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GUIDELINES FOR ATRIAL FIBRILLATION MANAGEMENT: ROLE OF THE AFFIRM TRIAL

Zina Butkevich, Pharm.D. Candidate

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequential deterioration of atrial mechanical function.[1] Although oftentimes asymptomatic, AF can manifest as palpitations, chest pain, dyspnea, fatigue, lightheadedness, or syncope.[1] It is the most commonly diagnosed arrhythmia estimated to affect 2.2 million people in the United States with a frequency increasing with age.[1-4] The prevalence of AF is projected to increase considerably to as many as 12 million people by 2050, making it crucial to expedite research geared towards determining the optimal management strategy as AF is associated with an increased risk of mortality. [2,5-8]

Several deleterious cardiac and hemodynamic consequences associated with AF may explain this high mortality. These include deficiencies in cardiac performance and decreased cardiac output secondary to the loss of atrioventricular synchrony causing rapid, irregular ventricular rates, and an increased risk of cardiomyopathy, heart failure, and coronary heart disease.[7,9] Most symptoms are caused by the irregular ventricular rate, and the associated risk of death is doubled in patients with a history of AF.[3] AF is also associated with a 5-fold incremental risk of stroke, an approximately 3-fold risk of heart failure, diminished quality of life, and substantial health care costs.[7,8]

There are currently two well established treatment strategies for AF: cardioversion plus antiarrhythmic drugs (AADs) to maintain normal sinus rhythm (NSR), otherwise known as rhythm control (RMC), and the use of ventricular rate-controlling drugs allowing AF to persist, otherwise known as rate control (RTC) strategy.[1,10] Given that complications arise from the irregularity of rhythm in AF, it seems logical that restoration of NSR would be a favorable approach to eliminate the risk of complications and improve overall health outcomes. However, superiority of one treatment strategy has not been clearly shown, and an approach to the management of AF remains a principle topic of debate, plagued with uncertainty and immersed in controversy.[7,8,11] Nevertheless, it is essential to understand the past methods for the management of AF and its evolution to more advanced, contemporary strategies.[8]

In 2001, the American College of Cardiology (ACC)/ American Heart Association (AHA)/ European Society of Cardiology (ESC) guidelines for the management of patients with AF were released.[12] At that time, there was scant data available in the form of randomized, controlled clinical trials to develop evidence-based recommendations for management of AF. The original guidelines proposed that maintaining sinus rhythm with RMC offers the theoretical advantage of reducing the risk of thromboembolism, thereby eliminating the requirement to use anticoagulants; however, the drugs used for RTC were considered safer than the AADs used for RMC.[9,12] Additionally, RMC was advised over RTC in the setting of acute heart failure, hypotension, or worsening angina in a patient with CAD that was precipitated by AF.[12]

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The Pharmacological Intervention in Atrial Fibrillation (PIAF) study was the first prospective, randomized trial to compare outcomes of a RTC versus RMC treatment strategy.[13] Prior to this study, many institutions employed a method of AF management to achieve NSR restoration and maintainance.[13] RTC control was usually an alternative option when RMC failed.[7] The study demonstrated non-inferiority of RTC compared to RMC with respect to symptoms, quality of life, and number of hospitalizations in patients with persistent AF.[13] Consequently, the original 2001 AF guidelines were unsuccessful at establishing a concrete recommendation of one treatment approach over the other for the management of AF.[12]

The highly anticipated results of large, randomized, controlled clinical trials comparing RTC to RMC led to the development of revised AF guidelines in 2006.[1] Among these trials were the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)[3] and the Rate Control vs. Electrical cardioversion for persistent atrial fibrillation (RACE)[14] trials, which were the first to evaluate the effects of rate vs. rhythm on morbidity and mortality as the primary outcome. The results of the AFFFIM trial found no significant difference in mortality between the RTC and RMC treatment groups.[3] Similarly, the RACE trial concluded that RTC was non-inferior to RMC for the prevention of morbidity and mortality in AF.[14]

Additional studies, including the Strategies of Treatment of Atrial Fibrillation (STAF)[15] and How to Treat Chronic Atrial Fibrillation (HOT CAFÉ)[16] trials, found similar results of no significant differences in outcomes between the RTC or RMC approach. The failure of these trials to demonstrate an advantage of one strategy amplified the uncertainty of a preferred approach making decisions for treatment of AF more challenging for physicians. The guidelines, however, trended towards a RTC strategy, as demonstrated by the treatment algorithms for new onset, paroxysmal, and permanent AF, which recommend initial treatment with RTC agents with the consideration of RMC as a long term therapy goal when symptoms are inadequately controlled.[1,8]

Among the five major clinical trials supporting current recommendations, AFFIRM[3], RACE[14], PIAF[13], STAF[15], and HOT CAFÉ[16], the largest was the AFFIRM trial. As there are compelling theoretical benefits to restoring and maintaining NSR, it was assumed that the AFFIRM trial would validate RMC as the superior approach for the management of AF.[3,10] Consequently, when the AFFIRM trial failed to endorse a RMC strategy, the controversy and criticism surrounding the appropriate treatment of AF was heightened.[8] This article will take a closer look at the AFFIRM trial and evaluate reasons for the reported lack of survival benefit within the RMC group.

AFFIRM Trial

The AFFIRM trial was a randomized, multicenter clinical trial, involving 4,060 patients, and the largest study to compare RMC with RTC in the management of AF.[3] A total of 2033 patients were enrolled in the RMC arm and 2027 patients were enrolled in the RTC arm of the trial. AFFIRM enrolled patients with documented AF who were at high risk for stroke, defined as being 65 years or older or having one or more stroke risk factors. Risk factors for stroke included hypertension, diabetes mellitus, CHF, previous stroke, previous transient ischemic attack, systemic embolism, left atrial size ≥ 5cm, left ventricular ejection fraction (LVEF) ≤ 40%, or fractional shortening ≤ 25%. Patients were assigned to either a RTC or RMC strategy at the discretion of their physician.[3] Physicians were also are entitled to choose the AAD based on patient characteristics, intended to mimic normal clinical practice.[11]

In the RMC arm, AF was considered to be controlled if the patient had less than 1 episode of AF in a 6-month period, or if the patient was deemed to be controlled by the investigators judgment. Goals for the RTC strategy included a resting target heart rate of less than or equal to 80 beats/minute, and a heart rate of less than or equal to 110 beats/minute during a 6 minute walk test.[3]

The AFFIRM trial was designed to determine whether, in the presence of anticoagulation therapy, a strategy of RMC using AAD therapy to maintain NSR was the superior to ventricular RTC alone for preventing mortality in patients with AF. The primary endpoint was total mortality, including cardiovascular and non-cardiovascular deaths, after a mean follow-up period of 3.5 years.[3]

The trial found that a RMC strategy had no clear advantage over a RTC strategy and results showed no significant difference in the total mortality between the two strategies. Furthermore, total mortality in the RMC group exceeded that of the RTC group (hazard ratio [HR] 1.15, p=0.08). However, there was a potential advantage of the RTC method in reducing the risk of hospitalization, adverse drug effects, and thromboembolism. The secondary composite endpoint of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest, were also similar between the groups (p=0.33).[3]

Expectations that reestablishing and maintaining NSR with a RMC approach in patients with AF may improve survival were not substantiated by AFFIRM, resulting in the implication that a RTC strategy should

be considered first-line as it offered potential advantages over RMC, such as lower risk of adverse drug effects.[3,10] Additionally, RMC may be abandoned early if outcomes are not satisfactory to the patient.[3] Adding to the controversy, recent data from sub-analysis of AFFIRM suggests that increased total mortality originally reported in the RMC group may be unrelated to the method of treatment, but rather attributed to the effects of the specific AAD used.[10] The analysis proposed that by accounting for confounding variables presented by the choice of AAD in AFFIRM, a strategy of RMC may have been proven more favorable.[7]

Mortality Outcomes in AFFIRM

In a sub-analysis of the cause-specific mortality in the AFFIRM trial, Steinberg et al. compared the modes of death in both treatment groups.[7] Primary causes of death were specified as cardiac, vascular, non-cardiovascular or uncertain mechanism. Of the 2033 patients randomized to the RMC strategy and the 2027 patients to the RTC strategy, a total of 356 and 310 deaths occurred in the RMC and RTC groups, respectively (5 year estimate, 24% versus 21%, respectively, p=0.07). Cardiac related deaths accounted for 129 deaths (9%) in the RMC group and 130 deaths (10%) in the RTC group (p=0.95). The number of vascular deaths, including ischemic and hemorrhagic strokes, were 35 (3%) in the RMC group and 37 (3%) in the RTC group (p= 0.82). Non-cardiovascular death was reported in 169 (47.5% of total deaths) in the RMC group compared to 113 (36.5% of total deaths) in the RTC group (p= 0.0008). The majority of non-cardiovascular deaths were further attributed to significant differences in pulmonary causes (39 [4%] in RMC versus 23 [3%] in RTC p=0.04) and cancer-related causes (81 [6%] with RMC versus 52 [4%] with RTC p=0.01). The difference in total mortality in the AFFIRM trial could be explained by the non-cardiovascular death rates.[7]

Cardiovascular Outcome Analysis

Patients with AF have demonstrated significantly worse cardiovascular survival.[8] The most recent data from the Framingham study calculated a 1.5-fold increase in cardiovascular mortality for men and a 1.9-fold increase for women with AF.[6] The failure of the RMC method to improve cardiac mortality may be explained by the incomplete suppression of AF.[8] If NSR was achieved permanently with AADs the negative physiological effects caused by uncontrolled AF may be resolved. However, AAD therapy rarely abolishes AF so a risk remains.[8] The limited efficacy of AAD therapy to achieve and maintain NSR in AF is demonstrated with a percentage of patients achieving NSR between 26% and 63% in multiple randomized trials.[8]

At the end of the 5 year follow-up in the AFFIRM trial, 62.6 percent of patients in the RMC group were in NSR. However, it was likely that many patients experienced asymptomatic, episodic occurrences of AF throughout the study, which were often left undetected.[3] This was likely due to infrequent ambulatory monitoring and recordings of AF throughout the AFFIRM trial.[7] Consequently, the recurrent episodes of an irregular rhythm likely exposed patients in the RMC group to the detrimental cardiovascular effects associated with AF.[7]

Additionally, during the study 594 patients crossed over from the RMC group to the RTC group, with only 61 of those patients crossing back to the RMC group.[3] The main reasons for the abandonment of the RMC strategy was the inability to maintain NSR and drug intolerance.[3] Moreover, a sub-analysis of AFFIRM, which evaluated NSR and AADs as separate variables, found that the presence of NSR was independently associated with a survival benefit and AAD use was associated with increased mortality.[10] Similarly, the more recent Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) studies showed that AF patients who had NSR, either with or without AAD therapy, had a superior prognosis, particularly increased survival, compared with patients with continued AF.[17] The failure of AFFIRM to demonstrate a substantial benefit from a RMC strategy potentially reflects the limited efficacy and adverse effects of the AADs used to maintain NSR.[3,7,8] Furthermore, these findings propose the idea that a method of effectively restoring NSR, with minimal to no recurrence, would result in better outcomes and would therefore be highly desirable.[8]

Vascular Outcome Analysis

AF is the most common cardiac cause of stroke, generally attributing to a 5-fold increase in stroke risk.[7] Prior to AFFIRM, the 2001 ACC/AHA/ESC practice guidelines allowed for the discontinuation of long-term anticoagulation once NSR was restored.[12] The goal international normalized ratio (INR) with warfarin therapy in the AFFIRM trial was between 2.0 to 3.0.[3] The study protocol allowed for discontinuation of warfarin in the RMC group if NSR was apparently maintained for at least four, but preferably 12, weeks with the use of an AAD. Alternatively, continuous anticoagulation was mandated in the RTC group. The overall proportion of patients in the RMC group receiving warfarin was approximately 70 percent

throughout the trial, with a total of 62.3 percent of INRs within the recommended therapeutic range of 2.0 to 3.0.[3]

Ischemic stroke occurred in 80 (7.1%) in the RMC group versus 77 (5.5%) in the RTC group (p= 0.79).[3] Most ischemic strokes occurred in patients in whom warfarin had been discontinued or in whom the INR was subtherapeutic, with the majority of patients being in the RMC group.[3,7] In the trial, the presence of AF was associated with a 60% increase in risk of stroke and use of warfarin was associated with a 69% decrease in risk of stroke. Coincidentally, only 56% of patients receiving AADs were in NSR at the time of stroke.[18,19]

Since most patients who experienced ischemic strokes in AFFIRM were in AF and not on warfarin, or had a subtherapeutic INR, the incidence of strokes should likely be considered an outcome secondary to the ineffectiveness of AADs to maintain NSR, as necessary to prevent strokes.[7,18]

Non-Cardiovascular Outcomes Analysis

The AFFIRM trial found a 50 percent increase in non-cardiovascular deaths in the RMC group at the end of a 5 years follow-up, with the divergence of the survival curve beginning at 1 year and continuing throughout the study.[7,18] Additionally, the risk of non-cardiovascular death was increased 1.5-fold (P=0.0007) in the RMC group.[7] The increased non-cardiovascular deaths in the RMC group of AFFIRM present a more compelling argument in favor of a RMC treatment strategy, as the AADs used were a potential cause for increased non-cardiovascular mortality.[4]

The treatment options in the RMC group for AFFIRM were any AAD; however, amiodarone was most commonly used, ultimately prescribed in approximately 62% of patients.[3] Although efficacious, and a common first line agent, amiodarone has been associated with increased non-cardiac mortality, including pulmonary and cancer related deaths.[8] In a subanalysis of the relationship between NSR, treatment, and survival in AFFIRM, amiodarone was found to have an increased risk of overall mortality (HR: 1.20 p = 0.15) and non-cardiovascular mortality (HR: 1.11, p= 0.04) when compared with the RTC group.[4] Similarly, the European Myocardial Infarct Amiodarone Trial (EMIAT) found that amiodarone use was notably associated with a 37% higher rate of non-cardiac morality, including higher rates of pulmonary and cancer related deaths.[4,7,10,20] Unfortunately, AFFIRM did not account for the potentially fatal non-cardiac effects of amiodarone as a potential cause for increased mortality. Therefore, the results of AFFIRM should not be directly interpreted as a lack of benefit with a RMC strategy, but rather that the impact of adverse effects of AADs may offset the survival benefit of maintaining NSR.[8]

Summary

AF is a widespread arrhythmia with hazardous long-term consequences.[21] The controversy surrounding rate vs. rhythm control for the management of AF has been longstanding, yet various efforts to resolve this debate have been largely futile. Although the results from AFFIRM failed to establish RMC as a favorable approach, it is likely premature to regard it as an ineffective endeavor. Generalizability to a broader demographic, including younger patients, those with fewer comorbidities, or those who poorly tolerate AF despite RTC, is deficient in many rate vs. rhythm trials, including AFFIRM.[8,11] Furthermore, data on the long-term prognosis of AF when treated with rate vs. rhythm is becoming increasingly available, and a RMC method is often proving beneficial.[21] Additionally, the development of more efficacious AADs with sustainable rate and rhythm control and fewer adverse effects may result in important gains in mortality of AF.[21] Nevertheless, additional clinical trials are necessary to determine an ideal treatment approach for AF, but RMC should not be ruled out as an optimal option.

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VASCEPA: A NEW FISH OIL FOR SEVERE HYPERTRIGLYCERIDEMIA

Andrew Lipshutz, Pharm.D. Candidate

The prevalence of elevated serum triglycerides (TG) has increased steadily in recent years. While low-density lipoprotein (LDL) cholesterol remains the target in patients with elevated plasma lipids, TG levels are an independent risk factor for cardiovascular disease.[1] According to data from the National Health and Nutrition Examination Surveys from 1999 to 2004, 33% of participants had serum TG ≥150mg/dl. Of those, 17.9% had TG over 200mg/dl, 1.7% over 500mg/dl, and 0.4% over 1000mg/dl.[1]

Elevated TG often occurs in the same setting as other factors contributing to the metabolic syndrome, such as obesity and insulin resistance. Secondary hypertriglyceridemia may be caused by a number of metabolic, endocrine, and drug-related factors. Obesity, insulin resistance, and hypothyroidism may cause mild hypertriglyceridemia due to altered lipid metabolism.[2] Larger increases in TG may be seen in pregnancy.[3] Drugs that may increase TG include antihypertensive medications like thiazide diuretics, furosemide, and beta adrenergic blockers, oral estrogens, bile acid sequestrants, and certain second-generation antipsychotics. Excessive alcohol use may also cause elevated triglycerides. Primary hypertriglyceridemia is caused by underlying genetic disorders affecting lipid metabolism, including familial combined hyperlipidemia (FCHL) and familial hypertriglyceridemia (FHTG).[4]

The diagnosis of hypertriglyceridemia is made using a fasting lipid panel. In 2010, The Endocrine Society adopted new criteria for diagnosis based on risk for cardiovascular disease and acute pancreatitis.[4] Increased risk for cardiovascular events is thought to be conferred at TG levels greater than 150mg/dl while levels greater than 2000mg/dl increase the risk for acute pancreatitis.

Three drug classes, fibrates, niacin, and omega-3 fatty acids (FA) have been shown to reduce serum triglycerides. In 2012, The Endocrine Society recommended that these classes be used alone or in combination with a statin for treatment in patients with moderate to severe TG (200-2000mg/dl).[4] Currently, Lovaza® (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) is the only FDA approved prescription-strength omega-3 FA product.

In July 2012, Amarin Corporation received FDA approval for Vascepa® (icosapent ethyl) to be used as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dl) hypertriglyceridemia.[5] It is expected to enter the market in early 2013.

This article will review the pharmacology, pharmacokinetics, clinical trial data, adverse effects, and dosing and administration of icosapent ethyl.

Pharmacology

Although the exact mechanism for FA-mediated reduction in serum TG is not known, the effect is likely due to reduced TG synthesis via reduced production of very low density lipoproteins (VLDL). There are three possible mechanisms for this action: reduced available fatty acids secondary to decreased lipogenesis in the liver, decreased activity of triglyceride-synthesizing enzymes such as diacylglycerol acyltranferase (DGAT) and phosphatidic acid phosphohydrolase (PAP), or increased phospholipid synthesis, which removes diacylgylcerol (DAG) that is necessary for DGAT activity.[6]

The major difference between icosapent ethyl and eicosapentaenoic acid/docosahexaenoic acid (EPA/DHA) is that icosapent ethyl does not contain docosahexaenoic acid (DHA). Studies with the combination EPA and DHA demonstrate increases in LDL compared to placebo.[7] When comparing EPA and DHA head to head, it was found that DHA was the cause of increased LDL.[8]

Pharmacokinetics

Icosapent ethyl is an ethyl ester of EPA; icosapent ethyl and EPA ethyl ester are often used interchangeably. It is de-esterified in the body to active EPA, which is absorbed in the small intestine. Peak plasma concentrations are achieved within 5 hours following administration (**Table 1**). The steady state volume of distribution of icosapent ethyl is approximately 88L. Most circulating EPA is incorporated into lipids and cholesterol esters. Over 99% of de-esterified EPA is bound to plasma proteins and <1% is present as the de-esterified free FA. EPA is mainly metabolized by beta oxidation in the liver. The elimination half life of EPA is approximately 89 hours. Icosapent ethyl does not undergo renal excretion, and no dose adjustments are recommended for patients with renal impairment.[5]

Although no studies have been performed to date on the effect of food with icosapent ethyl, the drug was administered with food or following a meal in all clinical trials. It is recommended that the drug be taken with or following a meal.

Table 1 | Pharmacokinetic Properties of Icosapent Ethyl [5]

Property	Data
Time to T_{max} (hours)	~5
Half-life (hours)	~89
Protein Binding (in vivo)	>99%
Vd	~88L
Metabolism	Hepatic beta-oxidation
Excretion	No renal excretion

T_{max} = time to peak concentration; Vd = volume of distribution

Table 2 | Selected Endpoints from Clinical Trials Icosapent Ester

Trial	Endpoint (% change, p value)	4g/day	2g/day
MARINE, 2011 [9]	TG	33.1%, p<0.0001	19.7%, p=0.0051
	LDL	-2.3%, p=0.677	5.2% , p= 0.302
	Non-HDL	-17.7%, p<0.0001	-8.1%, p=0.0182
ANCHOR, 2012 [10]	TG	21.5%, p<0.0001	10.1%, p=0.0005
	LDL	-6.2%, p=0.0067	-3.6%, p=0.0867
	Non-HDL	-13.6%, p<0.0001	-5.5%, p=0.0054

LDL: low—density lipoprotein; non-HDL: non-high density lipoprotein; TG: triglyceride

Special Populations

Periodic monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels is recommended in patients with hepatic impairment while taking icosapent ethyl.[5] No dose adjustment is recommended for elderly patients. No differences in safety or efficacy were observed in patients over 65 years of age in clinical trials compared to younger patients. Icosapent ethyl is classified as FDA Pregnancy Category C.[5] Animal studies at human equivalent doses resulted in increased fetal visceral and skeletal abnormalities. No studies have been published on use in pregnant humans. Icosapent ethyl should only be administered during pregnancy if the benefits outweigh the potential fetal harm.

Clinical Trials

FDA approval for icosapent ethyl was based on two randomized, double-blind, placebo-controlled trials conducted in a total of 931 patients with elevated serum TG (**Table 2**).[9, 10] Efficacy and safety was established for patients with both moderate (≥200 and <500mg/dl) and severe (≥500 and ≤2000mg/dl) hypertriglyceridemia. Potential limitations of both studies include that only changes in lipid parameters were analyzed and neither trial assessed cardiovascular disease or mortality outcomes. Another limitation present in both studies is that both compared icosapent ethyl treatment to placebo, rather than to currently available therapies.

MARINE

MARINE was a multi-center, placebo-controlled, randomized, double-blind, 12 week study involving patients with very high serum triglycerides.[9] This trial randomized 229 patients with severe hypertriglyceridemia (≥500 and ≤2000mg/dl) to one of two doses of icosapent ethyl or placebo. At the pre-randomization screening visit patients were placed on a diet and medication stabilization for four weeks if they were on a stable statin dose or were not on any lipid medications. The period was extended to six weeks if they were discontinuing any lipid modifying medications except a statin. During this period, subjects were instructed to maintain a stable diet for the study duration according to the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes Diet.[11] Following the stabilization period, participants were randomized to one of three dosing groups: icosapent ethyl 4g/day (n=77), icosapent ethyl 2g/day (n=76), or placebo (n=76). Median baseline TG level was 679.5mg/dl, and 39.9% of patient had a baseline TG level >750mg/dl. In total, 24.9% (n=57) of randomized patients received statin therapy. Of the total study population, 55% (n=126) were at high risk of cardiovascular events according to the patients' medical histories.

The primary outcome was percentage reduction in serum TG from baseline in the two treatment groups compared to placebo. In the intention-to-treat population, icosapent ethyl 4g/day and 2g/day reduced serum TG by 33.1% (p<0.0001) and 19.7% (p=0.0051) compared to placebo, respectively. This effect was stronger in patients with higher baseline triglycerides. In the subgroup of patient with baseline TG >750mg/dl, the 4g and 2g doses lowered TG 45.4% (p=0.0001) and 32.9% (p=0.0016) from baseline, respectively.[9]

Secondary endpoints included percent change from baseline in VLDL, apolipoprotein B, total cholesterol, LDL, HDL, and non-HDL cholesterol. Importantly, LDL decreased nonsignificantly in the 4g/day group (-2.3%, p=0.677) while it increased in the 2g/day group, but was not statistically significant (5.2%, p=0.302). In addition, the 4g and 2g doses significantly reduced VLDL (-28.6%, p=0.002 and -15.3%, p=0.038, respectively) and total cholesterol (-16.3%, p<0.0001 and -6.8%, p=0.0148, respectively), while showing no significant effect on HDL (-3.6%, p=0.217 and 1.5%, p=0.523, respectively). Icosapent ethyl 4g/day significantly reduced non-HDL cholesterol by

Table 3 | Statin Efficacy Levels as Defined by ANCHOR Study [10]

Efficacy	Regimen
Low	simvastatin 5-10mg
Medium	rosuvastatin 5-10mg
	atorvastatin 10-20mg
	simvastatin 20-40mg
	simvastatin 10-20mg plus ezetimibe 5-10mg
High	rosuvastatin 20-40mg
	atorvastatin 40-80mg
	simvastatin 80mg
	simvastatin 40-80mg plus ezetimibe 5-10mg

17.7% (p<0.0001) and apolipoprotein B by 8.5% (p=0.0019). The lower dose also reduced non-HDL cholesterol by 8.1% (p=0.0182).[9]

ANCHOR

ANCHOR was a multi-center, placebo-controlled, randomized, double-blind, 12 week trial assessing the safety and efficacy of icosapent ethyl in 702 patients with moderate hypertriglyceridemia who were on a statin.[10] Eligible patients were required to be on a stable, optimized statin dose for at least 4 weeks prior to enrollment, be defined by NCEP Adult Treatment Panel III (ATPIII)[11] as high risk for cardiovascular disease, and have serum TG ≥200 and <500mg/dl. After a 4-6 week diet and medication stabilization period, patients were randomized to icosapent ethyl 4g/day (n=233), icosapent ethyl 2g/day (n=236) or placebo (n=233). The median baseline TG level was 259.0mg/dl. Statin regimens at initiation were classified as low, medium, or high efficacy (**Table 3**); most patients (93.2%) were taking a statin regimen determined to be medium or high efficacy.

The primary endpoint was percent change in serum TG from baseline to week 12 across treatment groups compared to placebo. Maximum triglyceride-lowering effect was achieved approximately 4 weeks after starting therapy and icosapent ethyl 4g/day and 2g/day reduced serum TG by 21.5% (p<0.0001) and 10.1% (p=0.0005) compared to placebo, respectively. Patients treated with more effective statin regimens showed larger reductions in serum triglycerides. The 4g/day dose reduced TG by 26% (p<0.0001), 20.1% (p<0.0001), and 13.1% (p=0.5467) in the high, medium, and low-efficacy statin groups, respectively.[10]

Higher baseline TG resulted in larger TG reductions. Reductions of 31.1% (p<0.0001) were achieved in the third tertile of baseline triglycerides, compared to reductions of 17.9% (p<0.0001) and 14.4% (p=0.002) in the second and first tertiles, respectively.[10]

Secondary endpoints included percent change in non-HDL cholesterol, LDL, apolipoprotein B, VLDL, total cholesterol, and HDL. Both the 4g and 2g doses of icosapent ethyl were associated with a nonsignificant decrease in LDL cholesterol versus placebo (-6.2%, p=0.0067 and -3.6%, p=0.0867, respectively). Significant reductions in non-HDL cholesterol (-13.6%, p<0.0001 and -5.5%, p=0.0054), apolipoprotein B (-9.3%, p<0.0001 and -3.8%, p=0.0170), VLDL (-24.4%, p<0.0001 and -10.5, p=0.0093), and total cholesterol (-12mg/dl, p<0.0001 and -4.8mg/dl, p=0.0019) were noted with icosapent ethyl 4g and 2g, respectively. The larger dose was associated with a small but statistically significant decrease in HDL (-4.5mg/dl, p=0.0013).[10]

REDUCE-IT

There is currently no evidence for icosapent ethyl in reduction of cardiovascular events, despite evidence of efficacy in lowering triglycerides. The REDUCE-IT trial aims to evaluate if the combination of icosapent ethyl with a statin is superior to statin therapy alone in reducing cardiovascular risk in patients with hyperlipidemia and hypertriglyceridemia. This study began recruiting in 2011 with an estimated completion in November 2016.[12]

Adverse Events

In clinical trials, the most common reported adverse events were gastrointestinal (GI) related

Table 4 | Summary of Common Adverse Effects in Clinical Trials on EPA Ethyl Ester

	MARINE[9]			ANCHOR[10]		
Adverse Events	4g	2g	Placebo	4g	2g	Placebo
Diarrhea	1(1%)	4(5%)	5(7%)	8 (3.4%)	9 (3.8%)	10 (4.3%)
Nausea	1(1%)	5(7%)	4(5%)	5 (2.1%)	5 (2.1%)	7 (3.0%)
Nasopharyngitis	NA	NA	NA	1 (0.4%)	6 (2.5%)	7 (3.0%)
Arthralgia	NA	NA	NA	4 (1.7%)	8 (3.4%)	1 (0.4%)

NA = not applicable

(diarrhea and nausea), but also included nasopharyngitis and arthralgia (**Table 4**).

In MARINE, only diarrhea and nausea were present in >3% of study patients.[9] Of the four patients who discontinued due to adverse effects, three were from the placebo group (arthralgia); the fourth experienced diarrhea in 2g/day group. Changes in fasting blood glucose and hemoglobin A1c did not differ significantly between the study and placebo groups.

In ANCHOR, adverse events occurring in >3% of the study population included diarrhea and nausea, as well as nasopharyngitis and arthralgias.[10] Only arthralgia occurred more frequently in the study group compared to placebo (1.7% and 3.4% in icosapent ethyl 4g/day and 2g/day groups, respectively, compared to 0.4% in the placebo group).[10] Similarly, changes in fasting blood glucose were not significantly different between treatment and placebo groups.

There is some concern that omega-3 fatty acids may prolong bleeding time.[13] Omega-3 fatty acids inhibit thrombosis via competitive inhibition of cyclooxygenase which causes a decrease in thromboxane A_2 synthesis and decreased platelet aggregation.[13] This antithrombotic effect may be partially responsible for the cardiovascular and mortality benefits of omega-3 acids. However, the clinical significance of the theorized decreased platelet aggregation has not been shown in clinical trials.[14] Trials assessing bleeding risk when omega-3 acids are taken concomitantly with warfarin or antiplatelet medications such as aspirin have not shown an increase in bleeding.[15,16]

Dosage and Administration

Vascepa® is supplied as 1g soft gel capsules. The recommended dosing for adults is 4 grams daily, administered as 2 capsules twice daily.[5] There is no recommended geriatric dose adjustment. All clinical trial participants were at least 18 years of age, and therefore use in children is not recommended. Since Vascepa® has been administered with or just after a meal in all clinical trials, it is recommended that patients take this medication with food.

Vascepa® is approved specifically as an "adjunct to diet". Patients should be placed on a lipid-lowering diet and exercise plan prior to and during administration of Vascepa®. Since Vascepa® is not yet on the market (early 2013), currently no cost information is available.

Summary

The prevalence of hypertriglyceridemia is increasing, mirroring the rise in the incidence of obesity and diabetes. Elevated TG is a component of the metabolic syndrome and may be an independent risk factor for cardiovascular disease. Vascepa® is a new omega-3 fatty acid formulation that significantly lowers TG in patients with both moderate and severe hypertriglyceridemia. Unlike other omega-3 products, Vascepa® does not significantly increase LDL cholesterol and does not affect glucose metabolism. Adverse events associated with Vascepa® use in clinical trials include diarrhea, nausea, nasopharyngitis, and arthralgia. Recommended dosing for Vascepa® is 4g daily in two divided doses with meals. Vascepa® was recently FDA approved for severe hypertriglyceridemia (TG ≥ 500mg/dl).

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Clinical Trial Update

New drug and indication approvals:

Rivaroxaban—marketed under the brand name Xarelto® has gained FDA approval to be used for both the acute and long-term treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE). Based on the results of the EINSTEIN DVT and PE series rivaroxaban was found to be non-inferior to enoxaparin plus warfarin for acute treatment (up to 12 months) and superior to placebo for long-term treatment (up to an additional 12 months); bleeding was similar to enoxaparin plus warfarin but higher compared to placebo.

For the acute treatment it is dosed at 15 mg twice daily with meals for the first 21 days (3 weeks); it can be started at diagnosis and does not require the concomitant use of heparin or enoxaparin for the first 5 days. Starting on day 22 (start of week 4) it is dosed at 20 mg once daily with meals. Long-term treatment is accomplished with 20 mg once daily with food. It should be avoided in those with a creatinine clearance (CrCl) less than 30 mL/min.

Apixaban—marketed under the brand name Eliquis® has gained FDA approval for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation based on the ARISTOTLE trial (January 2012 PharmaNote). Compared to warfarin, apixaban reduced the incidence of stroke or systemic embolism with a reduced risk for major bleeding. It also reduced the risk for hemorrhagic stroke and improved all-cause mortality but failed to statistically significantly reduce the risk for ischemic strokes. Apixaban is dosed at 5 mg twice daily (without regard to food). If the patient is $\geq$ 80 years of age, $\leq$ 60 kg, or has a serum creatinine $\geq$ 1.5 mg/dL, it is dosed at 2.5 mg twice daily. It is not recommended if the CrCl is < 15 mL/min.

If converting from rivaroxaban to warfarin, start rivaroxaban when the INR is < 3. From warfarin to apixaban, start apixaban when the INR is < 2.

Both agents are brand--only at this time.

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