Cohort Study
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. Citiation: 1: Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019 Jan 3;380(1):11-22. doi: 10.1056/NEJMoa1812792. Epub 2018 Nov 10. PubMed PMID: 30415628.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/30415628
C. First date published study available to readers:1/3/19
D. PubMed ID: 30415628
E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: University of Missouri Columbia
G. Date Nominated: 2/18/2019
H. Identified Through: NEJM
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 2/22/19
K. Potential PURL Review Form (PPRF) Type: Cohort Study
L. Assigned Potential PURL Reviewer: Corey Lyon
M. Reviewer Affiliation: University of Colorado
A. Abstract:

BACKGROUND:
PATIENTS WITH ELEVATED TRIGLYCERIDE LEVELS ARE AT INCREASED RISK FOR ISCHEMIC EVENTS. ICOSAPENT ETHYL, A HIGHLY PURIFIED EICOSAPENTAENOIC ACID ETHYL ESTER, LOWERS TRIGLYCERIDE LEVELS, BUT DATA ARE NEEDED TO DETERMINE ITS EFFECTS ON ISCHEMIC EVENTS.

METHODS:
WE PERFORMED A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL INVOLVING PATIENTS WITH ESTABLISHED CARDIOVASCULAR DISEASE OR WITH DIABETES AND OTHER RISK FACTORS, WHO HAD BEEN RECEIVING STATIN THERAPY AND WHO HAD A FASTING TRIGLYCERIDE LEVEL OF 135 TO 499 MG PER DECILITER (1.52 TO 5.63 MMOL PER LITER) AND A LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVEL OF 41 TO 100 MG PER DECILITER (1.06 TO 2.59 MMOL PER LITER). THE PATIENTS WERE RANDOMLY ASSIGNED TO RECEIVE 2 G OF ICOSAPENT ETHYL TWICE DAILY (TOTAL DAILY DOSE, 4 G) OR PLACEBO. THE PRIMARY END POINT WAS A COMPOSITE OF CARDIOVASCULAR DEATH, NONFATAL MYOCARDIAL INFARCTION, NONFATAL STROKE, CORONARY REVASCULARIZATION, OR UNSTABLE ANGINA. THE KEY SECONDARY END POINT WAS A COMPOSITE OF CARDIOVASCULAR DEATH, NONFATAL MYOCARDIAL INFARCTION, OR NONFATAL STROKE.

RESULTS:
A TOTAL OF 8179 PATIENTS WERE ENROLLED (70.7% FOR SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS) AND WERE FOLLOWED FOR A MEDIAN OF 4.9 YEARS. A PRIMARY END-POINT EVENT OCCURRED IN 17.2% OF THE PATIENTS IN THE ICOSAPENT ETHYL GROUP,

AS COMPARED WITH 22.0% OF THE PATIENTS IN THE PLACEBO GROUP (HAZARD RATIO, 0.75; 95% CONFIDENCE INTERVAL [CI], 0.68 TO 0.83; P<0.001); THE CORRESPONDING RATES OF THE KEY SECONDARY END POINT WERE 11.2% AND 14.8% (HAZARD RATIO, 0.74; 95% CI, 0.65 TO 0.83; P<0.001). THE RATES OF ADDITIONAL ISCHEMIC END POINTS, AS ASSESSED ACCORDING TO A PRESPECIFIED HIERARCHICAL SCHEMA, WERE SIGNIFICANTLY LOWER IN THE ICOSAPENT ETHYL GROUP THAN IN THE PLACEBO GROUP, INCLUDING THE RATE OF CARDIOVASCULAR DEATH (4.3% VS. 5.2%; HAZARD RATIO, 0.80; 95% CI, 0.66 TO 0.98; P=0.03). A LARGER PERCENTAGE OF PATIENTS IN THE ICOSAPENT ETHYL GROUP THAN IN THE PLACEBO GROUP WERE HOSPITALIZED FOR ATRIAL FIBRILLATION OR FLUTTER (3.1% VS. 2.1%, P=0.004). SERIOUS BLEEDING EVENTS OCCURRED IN 2.7% OF THE PATIENTS IN THE ICOSAPENT ETHYL GROUP AND IN 2.1% IN THE PLACEBO GROUP (P=0.06).

CONCLUSIONS:
AMONG PATIENTS WITH ELEVATED TRIGLYCERIDE LEVELS DESPITE THE USE OF STATINS, THE RISK OF ISCHEMIC EVENTS, INCLUDING CARDIOVASCULAR DEATH, WAS SIGNIFICANTLY LOWER AMONG THOSE WHO RECEIVED 2 G OF ICOSAPENT ETHYL TWICE DAILY THAN AMONG THOSE WHO RECEIVED PLACEBO. (FUNDED BY AMARIN PHARMA; REDUCE-IT CLINICALTRIALS.GOV NUMBER, NCT01492361 .).

B. Pending PURL Review Date**:** 11/7/2019

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. The study address an appropriate and clearly focused question. Well covered
Comments:
The question is clearly defined. Does a highly purified eicosapentaenoic acid ethyl ester (Vascepa) have an effect on ischemic events?

B. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation. Well covered
Comments:
Patients were enrolled and followed at 473 participating sites in 11 countries, including 38% of patients from the US.

C. The study indicates how many of the people asked to take part in it in each of the groups being studied. Well covered
Comments:

D. The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis. Well covered
Comments:
Patients with planned coronary intervention or surgery excluded

E. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?
152 patients (1.9%) did not complete the final study visits, and 578 patients (7.1%) withdrew consent

F. Comparison is made between full participants and those lost to follow up, by exposure status.
Well covered
Comments:
All analyses were performed according to the intention-to-treat principle.

G. The outcomes are clearly defined. Well covered
Comments: The primary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infarction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis

H. The assessment of outcome is made blind to exposure status. Adequately addressed
Comments: the steering committee and the sponsor remained unaware of the trial-group assignments

I. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome. Not applicable
Comments:

J. What are the key findings of the study?
1606 primary end-points occurred
   a. 17.2% in the icosapent ethyl group vs 22% in the placebo group (HR, 0.75; 95% CI, 0.68-0.83; p<0.001)
   b. NNT=21/4.9 years

Among patients with elevated triglyceride levels who were receiving statin therapy, the risk of major ischemic events, including cardiovascular death, was significantly lower with 2 g of icosapent ethyl twice daily (total daily dose, 4 g) than with placebo.

K. How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests?
Funded by Amarin Pharma, the manufacturer of Vascepa. This is fairly standard with branded products seeking additional indications of CV prevention.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts
For Secondary Prevention of CAD:

- **Lipids**

Statins:

1. statins reduce mortality, myocardial infarction, and stroke in adults with coronary artery disease (level 1 [likely reliable] evidence), although reduction of mortality and stroke in women is based on limited data (level 2 [mid-level] evidence)
2. high-dose statins may reduce risk of stroke and nonfatal myocardial infarction more than moderate-dose statins in patients with cardiovascular disease (level 2 [mid-level] evidence)
3. more intensive statin therapy (such as atorvastatin 80 mg/day or simvastatin 80 mg/day) reduces mortality compared to less intensive statin therapy after acute coronary syndrome (level 1 [likely reliable] evidence)

PCSK9 inhibitors:

1. addition of evolocumab to statin therapy decreases 2-year risk of adverse cardiovascular events in patients with atherosclerotic cardiovascular disease (level 1 [likely reliable] evidence)
2. addition of evolocumab to statin therapy appears to reduce risk of major cardiovascular events in patients with high baseline high-sensitivity C-reactive protein levels (level 2 [mid-level] evidence)
3. addition of evolocumab to statin therapy reduces atheroma volume and increases plaque regression in patients with coronary artery disease (level 3 [lacking direct] evidence)

Fibrates:

1. fibrates may reduce coronary events but not mortality in patients with preexisting heart disease (level 2 [mid-level] evidence)
2. gemfibrozil may reduce risk for myocardial infarction and possibly stroke and coronary mortality in patients with coronary artery disease and low high-density lipoprotein cholesterol (level 2 [mid-level] evidence)

Other Medications

1. addition of ezetimibe to other lipid-modifying drugs may slightly reduce risk of major adverse cardiovascular events (level 2 [mid-level] evidence)

B. DynaMed citation/Title. Author. In: DynaMed [database online]. Available at: access date www.DynamicMedical.com Last Updated:Accessed

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. *T900316*, *Secondary Prevention of Coronary Artery Disease*; [updated *2018 Dec 04*, cited Dec 04, 2019]. Available from https://www.dynamed.com/topics/dmp~AN~*T900316*. Registration and login required.

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

Current standard is high intensity statin therapy, followed by addition of PCSK9 inhibitor or ezetimibe for further ASCVD risk reduction, if needed based on cholesterol values.

D. UpToDate excerpts

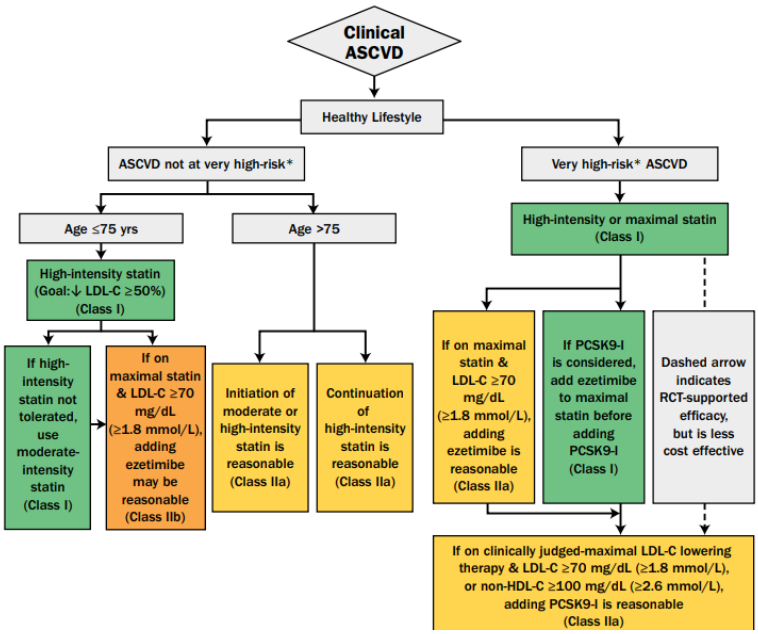
- Dyslipidemia : We treat all patients with atherosclerotic cardiovascular disease (CVD), as well as individuals with a 10-year risk >7.5 percent, with evidence-based doses of a high-intensity statin regardless of the baseline low-density lipoprotein (LDL) cholesterol.

E. UpToDate citation/Always use Basow DS as editor & current year as publication year. Access date Title. Author. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: Accessed
Hennekens CH, Lopez-Sendon J. Overview of the prevention of cardiovascular disease events in those with established disease (secondary prevention) or at high risk. Basow DS, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (Accessed on December 04, 2019.)

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
Current standard is high intensity statin therapy for secondary prevention of ASCVD.

G. Other excerpts (USPSTF; other guidelines; etc.)
2018 Guideline on the Management of Blood Cholesterol:

Figure 1:
Secondary Prevention in Patients with Clinical ASCVD



H. Citations for other excerpts
J Am Coll Cardiol. Nov 2018; DOI: 10.1016/j.jacc.2018.11.003

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)
High intensity statin therapy with the addition of ezetimibe and/or PCSK9 inhibitor.

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

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?

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.

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.

Current practice recommends statin therapy for secondary prevention of ASCVD with non-statin therapies such as ezetimibe or PCSK9 inhibitors to be considered as add-on therapy if further LDL-lowering is needed. The change in practice for patients requiring pharmacologic therapy for secondary prevention of ASCVD would be to add Vascepa (icosapent ethyl) at 2 g twice daily to a statin, regardless of lipid panel values, to provide additional risk reduction of ASCVD events or cardiovascular-related deaths.

While the trial also included primary prevention patients, the majority (70%) of patients were secondary prevention.

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**.

The change in practice is accomplished by prescribing icosapent ethyl (Vascepa) which is readily available and has no prescribing restrictions.

I. **Immediacy of Implementation**:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? No

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

While still a brand name drug with a cash price of approximately $350 for a 30 day supply, Vascepa appears to be covered by major Medicare Part D plans. Further, a cost-effectiveness analysis concluded that icosapent ethyl was a dominant strategy (i.e., cost saving) in 70% of simulations, offering the rare finding of better outcomes at lower healthcare costs. In probabilistic sensitivity analysis, >85% of simulations indicated that icosapent ethyl would be cost-effective (i.e., below $50,000 per QALY gained) compared with placebo.

Still, the cost (co-pay) to the patient would need to be considered.

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.
The benefits of a reduction in cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina by 25% outweighs the low incidence of risks in the treatment group, including higher rates of hospitalization for atrial fibrillation or atrial flutter and nonfatal bleeding events.

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

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

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

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.

4. Applicability in medical setting.

5. Immediacy of implementation

N. Comments on your response for question M.
Please see comments under individual sections.