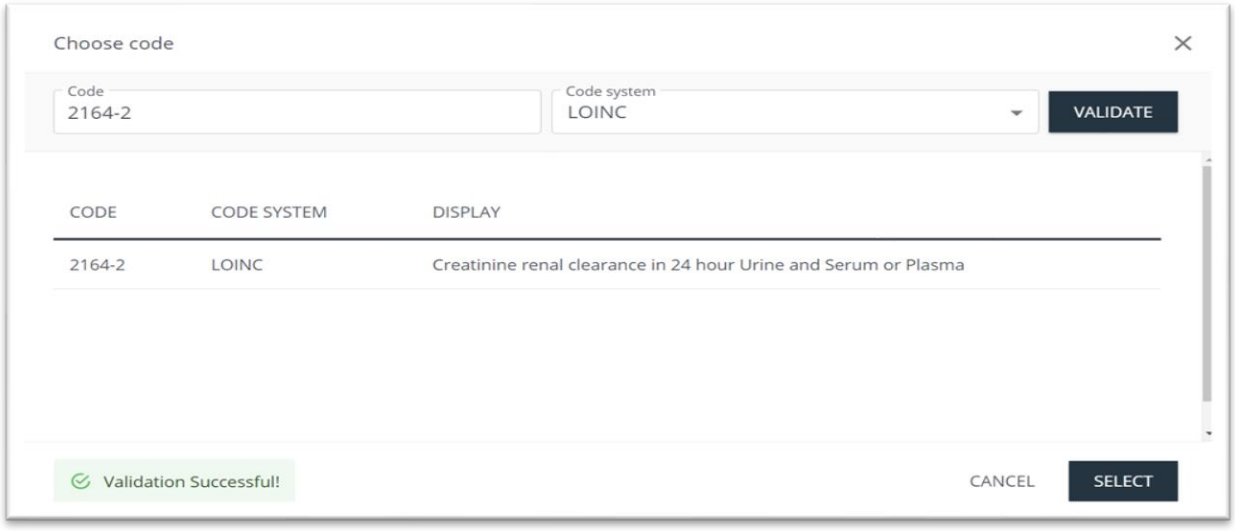

Figure 10: Observation-Creatinine clearance Code

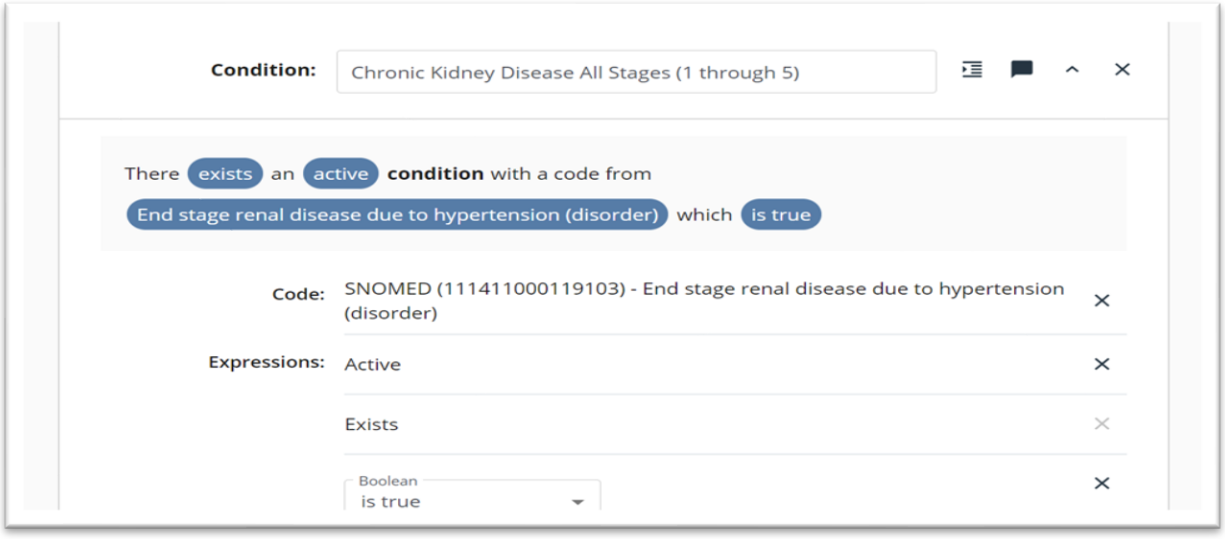

Figure 11: Condition-Chronic Kidney Disease Subpopulation

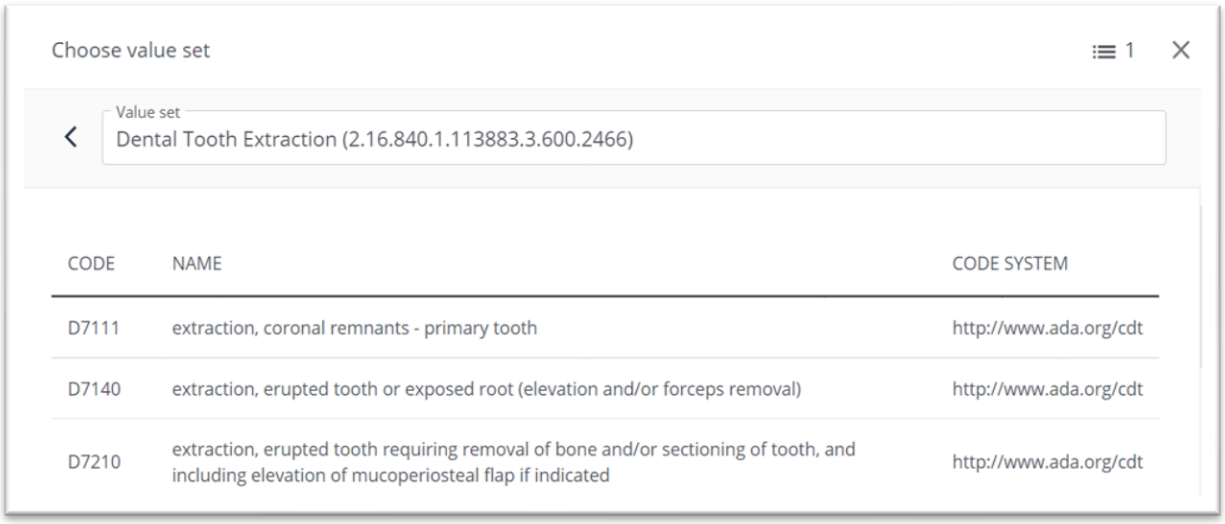

Figure 12: Dental Procedure Code

Creating Recommendations: A patient who meets the Inclusion criteria and does not meet the Exclusion criteria is eligible for a recommendation. Once the CDS artifact is triggered, the recommendations are provided as decision support notices to the clinician [16]. Recommendations are created using the 'New Recommendation' button. Patients who do not meet the inclusion criteria will not receive a recommendation. Recommendations are provided corresponding to the subpopulations to which they apply [16]. This is done by selecting the 'Add subpopulation' button.

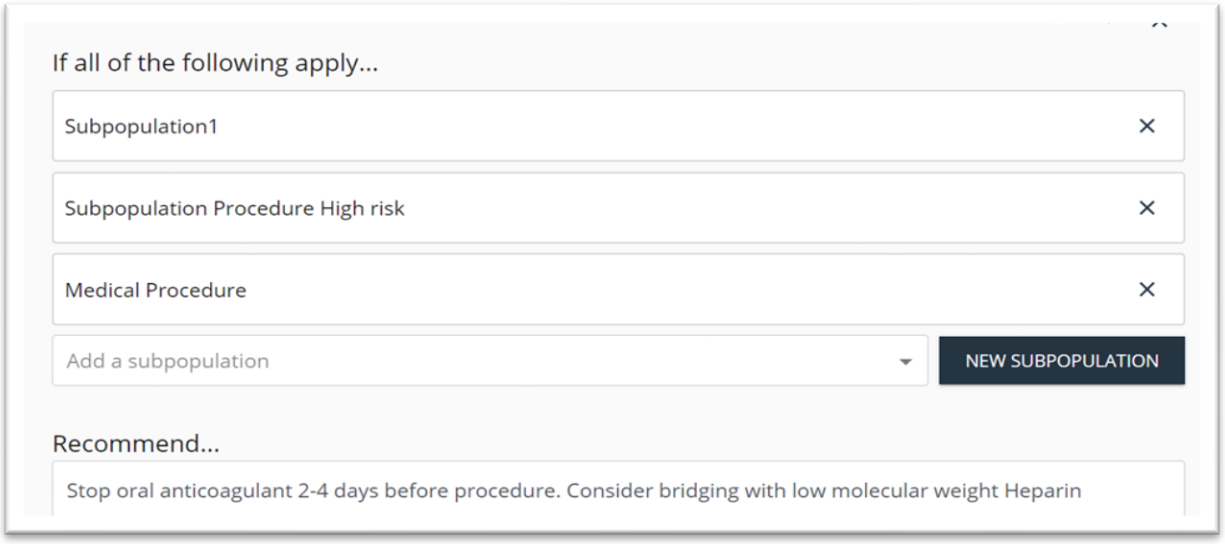

Figure 13: Creating Recommendations for Subpopulations

***CDS Logic**:* The artifact that was built represent medical knowledge and creates computable, interoperable translations using CQL. "CQL is a data standard governed by Health Level 7 (HL7) that is currently a Standard for Trial Use (STU)" [17]. The CQL logic is expressed in a human-readable format. The CDS uses a decision tree model consisting of multiple steps of 'if then else' logic to define recommendations. The computer program uses Boolean expressions (true/false) and conditionals (if/then/else) that help respond differently based on different inputs and parameters.

```
define "InPopulation":
  "MeetsInclusionCriteria"

define "Recommendation":
  if "Subpopulation1" and "Subpopulation Procedure low risk"
     then 'Do not stop oral anticoagulant. Continue with the procedure.'
  else if "Subpopulation1" and "Subpopulation Condition" and "Subpopulation Procedure low risk"
     then 'Stop oral anticoagulant 24hrs before procedure. Restart the drug at least 24hrs postoperatively '
  else if "Subpopulation 2" and "Subpopulation Procedure low risk"
     then 'Stop oral anticoagulant 24hrs before procedure. Restart the drug at least 24hrs postoperatively'
  else if "Subpopulation 2" and "Subpopulation Procedure High risk"
     then 'Stop oral anticoagulant 2-4 days before procedure. Restart the drug at least 24hrs postoperatively'
  else if "Subpopulation 3" and "Subpopulation Procedure low risk"
     then 'Stop oral anticoagulant >48hrs before procedure. Restart the drug at least 24hrs postoperatively'
  else if "Subpopulation 3" and "Subpopulation Procedure High risk"
     then 'Stop oral anticoagulant 4-5 days before procedure. Restart the drug at least 24hrs postoperatively'
  else if "Subpopulation1" and "Subpopulation Procedure High risk" and "Medical Procedure"
     then 'Stop oral anticoagulant 2-4 days before procedure. Consider bridging with low molecular weight Heparin'
  else null
```

Figure 14: CQL

Testing CDS Artifact

Uploading Test patients:

CDS artifacts can be tested in the Testing link, in the CDS authoring tool. In order to test the artifact, synthetic patient data has been sourced from ‘Synthea’, which provides synthetic patient data and associated health records as JSON (JavaScript Object Notation) files (Conditions, Medications, Care plans, Encounters, Observations, Procedures etc). The patent records are customized to suit the elements and codes that have been created in the CDS artifact. It is done by editing the downloaded JSON files using NotePad++ text editor. These files are uploaded to the CDS authoring tool as DTSU2 FHIR bundle.

```
{
  "fullUrl": "urn:uuid:396277af-3544-4750-bb2d-37962f715e48",
  "resource": {
    "resourceType": "MedicationOrder",
    "id": "396277af-3544-4750-bb2d-37962f715e48",
    "dateWritten": "2019-06-18T02:19:38-04:00",
    "status": "active",
    "patient": {
      "reference": "urn:uuid:f0e6db09-3d74-4a87-b95c-2fbdb0716059"
    },
    "prescriber": {
      "reference": "urn:uuid:0000016d-3a85-4cca-0000-0000000001ae"
    },
    "encounter": {
      "reference": "urn:uuid:85d636f9-e713-4fc0-9783-2b28081136f5"
    },
    "medicationCodeableConcept": {
      "coding": [
        {
          "system": "http://www.nlm.nih.gov/research/umls/rxnorm",
          "code": "1037044",
          "display": "dabigatran etexilate Oral Capsule"
        }
      ],
      "text": "dabigatran etexilate Oral Capsule"
    },
    "dosageInstruction": [
      {
        "asNeededBoolean": true
      }
    ]
  },
  "request": {
    "method": "POST",
    "url": "MedicationOrder"
  }
```


Figure 15: Synthea JSON file

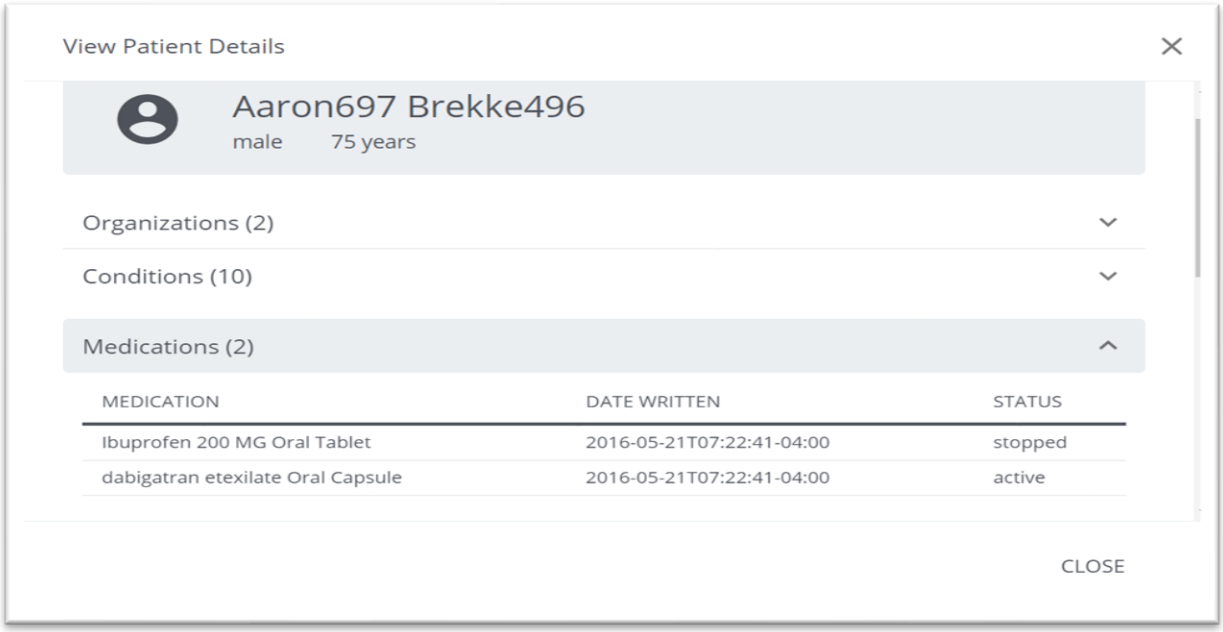

Figure 16: Patient file uploaded in CDS authoring tool

Test Execution:

The generated CQL can be executed on selected test patients. In order to run the CQL the VSAC must be authenticated. Then, the test patients are selected. CQL is executed on the selected patients by selecting the FHIR compatible CDS artifact that has been created - '001_CDS_Project'.

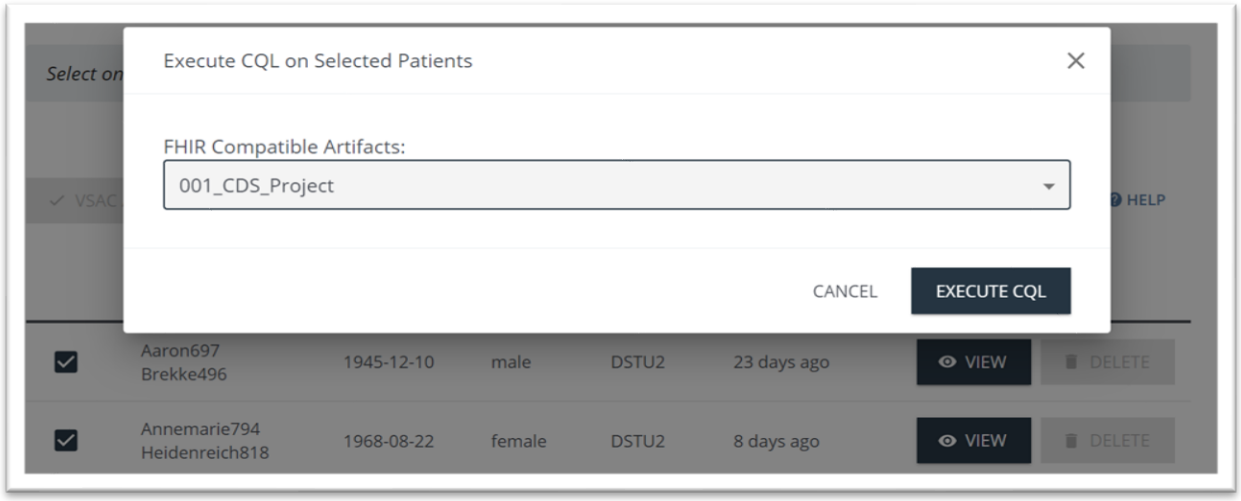

Figure 17: CQL Execution

Results

Once the CQL is executed, the results appear on the Testing page. It displays the name of the artifact, number of test patients that met the inclusion criteria and exclusion criteria. It also displays if each patient has met the inclusion or exclusion criteria, any recommendation, rationale, and errors, that the CDS indicates to the particular patient, otherwise it displays the phrase 'No Value'.

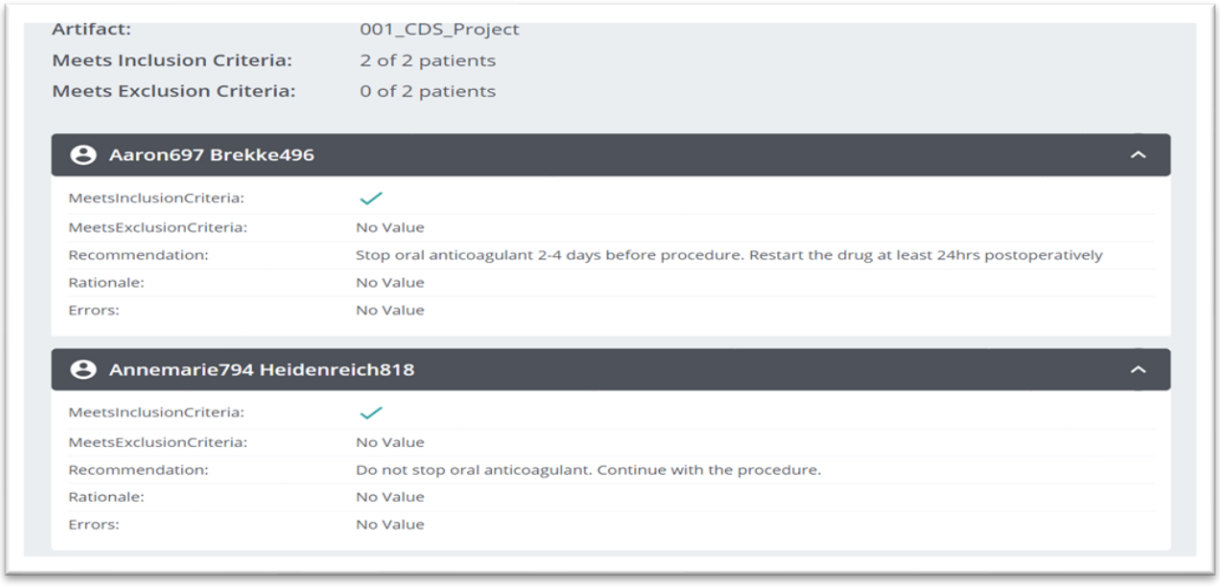

Figure 18: Results

Discussion

The extensive use of NOAs in recent times have shown to impact various dental surgical procedures. These NOAs have been introduced recently and evidence available on the effects of these drugs during dental procedures is limited [2]. Research studies regarding management of patient taking NOAs during dental procedures are being performed recently and the knowledge continues to expand to help develop new guidelines.

The risk of bleeding complications during and following a dental procedure is usually considered low unless the patient has bleeding disorders, comorbidities, and using anticoagulant and antiplatelet medications [10]. Hence before performing a dental procedure in such patients, the dentist must carefully judge the risk associated with the procedure for each patient and ascertain whether hemostasis can be achieved. Although very limited evidence is available on the risk of bleeding after dental procedures on patient using newer oral anticoagulants, such as NOAs, based on limited evidence as reviewed in the literatures, in most cases, there is no need

to alter the anticoagulation regimen prior to most dental interventions [3]. However, in patients considered to be at a higher risk of bleeding, there may be a need to postpose the timing of daily dose or adjust timing of procedures as late as possible after the last dose or stop taking the drug for 24 to 48 hrs. [2,3]. The consideration as to how long the dose many be stopped before and after a procedure may be assessed based on half-life of the drug, age, sex, weight of the patient, renal and liver function. The clinicians may have to carefully assess the risk of stopping or altering the medication that may lead to thromboembolic episodes, to the consequences of bleeding which can be controlled by local hemostatic measures. The dentist must consult the patient's physician for altering the medication, in patients with higher risk of thrombo-embolic events [3].

One way to improve adherence to these evolving guidelines is to develop a clinical decision support system which is integrated into dentist's and clinician's workflows in the electronic health record systems. This provides clinicians with the most recent and updated knowledge for dosing at the point of care, offering support for adherence to guideline recommendations, reduce errors and improve safety of the patients.

The CDS authoring tool used in this project, offers an interface to create a sharable CDS logic, which can be exported as HL7 CQL artifacts. This can be integrated into the EHRs using HL7 FHIR data model. This tool allows easy translation of clinical guidelines into computable CDS logic. The artifacts developed in this tool are interoperable. They can be published through CDS connect which can be tested and implemented in different health IT systems and offer possibilities of improving quality of patient care [17].

However, there is still a dearth in the resources available for building CDS for dental procedures in this tool. There were not many value sets and codes available for different dental surgical procedures. For a dental surgical procedure, only 'Extraction of tooth' was found to be available in the tool, limiting the scope of expanding to other major dental procedures with increased bleeding risk. Hence dental extraction with varying complexity have been used to represent both high and low risk procedures for this project.

Summary

The newer oral anticoagulants were found to have the same bleeding risk as the conventional oral anticoagulants while performing dental procedures according to available literatures. However, there are no specific reversal agents or antidotes available for these drugs, except for dabigatran etexilate. In October 2015, the U.S. Food and Drug Administration approved Idarucizumab, a monoclonal antibody fragment, when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures, or in life-threatening or uncontrolled bleeding [10]. Antidotes for the other new drugs are not yet available. As evidence base is lacking about the best practices for assessing the risk of bleeding due to these newer anticoagulants, dentists must practice with caution. Providing timely decision support for dental surgical procedures helps to prevent any untoward adverse events, especially in complex dental procedures, in patients taking NOAs and with comorbidities.

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