CERTIFIED MEDICAL EDUCATORS

Cardiac Pharmacology

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Learning Objectives

- Review and update new medications used to treat cardiac issues
- Identify medications utilized for each condition
- Review dosing of each medication and proper usage to prevent interactions with other medications
- Discuss outcomes of each medications, and any prescribing protocols needed by PAs

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No Disclosures

Cardiac Pharmacology

- C3 – Three Cardiac Clinical Conditions
  - Atrial Fibrillation
  - Pulmonary Hypertension
  - Hypertriglyceridemia

Atrial Fibrillation

- Most common cardiac arrhythmia
- Definition: irregular conduction of disorganized atrial electrical impulses
- Classification
  - Paroxysmal: recurrent episodes that self-terminate in less than 7 days
  - Persistent: recurrent episodes that last more than 7 days
  - Permanent: an ongoing long-term episode

Atrial Fibrillation

- Signs & Symptoms
  - Irregularly irregular heart beat
  - Palpitations, angina, SOB, TIA, diaphoresis, syncope or asymptomatic
- Causes
  - HTN, Heart Disease (CAD, Mitral valve disease, hypertrophic cardiomyopathy, heart surgery, lung disease, excessive alcohol, hyperthyroidism
  - Electrolytes: hypokalemia, hypomagnesemia

Atrial Fibrillation

- Management
  - Rate Control
    - Beta blockers, calcium channel blockers, digoxin
  - Rhythm Control
    - Amiodarone, dronedarone, procainamide, ibutilide
    - Electrical cardioversion
  - Procedures
    - Catheter ablation
    - MAZE procedure
  - Anticoagulation: ASA, heparin, warfarin, dabigatran

Amiodarone

- Trade names: Pacerone, Cordarone
- Indications
  - Acute life-threatening arrhythmias
  - Chronic suppression of arrhythmias
- MOA: Class III antiarrhythmic agent
  - Blocks potassium channels
  - Has beta blocker-like actions on SA and AV nodes
  - Prolongs phase 3 of the cardiac action potential
  - Chemically resembles thyroxine

Amiodarone

- Indications
  - Ventricular fibrillation (ARREST trial)
    - 2nd line agent after epinephrine or vasopressin
  - Ventricular tachycardia (monomorphic)
    - NOT to be used in UNSTABLE V.Tach
  - Atrial Fibrillation
    - Open heart surgery (ARCH trial)
    - Electrophysiology – acute onset
- Contraindications
  - Pregnancy, Polymorphic V. Tach, sinus nodal bradycardia, second or third degree heart block

Amiodarone

- Metabolism: Cytochrome P450 inhibitor
  - Reduces the clearance of (or increases levels of)
    - Cyclosporine, Digoxin, Warfarin, Sildenafil
    - Flecainide, Procainamide
    - SIMVASTATIN
- Half-life: 58 days
- Excretion: hepatic

Amiodarone

- Side Effects
  - More Common
    - Acute: Hypotension
    - Subacute: Hypo/Hyperthyroidism, corneal deposits
    - Long term: Irreversible interstitial lung disease
  - Less Common
    - Liver: elevated liver enzymes, hepatitis, jaundice
    - Skin: blue-grey discoloration of the skin
    - Neuro: peripheral neuropathies

Amiodarone

- IV Dosing (ACLS)
  - Cardiac Arrest loading: 300 mg
  - Dysrhythmia loading: 150 mg
  - Maintenance: 1mg/kg x 6 hrs, 0.5 mg/kg x 18 hrs
- Oral Dosing
  - Loading: 10 grams over 1-2 weeks
  - Maintenance: 100-200mg daily or bid
- Maximum daily dose: 2.2 grams

Dronedarone (MULTAQ®)

- Classification: antiarrhythmic, mainly Class III
- Indications
  - Reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal of persistent AF
- Dosage: 400 mg tablet bid in adults
- Advantages compared to amiodarone
  - Lacks iodine moieties
  - Elimination half-life of 24 hours
- Pregnancy Class: X

Dronedarone (MULTAQ®)

- Metabolism – liver (CYP3A)
- Drug-Drug Interactions
  - Contraindicated
    - Ketoconazole, Erythromycin
  - Avoid concomitant use
    - Grapefruit Juice, Rifampin
  - Reduce medication dose
    - Simvastatin to 10 mg once daily
    - Digoxin to ½ dose or consider discontinuation

Dronedarone (MULTAQ®)

- Clinical trials
  - EURIDIS and ADONIS (2007)
    - Significantly more effective than placebo in maintaining sinus rhythm
  - ANDROMEDA (2007)
    - Doubled the death rate compared to placebo
  - PALLAS (2011)
    - Stopped early finding dronedarone increased rates of heart failure, stroke, and death from cardiovascular causes

Dronedarone (MULTAQ®)

- Contraindications
  - Permanent atrial fibrillation
  - Class IV heart failure or recently decompensated heart failure requiring hospitalization
  - Second or third degree atrioventricular block or sick sinus syndrome (except with pacemaker)
  - Bradycardia < 50 bpm
  - Concomitant use of a strong CYP3A inhibitor
    - Ketoconazole, cyclosporine, and some macrolide antibiotics

Dronedarone (MULTAQ®)

- Contraindications
  - Liver or lung toxicity related to the previous use of amiodarone
  - Severe hepatic impairment
  - QTc > 500 ms or with drugs that prolong the QT
    - Class I or III antiarrhythmics, TCAs, anti-psychotics
  - Pregnancy and nursing mothers
  - Hypersensitivity

Pulmonary Hypertension

- Definition
  - Increase of blood pressure in the pulmonary vasculature
- Classification
  - WHO Group I – Arterial
    - Idiopathic, Familial, Scleroderma, HIV, Drugs, Toxins
  - WHO Group II – Venous (left heart disease)
  - WHO Group III – Hypoxic (lung diseases)
  - WHO Group IV – Thromboembolic
  - WHO Group V - Miscellaneous

Pulmonary Hypertension

- Signs and Symptoms
  - Shortness of breath, fatigue, non-productive cough, angina, syncope, peripheral edema
  - Loud P2, parasternal heave, JVD, edema
- Diagnosis
  - Mean Pulmonary Artery Pressure ≥ 25 mmHg at rest or 30 mm Hg with exercise
  - Pulmonary Capillary Wedge Pressure ≤ 15 mmHg
  - Pulmonary Vascular Resistance ≥ 3 Wood units

Pulmonary Hypertension

- Treatment
  - Prostacyclins
    - Epoprostenol (Flolan), Treprostinil (Remodulin), Iloprost (Ilomedin)
  - PDE5 Inhibitors
    - Sildenafil (Revatio), tadalafil (Adcirca)
  - Calcium channel blockers if vasoreactive
    - MAP falls by more than 10 mm Hg to less than 40 mm Hg with adenosine, epoprostenol, or nitric oxide
  - Surgery
    - Atrial septostomy, lung transplantation

Nifedipine (PROCARDIA®)

- Classification: Calcium Channel Blocker
- Indications
  - Vasospastic Angina
  - Chronic Stable Angina
    - Second line after beta blockers and/or nitrates
  - Hypertension
- Dosing
  - Usually 10 mg or 20 mg tid or extended release daily
  - Extended release doses over 120 mg per day is not recommended

Nifedipine (PROCARDIA®)

- Metabolism: GI, Hepatic
- Excretion: Renal
- Half-Life: 2 hours
- Pregnancy Class: C

Nifedipine (PROCARDIA®)

- Precautions/Adverse Effects
  - Hypotension
  - Peripheral edema
  - Headache
  - Fatigue / Dizziness
  - Constipation / Nausea

Nifedipine (PROCARDIA®)

- Other medical benefits
  - Pulmonary Hypertension
  - Raynaud's phenomenon
  - Migraine prevention
  - Premature labor
  - Esophageal painful spasms
  - High altitude pulmonary edema
  - Topically for anal fissures

Tadalafil (ADCIRCA®)

- Classification: PDE5 inhibitor
- MOA: Increases cGMP resulting in relaxation of pulmonary vascular smooth muscle cells
- Indications
  - Pulmonary artery hypertension to improve exercise ability
  - After 16 weeks of treatment, patients taking ADCIRCA increased their 6-minute walk distance by an average of 33 meters, 108 feet
- Dosage: 40 mg once DAILY (two 20 mg tablets)

Tadalafil (ADCIRCA®)

- Contraindications
  - Concomitant organic nitrates
  - Hypersensitivity
- Warnings/Precautions
  - Prolonged erection
  - Sudden loss of vision *
  - Hearing impairment *
  - Careful use in cardiovascular disease
  - Hypotension

Tadalafil (ADCIRCA®)

- Half-life: 17.5 hours
- Adverse or Side Effects
  - Headache: most common
  - Muscle pain
  - Flushing
  - Nausea
- Pregnancy Class: B

Tadalafil (ADCIRCA®)

- Metabolism: Liver, CYP3A
  - Levels of tadalafil increased by CYP3A inhibitors
    - Ritonavir
    - Ketoconazole
    - Erythromycin
    - Grapefruit juice
  - Levels of tadalafil decreased by CYP3A inducers
    - Rifampin
    - Carbamazepine
    - Phenytoin
    - Phenobarbital

Hypertriglyceridemia

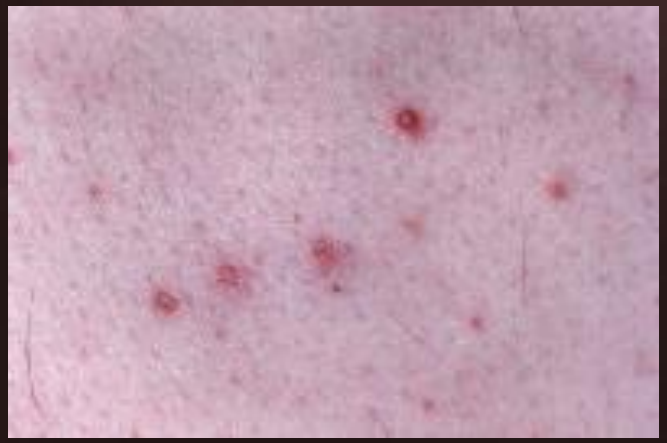
- Definition
  - Elevated triglycerides ≥ 150mg/dL
- Prevalence
  - Men = 35%
  - Women = 25%
- Severe Hypertriglyceridemia
  - Elevated triglycerides > 2,000 mg/dL

Hypertriglyceridemia

- Causes
  - Genetic (Familial hypertriglyceridemia)
  - Metabolic
    - Diabetes, Obesity, Hypothyroidism, Nephrotic syndrome
  - Medications
    - High-dose thiazide diuretics & beta blockers
    - Unopposed oral estrogen replacement therapy
    - Tamoxifen, Glucocorticoids, Oral isotretinoin
  - Other
    - Acute pancreatitis, alcohol, pregnancy

Hypertriglyceridemia

- Signs & Symptoms
  - Usually asymptomatic
  - Severe: Xanthomas, lipidemia retinalis, neurologic



- Treatment
  - Diet, Exercise
  - Fibric acid derivatives, niacin, and omega-3 fatty acids

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Fish Oil

- Fish oil
  - Omega-3 fatty acids: EPA & DHA
    - Reduces triglycerides
    - Reduces cellular inflammation
- Sources (Grams of omega-3 per 3 oz)
  - Herring, sardines (1.7), salmon (1.5), halibut (0.7), flounder (0.4)
  - Albacore tuna (0.7), shark (0.8), king mackerel (1.5), swordfish (0.9)
    - Toxins: mercury, dioxin, PCBs, chlordane

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Fish Oil

- Health Benefits
  - Cardiovascular
    - US National Institutes of Health
      - Hypertriglyceridemia
      - Secondary cardiovascular disease prevention
      - High blood pressure
- Fish Oil DOES NOT EQUAL Omega-3
  - Typical 1,000 mg fish oil has about 300 mg of omega-3

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Fish Oil

- Recommendations
  - American Heart Association
    - Patients without coronary heart disease
      - Eat fish (preferably fatty) at least twice a week
    - Patients with coronary heart disease
      - 1 gram of omega-3 per day, preferable from fatty fish
    - Patients who need to lower triglycerides
      - 2-4 grams of omega-3 per day under medical care
  - FDA
    - Not exceeding 3 grams of omega-3 per day (↑ risk of bleeding), with no more than 2 grams per day from a dietary supplement

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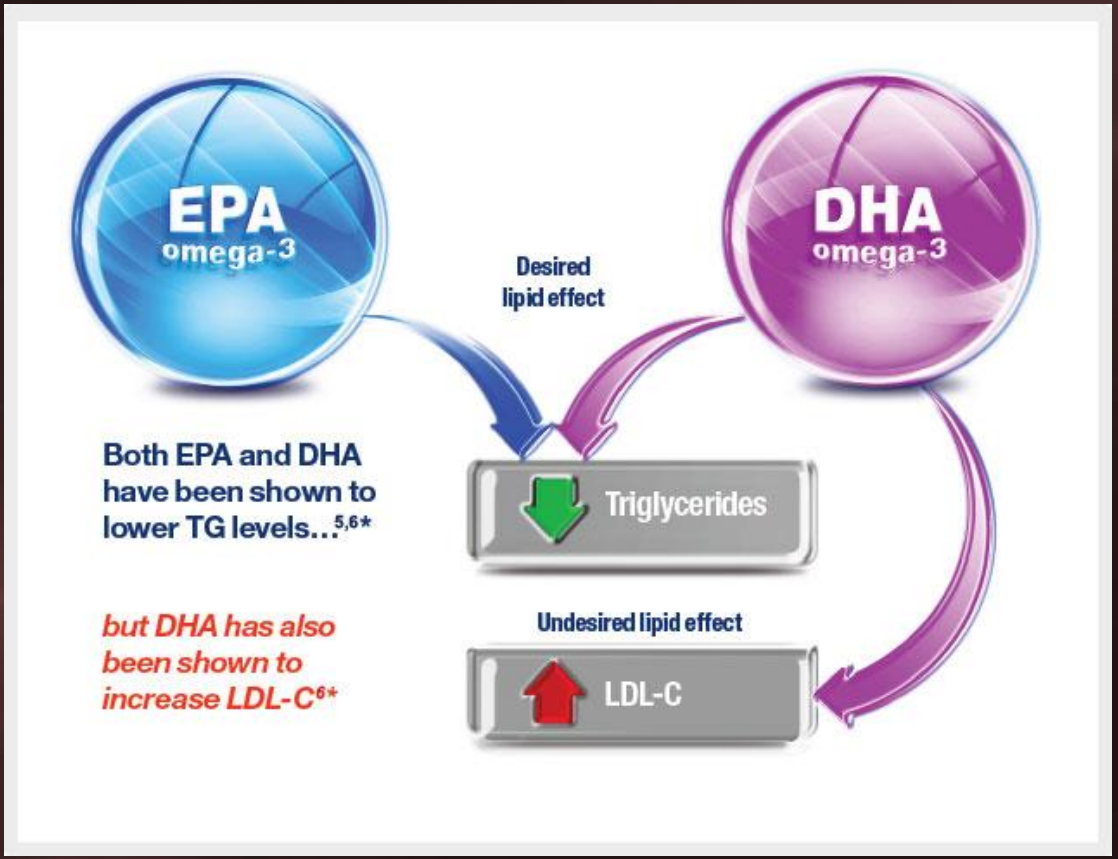
Fish Oil

- Possible Health Benefits
  - Cancer: breast, colon, prostate
  - Depression & Suicide
  - Schizophrenia
  - Alzheimer's disease
  - Lupus
  - Parkinson's disease
  - Psoriasis
  - Pregnancy

Fish Oil

- Adverse effects (high doses)
  - Bleeding
  - Increased LDL levels
  - Toxic pollutants



Icosapent Ethyl (VASCEPA®)

- Classification: EPA (but no DHA)
- MOA: reduces hepatic VLDL triglycerides
- Indications
  - Adjunct to diet to reduce triglyceride levels in adult patients with (>500 mg/dL) hypertriglyceridemia
- Dosage: 4 grams per day (2 capsules bid)
- Pregnancy Class: C

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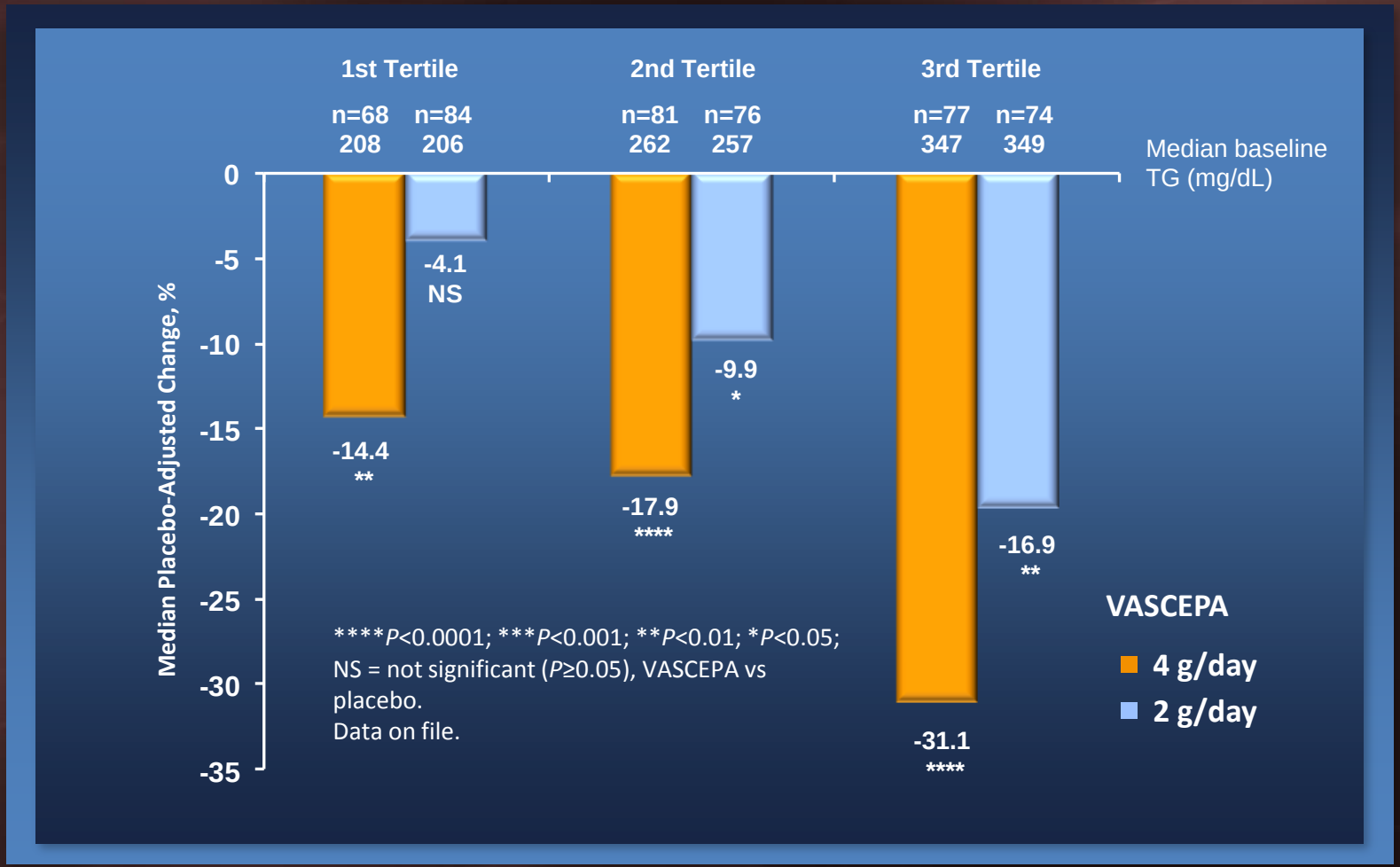
Icosapent Ethyl (VASCEPA®)



ANCHOR: VASCEPA Change in TG Levels by Baseline TG Level

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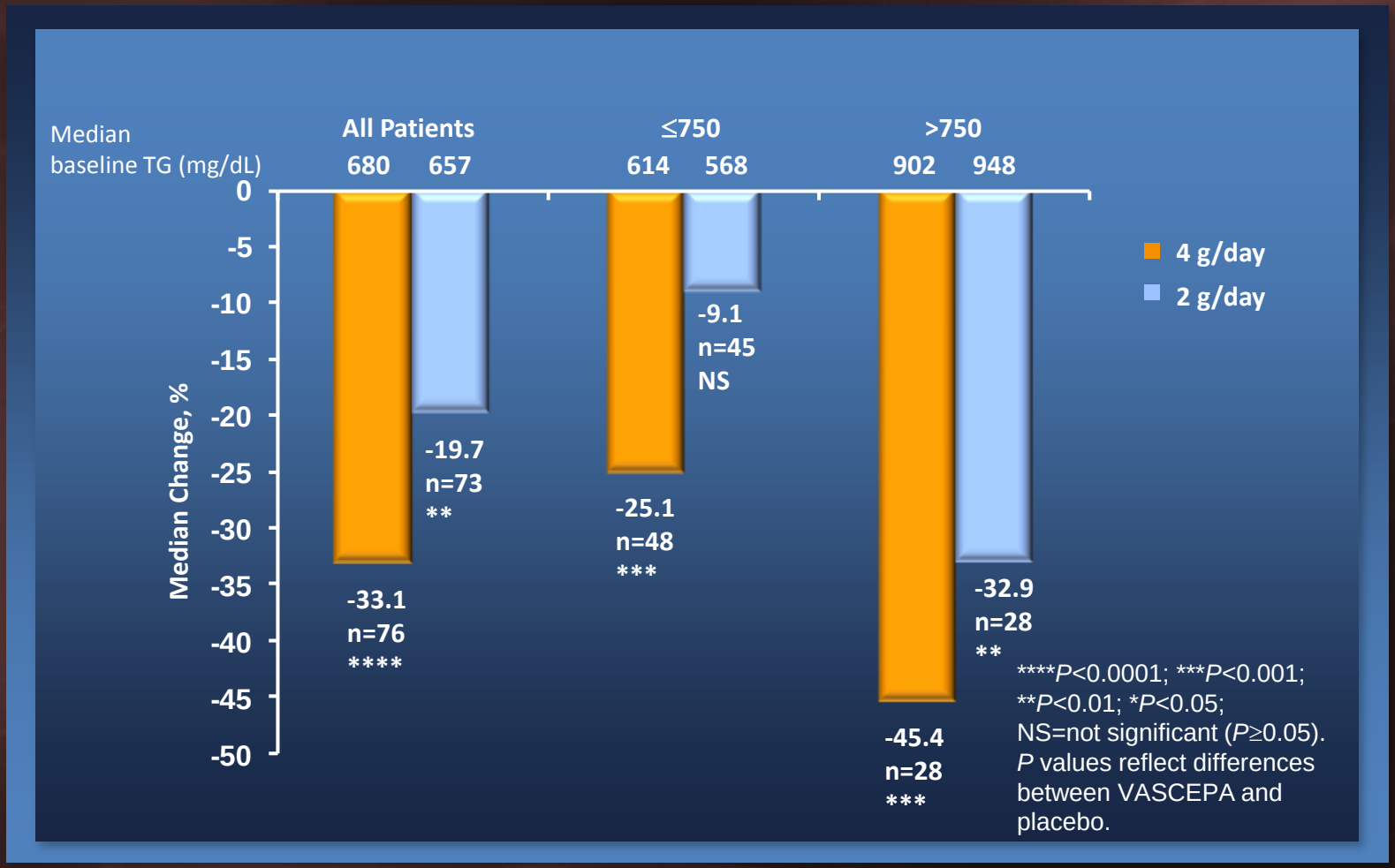
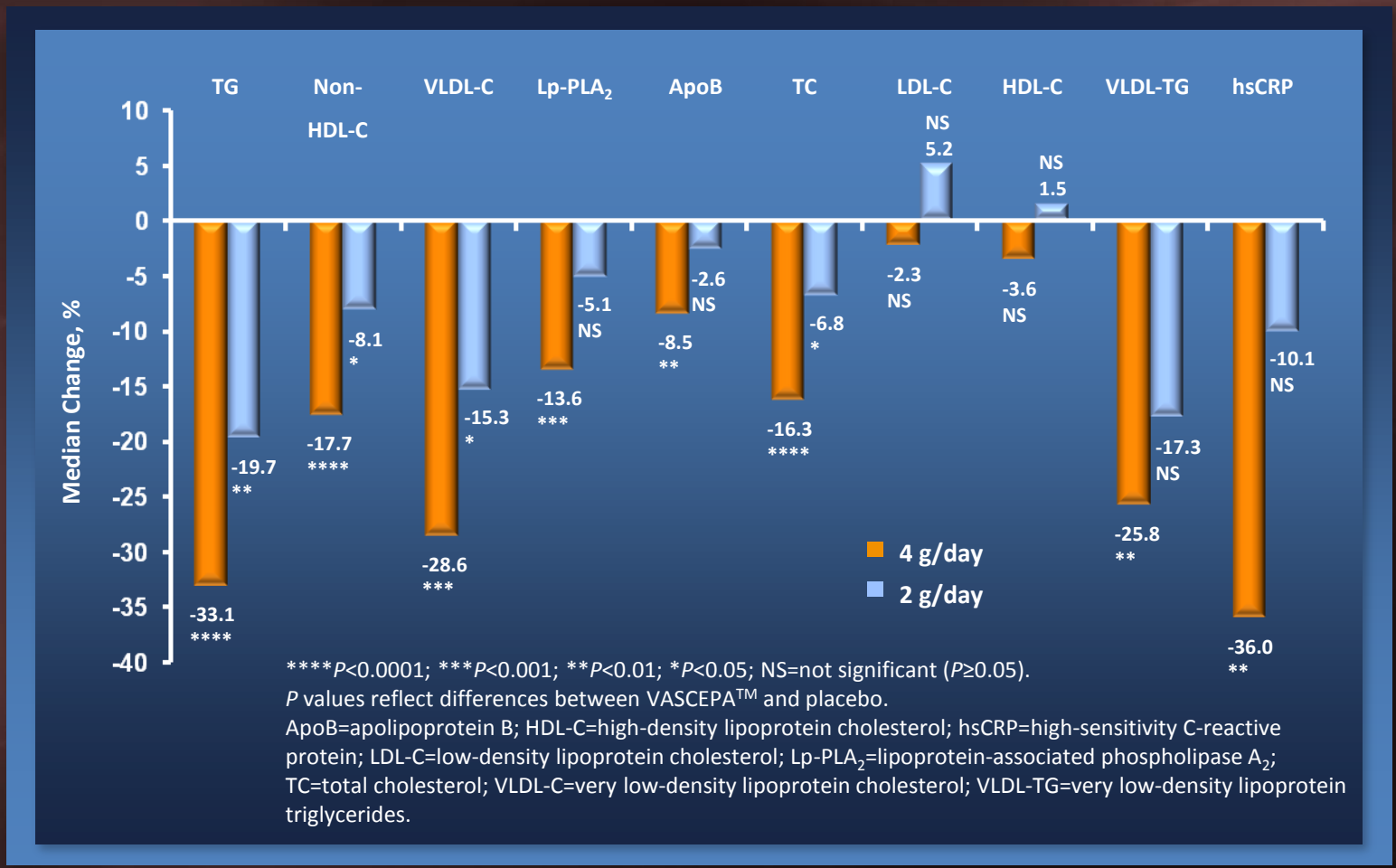
Icosapent Ethyl (VASCEPA®)



MARINE: VASCEPA Shows Significant TG-Lowering Effects

Icosapent Ethyl (VASCEPA®)



****P<0.0001; ***P<0.001; **P<0.01; *P<0.05; NS=not significant (P≥0.05).
P values reflect differences between VASCEPA™ and placebo.
ApoB=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; Lp-PLA_2=lipoprotein-associated phospholipase A_2; TC=total cholesterol; VLDL-C=very low-density lipoprotein cholesterol; VLDL-TG=very low-density lipoprotein triglycerides.

MARINE: VASCEPA Benefits Across a Broad Range of Lipids and Inflammatory Markers

Icosapent Ethyl (VASCEPA®)

- Metabolism: Liver
- Half Life: 89 hours
- Adverse Reactions
  - Arthralgia (2.3%)
- Drug Interactions
  - No significant drug-drug interactions
  - Omega-3 fatty acids = prolonged bleeding times

Icosapent Ethyl (VASCEPA®)

- Other possible effects
  - Anti-inflammatory effects
  - Cardiovascular
    - CAD, thickening of carotid arteries
  - Gastrointestinal
    - Improve non-alcoholic fatty liver
    - Ulcerative colitis
  - Psychiatic
    - Antipsychotic effects
    - Antidepressive effects
    - Anorexia nervosa

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References

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- http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm
- Nifediac package insert, TEVA Pharmaceuticals, Sellersville, Pennsylvania, August, 2009.
- "FDA Announces Revisions to Labels for Cialis, Levitra and Viagra". Food and Drug Administration. 2007-10-18
- Prescriber information sheets for each medication from the FDA

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Thank You !!

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