What medical societies have recognized icosapent ethyl (VASCEPA®/VAZKEPA) in their medical treatment guidelines or scientific statements?

A growing number of medical societies are recommending the usage of icosapent ethyl (VASCEPA/VAZKEPA) in appropriate patients. In addition to recommending the use of icosapent ethyl, many of these guidelines emphasize that the positive clinical results of the REDUCE-IT® cardiovascular outcomes study should not be generalized to any product other than icosapent ethyl (i.e., the clinical results are unique to VASCEPA).

Medical societies that have updated their guidelines and/or issued scientific statements include:

North America

- American Diabetes Association (ADA)
- American Heart Association (AHA)
- American Stroke Association (ASA)
- National Lipid Association (NLA)
- American Association of Clinical Endocrinologists (AACE)
- American College of Endocrinology (ACE)
- Thrombosis Canada
- Endocrine Society (ENDO)
- Canadian Cardiovascular Society (CCS)
- Canadian Stroke Best Practice Recommendations Advisory Committee, in collaboration with the Canadian Stroke Consortium
- American College of Cardiology (ACC)

Europe

- European Society of Cardiology (ESC)
- European Atherosclerosis Society (EAS)

South America

- Brazilian Society of Cardiology (SBC)
- Colombian Association of Endocrinology, Diabetes and Metabolism, Colombian Society of Cardiology and Cardiovascular Surgery

Asia/Africa

- Japan Circulation Society (JCS)
- Chinese Society of Cardiology (CSC)
- Chinese Journal of Internal Medicine (a journal of the Chinese Medical Association [CMA])
- The Egyptian Heart Journal (the official journal of the Egyptian Society of Cardiology)
- Chinese Association of Cardiovascular Surgeons (CACS)/Chinese Society of Thoracic and Cardiovascular Surgery (CSTCVS)

Middle East

- Saudi National Diabetes Center (SNDC)

Below are more details regarding these guidelines and scientific statements (listed in chronological order):

- The American Diabetes Association (ADA) updated their *Standards of Medical Care in Diabetes* in March of 2019 to recommend that icosapent ethyl be considered for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD) or other cardiac risk factors on a statin with controlled low-density lipoprotein cholesterol (LDL- C), but with elevated triglyceride (TG) levels (135–499 mg/dL) to reduce cardiovascular (CV) risk.

  The findings were made with a level "A" grade of scientific evidence which, under ADA standards, reflects that REDUCE-IT was considered to be a large well-designed clinical trial. Generally, according to ADA, A-level recommendations have the best chance of improving outcomes when applied to the population to which they are appropriate.

  The ADA is a United States–based nonprofit that seeks to prevent and cure diabetes and to improve the lives of all people affected by diabetes.[1]

- In May 2019, the Japan Circulation Society (JCS) referenced REDUCE-IT and eicosapentaenoic acid (EPA) in their publication of updated guidelines.[2]

- The American Heart Association (AHA) issued a Scientific Advisory in August of 2019 recognizing that elevated TG levels may be a causal factor for CV disease (CVD); that dietary supplements are not recommended, nor FDA approved, to treat medical conditions; and that positive outcomes results were demonstrated in REDUCE-IT.

  The AHA is the nation's oldest and largest voluntary organization dedicated to fighting heart disease and stroke.[3]

- The European Society of Cardiology (ESC) updated their patient treatment guidelines on September 1, 2019 to include icosapent ethyl to address high-risk CV patients with elevated TG levels (135–499 mg/dL). They updated their guidelines jointly with the European Atherosclerosis Society (EAS). The classification is a Level B recommendation, which reflects a relatively high weight of scientific evidence under ESC and EAS standards.

  ESC is a not-for-profit medical society led by expert volunteers. They unite Member National Cardiac Societies, cardiovascular ESC subspecialty communities, Affiliated Cardiac Societies, distinguished Fellows of the ESC, and individual members from around the world.[4]

- The EAS joined ESC to jointly issue the above-described patient treatment guidelines.

  EAS was founded in 1964 with the aim of "advancing and exchanging knowledge concerning the causes, natural history, treatment and prevention of atherosclerotic disease." For more than 50 years, the society's expertise has been used to teach clinicians how to manage lipid disorders and prevent atherosclerosis.[5]

- The National Lipid Association (NLA) issued a position statement on September 13, 2019 recommending icosapent ethyl for ASCVD risk reduction in high- and very-high-risk patients, 45 years of age or older with clinical ASCVD, or 50 years of age or older with type 2 diabetes requiring medication and with ≥1 additional risk factor, and fasting TG levels of 135–499 mg/dL on maximally tolerated statin, with or without ezetimibe. The NLA recommendation was issued as a Class I, Level B-R (STRONG) recommendation, its highest designation, for icosapent ethyl.

  The NLA is a leading professional society dedicated to enhancing the practice of lipid management in clinical medicine.[6] The NLA's Board of Directors comprises leading experts who specialize in clinical lipidology.

- In November 2019, The Brazilian Society of Cardiology (SBC) released an *Updated Cardiovascular Prevention Guideline*.[7] SBC has 12 scientific departments and 10 study groups, as well as an organization in 26 regional societies throughout Brazil.

  SBC provided the following update regarding icosapent ethyl with a Level I, Grade B rating:

  - Supplementation with an E-EPA (ethyl eicosapentaenoic acid) formulation (4 g/day) can be recommended for high-risk patients with elevated TG levels using statins, as it seems to reduce the risk for ischemic events, including CV death.

    Data from these studies suggest that high doses of EPA (4 g) can be used in patients with prior CVD and who remain with elevated TG levels, despite taking statins to prevent CVD. However, there is no evidence for the use of lower doses and other formulations of omega-3 for CV prevention, both primary and secondary.

- In February 2020, a consensus statement by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) on the comprehensive management of type 2 diabetes was released.[8] The AACE diabetes algorithm is a comprehensive management algorithm that covers lifestyle, obesity, prediabetes, lipids, hypertension, and glucose-management strategies. It is the most up-to-date and progressive management algorithm; it includes strategies based on all the newest diabetes and related metabolic CV outcomes trials and incorporates the latest FDA-approved indications.

  Strategies included in the 2020 AACE diabetes algorithm go beyond just managing and controlling CV risk factors to preventing subsequent CV events, including morbidity and mortality in patients with established ASCVD and those at high risk for CVD.

  The specific update regarding icosapent ethyl in the new guidance includes the following:

- Management of patients with established or at high risk for CVD who have TG levels between 135 and 499 mg/dL with EPA with proven benefits to prevent the next event

- In February 2020, the *Thrombosis Canada Clinical Guide on Stroke–Secondary Prevention* was updated. This update mentions icosapent ethyl as a therapeutic approach to reduce the risk of recurrent vascular events in patients who have already suffered a stroke or transient ischemic attack (TIA).[9]

    - The Thrombosis Canada clinical guides have been developed to assist clinicians with point-of-care decision making. They are not intended to be taken as guidelines. The Thrombosis Canada Clinical Guides are:
        - Developed voluntarily by Thrombosis Canada members, who are internationally recognized as experts
        - Peer reviewed by the Thrombosis Canada Clinical Guide Committee
        - Reviewed for applicability to primary care by members of the College of Family Physicians of Canada
        - Reflect recommendations of evidence-based clinical practice guidelines
        - Not supported financially by any external funders

- In February 2020, the Colombian Association of Endocrinology, Diabetes and Metabolism and the Colombian Society of Cardiology and Cardiovascular Surgery published the recommendations of the expert panel on the diagnostic pathophysiology and treatment of dyslipidemias in the adult population[10]:

    - Issued post FDA approval in US and prior to application in Columbia
    - Referenced the REDUCE-IT results and the CV risk-lowering effects of icosapent ethyl in joint dyslipidemia recommendations
    - Recommend pharmacologic forms of omega-3 fatty acids (non-supplements) and in doses of 4 g/day (as described in the REDUCE-IT study, where icosapent ethyl was administered as 2 g every 12 hours)

- On April 13, 2020, The AHA issued the *Scientific Statement on the Clinical Management of Stable Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus*.[11]

    - Within this scientific statement, the AHA identifies icosapent ethyl as a consideration for further CV risk reduction when TG levels remain elevated (>135 mg/dL) despite maximally tolerated statin based on the results of REDUCE-IT.

- In August 2020, the ESC updated guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.[12]

    - These guidelines reference the REDUCE-IT results in the guidelines for the management of non-ST elevation-acute coronary syndrome

- Highlights use of very high doses of icosapent ethyl (2 g twice daily)
- Refers to the icosapent ethyl IIa recommendation in 2019 ESC/EAS guidelines for the management of dyslipidemias

- In October 2020, The Endocrine Society (ENDO) published their *Full Guideline: Lipid Management in Patients with Endocrine Disorders*.[13]

    - Within this guideline, based upon the results of REDUCE-IT, ENDO recommends that icosapent ethyl should be considered first-line therapy in patients on statin therapy with TG levels >150 mg/dL and with either ASCVD or diabetes plus 2 additional risk factors.
    - The guideline also conveys that CVD benefit seen in REDUCE-IT does not apply to other omega-3 fatty acids, particularly those with a mix of EPA and docosahexaenoic acid (DHA).

- In December 2020, the Chinese Society of Cardiology (CSC) published their *Guidelines for Primary Prevention of Cardiovascular Diseases in China*.[14]

    - The guidelines reference the use of icosapent ethyl (as studied in REDUCE-IT).
    - If TG level is >2.3 mmol/L in people at high risk of ASCVD after receiving moderate-dose statin therapy, consider giving high-dose EPA ethyl ester (icosapent ethyl) (2 g, twice daily) to further reduce the risk of ASCVD (Category IIa, Evidence Level B)

- In February 2021, the *Egyptian Heart Journal* published a practical guidance in lipid management. In this guidance, icosapent ethyl was listed as a consideration in patients with high TG levels (>200 mg/dL). The recommendation states to exclude and treat secondary causes of hypertriglyceridemia (TG levels >200 mg/dL). Patients with hypertriglyceridemia and at high risk must receive a statin as a first-line treatment to reduce CVD risk. In high-risk (or above) patients with TG levels between 135 and 499 mg/dL despite statin treatment, omega-3 polyunsaturated fatty acids (icosapent ethyl 2 × 2 g/day) should be considered in combination with a statin.[15]

- In March 2021, the Canadian Cardiovascular Society (CCS) published their *Guidelines for Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult*.[16] In this guidance, icosapent ethyl was recommend for use to lower the risk of CV events in patients with ASCVD, or with diabetes and ≥1 CVD risk factors, who have an elevated fasting TG level of 1.5–5.6 mmol/L despite treatment with maximally tolerated statin therapy (Strong Recommendation; High-Quality Evidence). In addition, the guidelines do not recommend the use of over-the-counter omega-3 polyunsaturated fatty acids supplements (marketed as natural health products in Canada) to reduce CVD risk (Strong Recommendation; High-Quality Evidence).

- In April 2021, the Task Force for Coronary Heart Disease of the Chinese Association of Cardiovascular Surgeons (CACS) and the Task Force for Coronary Heart Disease of the Chinese Society of Thoracic and Cardiovascular Surgery (CSTCVS) jointly developed a consensus statement on secondary prevention after coronary artery bypass surgery.[17] The consensus was developed with input from domestic experts across multiple disciplines, including cardiac surgery, cardiology, endocrinology, neurology, nephrology, gastroenterology, rehabilitation, and others, as well as recommendations from a number of key organizations including the Chinese Medical Association, Chinese Medical Doctor Association, and mainstream European and American associations.
    - The consensus states that for patients with concomitant hypertriglyceridemia following coronary artery bypass surgery, supplementation with high-purity EPA, instead of omega-3 polyunsaturated fatty acids blended with DHA, can be considered for secondary prevention to further reduce CV events. The authors indicate this is similar to an evidence-based Class IIb recommendation, where the benefits balance or outweigh the risks.
- In May 2021, the *Chinese Journal of Internal Medicine*[18] (one of the journals of the Chinese Medical Association) published the *Expert Consensus on Diagnosis and Treatment of Diabetic Patients With Cardiovascular Disease*, which references icosapent ethyl:

    - On the basis of strict lifestyle intervention and statin therapy, patients at high risk/extremely high risk for CVD tend to use high-dose ethyl eicosapentaenoate (also known as icosapent ethyl) (2 g, twice daily) to further reduce the risk for CVD if TG levels are >2.3 mmol/L.

- In May 2021, the AHA/American Stroke Association (ASA) published the *2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack*.[19] This guideline was reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons; endorsed by the Society of Vascular and Interventional Neurology; and the American Academy of Neurology affirmed the value of this statement as an educational tool for neurologists.

    - This stroke guideline from the AHA/ASA contains the following recommendations:
        - *In patients with ischemic stroke or TIA, with fasting TG levels 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL, on moderate- or high-intensity statin therapy, with HbA1c <10%, and with no history of pancreatitis, atrial fibrillation, or severe heart failure, treatment with icosapent ethyl 2 g twice a day is reasonable to reduce risk of recurrent stroke.*
    - This guideline also recognized the potential mechanism of CV risk reduction with icosapent ethyl as well as differences between icosapent ethyl/EPA as compared to DHA, another omega-3 fatty acid, with the following language:
        - *Because TG levels were similar, higher EPA levels may account for the results seen in REDUCE-IT. In addition, the differing effects of EPA and DHA on membrane stabilization may contribute to the lack of effect with EPA/DHA compared with EPA alone or icosapent ethyl.*
- In June 2021, the Canadian Stroke Best Practice Recommendations Advisory Committee, in collaboration with the Canadian Stroke Consortium, published the *Canadian Stroke Best Practice Recommendations: Secondary Prevention of Stroke Update 2020*, which was published in the

Canadian Journal of Neurological Sciences.[20]

- This stroke best practices paper contains the following new recommendation regarding icosapent ethyl:
  - Add-on therapies for hypertriglyceridemia (NEW 2020)
    - *For ischemic stroke patients with established ASCVD or diabetes plus additional vascular risk factors, who have elevated serum TG levels (≥1.5 mmol/L) despite statin therapy, icosapent ethyl 2 g bid may be considered to decrease the risk of vascular events (Level of Evidence B).*

- In June 2021, the Hypertension Study Group of the Chinese Society of Cardiology, Chinese Medical Association, published a consensus statement on the management of blood pressure and dyslipidemia in Chinese patients with hypertension.[21] The consensus statement emphasizes the importance of blood lipid management in hypertensive patients for the prevention of ASCVD, and notes that high-dose icosapent ethyl (2g, twice per day) can reduce TG levels and the incidence of CV events "to some extent."
- In July 2021, the American College of Cardiology (ACC) published the *2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia*.[22] This consensus document was reviewed and endorsed by the National Lipid Association (NLA) and published in the *Journal of the American College of Cardiology* (https://www.jacc.org/doi/pdf/10.1016/j.jacc.2021.06.011).
  - ACC developed this consensus document to address current gaps in care for high-risk patients with mild to moderate hypertriglyceridemia (fasting TG levels ≥150 mg or non-fasting TG levels ≥175 mg/dL and <500 mg/dL) and severe hypertriglyceridemia (fasting TG levels ≥500 mg/dL and especially TG levels ≥1000 mg/dL). The goal was to provide practical guidance for clinicians and patients in situations not covered by the 2018 AHA/ACC/multi-society cholesterol guideline.
    - The document reports that non-prescription fish oil products are classified as dietary supplements and are not interchangeable with prescription omega-3 products.
    - This document also reports that the only TG risk-based non-statin therapy approved for reduction in ASCVD risk by the US FDA is icosapent ethyl.
    - In adults with clinical ASCVD and fasting TG levels ≥150 or non-fasting TG levels ≥175 mg/dL and TG levels <500 mg/dL, and on statins with LDL-C <70 or 70–100 mg/dL, icosapent ethyl may be considered.
    - In adults aged ≥50 years with diabetes mellitus and additional CVD risk factor(s) and fasting TG levels ≥150 or non-fasting TG levels ≥175 mg/dL and TG levels <500 mg/dL, and on maximally tolerated statin therapy, icosapent ethyl may be considered.

- On August 30, 2021, the ESC released their *2021 Guidelines on Cardiovascular Disease Prevention in Clinical Practice*.[23] This guideline was developed by the Task Force for Cardiovascular Disease Prevention in Clinical Practice with representatives of the ESC and 12 medical societies and the special contribution of the European Association of Preventive Cardiology (EAPC).
  - This ESC guideline now includes icosapent ethyl as a new recommendation to address high-risk CV patients with elevated TG levels (135–499 mg/dL) despite statin treatment and lifestyle measures. The classification is a Level B recommendation, which reflects a relatively high weight of scientific evidence under ESC and EAS standards.

- In August 2021, the Saudi National Diabetes Center (SNDC) issued the *Saudi Diabetes Clinical Practice Guidelines*[24] (SDCPG) to give healthcare providers practical guidance in caring for patients with diabetes. This first edition of the guidelines was developed by adult and pediatric endocrinologists from different healthcare sectors in the Kingdom of Saudi Arabia, and guided by state-of-the-art literature and recommendations from other major organizations including the ADA, AACE, National Institute for Health and Care Excellence (NICE), and the International Diabetes Federation. The authors note that a grading system for the considered evidence was not employed for this first edition, but will be implemented in future updates.
    - In its recommendations for lipid management in patients with diabetes, the SDCPG mentions that icosapent ethyl was shown to reduce CV events, including deaths, in patients with elevated TG levels. However, the guidelines also note that icosapent ethyl is not available in the Kingdom of Saudi Arabia.

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