The Mediterranean diet and endothelial function: Why some dietary fats may be healthy

ROBERT A. VOGEL, MD
Herbert Berger Professor of Medicine; head, Division of Cardiology; Associate Chairman of Medicine for Clinical Affairs; co-director, Center for Vascular Biology and Hypertension, University of Maryland Medical Center, Baltimore

ABSTRACT
Evidence from both diet and physiologic studies suggests that some dietary fats—but not others—impair endothelial function in the short term, possibly by a mechanism of oxidative stress. This insight may affect our advice to patients about heart-healthy eating.

It may be time to change our standard advice about limiting cholesterol and high-fat foods, and take into account the effect of specific dietary fats on endothelial function.

To be sure, cholesterol is important: six large trials in the past 5 years demonstrated that lowering the serum cholesterol level with HMG-CoA reductase inhibitors (statins) decreased the rates of mortality, cardiovascular events, and disease progression. As we shall see however, cholesterol is only part of the story.

THE STANDARD MODEL AND THE MEDITERRANEAN DIET

Partially owing to the success of the large cholesterol-lowering trials, many people may view coronary artery disease in simplistic terms: high cholesterol leads to atherosclerosis, which leads to coronary events.

Against this background, the results of the Lyon Diet Heart Study came as a surprise: patients with coronary artery disease who followed a so-called Mediterranean diet had a 70% lower rate of coronary events compared with controls. Yet their serum cholesterol levels were no lower. Fish and fish-oil supplements were also found to be beneficial in the DART, Indian, and GISSI studies.

HIGH-FAT FOODS INHIBIT ENDOTHELIAL FUNCTION

How can diet affect cardiovascular disease risk without changing cholesterol levels?

Certain foods have direct effects on endothelium-dependent vasoactivity. We can observe and measure these effects by noninvasively measuring the diameter of the brachial artery with ultrasound before and after eating.

A blood pressure cuff is placed on the arm, inflated for 5 minutes, then released. In normal subjects in the fasting state, the artery responds to the increase in blood flow by
In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients without apparent pre-existing renal vascular disease may develop acute renal failure, may progress to fulminant hepatic necrosis and (sometimes) death. The mechanism of this occurrence is not understood. If oligohydramnios is observed, ACE inhibitor therapy should be discontinued unless it is felt that the benefit outweighs the risk to the fetus.

**CONTRAINDICATIONS**

Vascular disease. Available data are insufficient to determine whether ACEON has a neutral effect on the risk of cardiovascular disease in patients with vascular disease. The risk of cardiovascular disease is increased in patients with chronic renal insufficiency, diabetics, and hypertensive patients with left ventricular hypertrophy.

ACE inhibitors should not be given to women who may be pregnant because fetal and neonatal morbidity and mortality may occur whenever ACE inhibitors are given to pregnant women (see Clinical Studies). In the U.S. placebo-controlled trials, the overall frequency of reported adverse events was similar in patients receiving ACEON and placebo; however, a larger percentage of patients receiving ACEON experienced angioedema (3.2% vs. 0.5% in placebo), hyperkalemia (1.3% vs. 0.5% in placebo), and a specific changes in hematology and serum chemistries. The most common adverse events in clinical trials of perindopril were cough, headache, and gastrointestinal (GI) symptoms (nausea, vomiting and diarrhea) and the rates were generally similar to those seen in patients treated with placebo (1.5%).

**INDICATIONS AND USAGE**

ACEON (perindopril erbumine) is indicated for the treatment of patients with essential hypertension and in diabetic patients with nephropathy. It is a potent and long-lasting inhibitor of the enzyme that catalyzes the conversion of angiotensin I to angiotensin II, the principal vasoactive peptide in the renin-angiotensin system. ACEON is approved for the treatment of hypertension and renal disease. It is also approved for the treatment of diabetic nephropathy. **CONTRAINDICATIONS**

**WARNINGS**

Anaphylaxis and Possibly Fatal Reactions: Preparatory sera obtained from women who have received ACE inhibitors during pregnancy have been reported to cause fetal harm when given to pregnant women. It is not known whether perindopril could cause fetal harm when given to pregnant women. It is not known whether the risk of angioedema is increased in pregnant women. Therefore, perindopril should be avoided in pregnant women.

**WARNINGS:** Fetal/Neonatal Morbidity

Hepatic Failure: Hepatic failure has been reported in patients treated with ACE inhibitors. In patients with severe liver disease, the metabolism of angiotensin-converting enzyme (ACE) inhibitors is slowed, resulting in increased levels of ACE inhibitors. The combination of low serum ACE inhibitor levels and increased levels of angiotensin II may result in an increase in blood pressure and renal function. In patients with severe liver disease, the use of ACE inhibitors should be avoided.

**WARNINGS:** Fetal/Neonatal Morbidity

Hepatic Failure: Hepatic failure has been reported in patients treated with ACE inhibitors. In patients with severe liver disease, the metabolism of angiotensin-converting enzyme (ACE) inhibitors is slowed, resulting in increased levels of ACE inhibitors. The combination of low serum ACE inhibitor levels and increased levels of angiotensin II may result in an increase in blood pressure and renal function. In patients with severe liver disease, the use of ACE inhibitors should be avoided.

**WARNINGS:** Fetal/Neonatal Morbidity

Hepatic Failure: Hepatic failure has been reported in patients treated with ACE inhibitors. In patients with severe liver disease, the metabolism of angiotensin-converting enzyme (ACE) inhibitors is slowed, resulting in increased levels of ACE inhibitors. The combination of low serum ACE inhibitor levels and increased levels of angiotensin II may result in an increase in blood pressure and renal function. In patients with severe liver disease, the use of ACE inhibitors should be avoided.

**WARNINGS:** Fetal/Neonatal Morbidity

Hepatic Failure: Hepatic failure has been reported in patients treated with ACE inhibitors. In patients with severe liver disease, the metabolism of angiotensin-converting enzyme (ACE) inhibitors is slowed, resulting in increased levels of ACE inhibitors. The combination of low serum ACE inhibitor levels and increased levels of angiotensin II may result in an increase in blood pressure and renal function. In patients with severe liver disease, the use of ACE inhibitors should be avoided.
dilating by approximately 20% (FIGURE 1). This flow-mediated vasodilation lasts a few minutes and depends on the presence of endothelial nitric oxide, the most potent antiatherosclerotic molecule known.

**Short-term effects of a high-fat vs low-fat meal**

**Effects on vasodilation.** When we performed this experiment in healthy hospital employees, we found that a 900-calorie, low-fat meal (5.5 oz Kellogg's Frosted Flakes, 8 oz skimmed milk, and 16 oz orange juice, containing 0 mg of fat) had no effect. The arteries continued to dilate by approximately the same amount as at baseline. On the other hand, a 900-calorie, high-fat meal (one Egg McMuffin, one Sausage McMuffin, two hash brown patties, and a noncaffeinated beverage containing 50 mg of fat) reduced the amount of flow-mediated vasodilation by approximately half at 4 hours \((P < .001)\). Surprisingly, subjects who took 1 g vitamin C and 800 IU vitamin E immediately before eating a high-fat meal showed no change in flow-mediated vasodilation (FIGURE 1).

**Effects on triglycerides.** In the same experiment we measured serum triglyceride levels before and 2 hours after eating. The mean value at baseline was 97 mg/dL; this did not change after the low-fat meal but increased to 147 mg/dL after the high-fat meal, with or without vitamins \((P < .005)\). Levels of cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) did not change significantly. In the subjects who ate the high-fat meal without vitamins, the change in vasodilation had a statistically significant inverse correlation with the change in triglyceride levels \((r = -0.54, P < .001; \text{FIGURE 2})\).

**Proposed mechanism: oxidative stress.** How to interpret these results? I believe that high-fat foods impair endothelial function by a mechanism of oxidative stress that involves triglyceride-rich lipoproteins. Triglyceride-rich remnant particles and/or free fatty acids may stimulate the endothelial cells to increase production of free-radical superoxide anions, which deactivate nitric oxide. Oxidative stress also contributes to the pathogenesis of atherosclerosis. (Cigarette smoking, a powerful risk factor for atherosclerosis, also increases oxidative stress and abolishes endothelial function in the short term.) This mechanism may explain why the antioxidant vitamins C and E seem to preserve endothelial function.

**WHAT ABOUT OLIVE OIL?**

Different fats have different effects on endothelial function. We recently evaluated the effects of four different meals that each contained 50 g of fat (TABLE 1). Three meals derived the fat from olive oil, and one from fish oil in the form of salmon. Surprisingly, olive oil, a predominantly omega-9 fatty acid, produced almost the same decline in flow-mediated vasodilation as did the fast-food breakfast. However, mixing olive oil with vitamins C and E or with balsamic vinegar and salad (which contain natural antioxidants) substantially reduced the impairment of endothelial function. The fish oil contained in salmon had very little effect on endothelial function.
One would expect that olive oil, a staple of the diet in the Mediterranean region, would be relatively benign, in view of the results of the Lyon study. However, the Lyon study's Mediterranean diet used canola oil, not olive oil. Canola oil, containing an omega-3 fatty acid akin to fish oil, produced only an insignificant impairment in endothelial function compared with olive oil.

## DIET: WHAT IS IMPORTANT?

In view of these findings, the ideal diet would be high in fruits, vegetables, and breads and low in red meat and fat. One menu could be based on the one we used in our study: baked salmon along with bread, greens served with canola oil and vinegar, and fruit. In general, we should encourage our patients to eat more breads, vegetables, fruits, beans, and fish, and less meat, and to substitute canola oil margarine for butter and cream. These were the diet recommendations in the Lyon Diet Heart Study.1

As for alcohol, moderation is advised. However, red wine, with or without alcohol, has been found to improve flow-mediated vasodilation in a small study.9

### WHAT SHOULD WE RECOMMEND TO PATIENTS?

Based on what we know about the effects of poor diet and other risk factors for cardiovascular disease, the following recommendations are reasonable:

- Don't smoke cigarettes or cigars
- Avoid exposure to secondhand smoke
- Eat less
- Eat more fruits and vegetables
- Exercise. This need not be strenuous—walking 1.5 miles per day decreases the cardiovascular risk of a 70+ year old man by 50%.10

Even without going to the gym, individuals who are physically active have the same cardiovascular benefit as those who work out regularly.

### TRADITIONAL RISK FACTORS STILL IMPORTANT

This discussion should in no way detract from the need to target all the well-established modifiable risk factors—cigarette smoking, sedentary lifestyle, hypertension, truncal obesity, hyperinsulinemia, insulin resistance, hypertriglycerideremia, low HDL, high LDL, and hypercoagulability. This is especially true in patients with more than one risk factor, since the average patient with coronary disease has 3.5 risk factors. However, lipid-lowering drugs should be used in addition to lifestyle changes—ie, diet and exercise.

### REFERENCES


### ADDRESS:

Robert A. Vogel, MD, University of Maryland Medical Center, 22 South Greene Street, Baltimore, Maryland 21201.
ZOSYN® (Stereotactic Piperacillin Sodium and Tazobactam Sodium) Brief Summary

See package insert for full prescribing information.

INDICATIONS AND USAGE

For the treatment of patients with moderate to severe infections caused by piperacillin-resistant, piperacillin-susceptible gram-negative organisms, maintenance therapy is recommended for patients designated as in the specified conditions listed below:

- Appropriate chemotherapy for organ transplantation
- Appropriate chemotherapy for leukemia or lymphoma
- Postcibal endocarditis or viral inflammatory disease caused by Escherichia coli
- Postcibal encephalitis or systemic inflammatory disease caused by maternal infection
- Neurodegenerative disease (moderate to severe)

Intravenous piperacillin has been shown to be effective, is also amenable to ZOSYN treatment due to its piperacillin content. Treatment of mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant, beta-lactamase producing organisms even in the presence of the nephrovascular syndrome, has revealed no evidence of impaired fertility or fetal harm due to piperacillin administered up to a dose which is half (male) or similar to (rats) the human dose based on BSA (mg/m²).

ZOSYN has been evaluated in two phase II trials in mice and rats have revealed no evidence of impaired fetal harm due to piperacillin administered at doses up to 16 and 14 times, respectively, the human dose based on BSA (mg/m²). In rats, tobramycin crosses the placenta and is excreted in the milk, therefore, it is not recommended in lactating females. There are no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin alone in pregnant women; however, dosage recommendations for pregnant women are the same as for nonpregnant females.

Drug Interactions:

- Piperacillin: 
  - Piperacillin and tazobactam should be administered together only in patients with documented or strongly suspected infections due to beta-lactamase producing organisms. Piperacillin administered alone is considered ineffective, bacteriostatic, and likely to cause overgrowth of non-β-lactamase-producing bacteria. The addition of tazobactam results in a synergistic combination with piperacillin against Enterobacteriaceae species, N. gonorrhoeae, P. mirabilis, Bacteroides fragilis, and other susceptible anaerobes.
  - Piperacillin and tazobactam administered together may result in pharmacokinetic interactions with other therapeutic agents.

- Tazobactam: 
  - Tazobactam may reduce the serum levels of certain agents with a short serum half-life, such as gentamicin. 
  - Tazobactam has been shown to reduce serum levels of aminoglycosides, including gentamicin, tobramycin, and amikacin.

CONTRAINDICATIONS

ZOSYN is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or beta-lactamase inhibitors.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibiotics. In addition, allergic reactions of varying severity have been reported in patients receiving piperacillin alone or in combination with other antimicrobials. Thus, these reactions are considered to be related to the parent compound. As with other penicillins, piperacillin can be removed from the circulation by hemodialysis, peritoneal dialysis, and charcoal hemoperfusion.

After the diagnosis of pseudomembranous colitis has been established, initiate therapeutic measures. Mild cases can be treated with fluid and electrolyte replacements, for more severe cases, false cellulitis, fever, and protein supplementation, and treatment with an antibacterial drug clinically effective against C. difficile may be necessary.

PRECAUTIONS

General: 

- Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics, including piperacillin. While it has not been established whether bleeding is due to the drug or is related to the patient's disease status, the possibility of such complications should be considered. The use of piperacillin with other agents that may produce similar effect should be considered. The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind during prolonged antibiotic therapy.

- As with other penicillins, patients may experience new-onset or exacerbation of pre-existing hirsutism or rashes which may be related to piperacillin administration.

- Clotting time, platelet aggregation, and prothrombin time and are more likely to occur in renal failure patients and are less likely to occur in normal subjects. The possible prolongation of the prothrombin time should be considered in patients receiving ZOSYN who are also receiving anticoagulants.

- The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind during prolonged antibiotic therapy.

- As with other penicillins, piperacillin has been associated with an increased incidence of fever and rash in cyclic patients.

Laboratory Tests: 

- The presence of an infusion pump in patients receiving piperacillin/tazobactam in vitro can result in substantial inactivation of the aminoglycoside. (See Full Prescribing Information—Compatibility Interventions Brief Solutions, Dosage and Administration.)

Drug Interactions:

- Piperacillin: 
  - Piperacillin administered with tobramycin, ciprofloxacin, or rifampin may result in reduced serum levels of piperacillin, with an increased incidence of bacterial pathogens or gut flora.

- Tazobactam: 
  - Tazobactam reduces the serum levels of aminoglycosides, including gentamicin, tobramycin, and amikacin.

OVERDOSAGE

Intravenous piperacillin-susceptible organisms, for which piperacillin has been shown to be effective, bacteriostatic, and likely to cause overgrowth of non-β-lactamase-producing bacteria. The addition of tazobactam results in a synergistic combination with piperacillin against Enterobacteriaceae species, N. gonorrhoeae, P. mirabilis, Bacteroides fragilis, and other susceptible anaerobes.

- Piperacillin administered alone is considered ineffective, bacteriostatic, and likely to cause overgrowth of non-β-lactamase-producing bacteria. The addition of tazobactam results in a synergistic combination with piperacillin against Enterobacteriaceae species, N. gonorrhoeae, P. mirabilis, Bacteroides fragilis, and other susceptible anaerobes.

- Tazobactam may reduce the serum levels of certain agents with a short serum half-life, such as gentamicin. 
  - Tazobactam has been shown to reduce serum levels of aminoglycosides, including gentamicin, tobramycin, and amikacin.

- Piperacillin and tazobactam administered together may result in pharmacokinetic interactions with other therapeutic agents.

- Piperacillin administered alone is considered ineffective, bacteriostatic, and likely to cause overgrowth of non-β-lactamase-producing bacteria. The addition of tazobactam results in a synergistic combination with piperacillin against Enterobacteriaceae species, N. gonorrhoeae, P. mirabilis, Bacteroides fragilis, and other susceptible anaerobes.

- Tazobactam may reduce the serum levels of certain agents with a short serum half-life, such as gentamicin. 
  - Tazobactam has been shown to reduce serum levels of aminoglycosides, including gentamicin, tobramycin, and amikacin.

- Piperacillin administered alone is considered ineffective, bacteriostatic, and likely to cause overgrowth of non-β-lactamase-producing bacteria. The addition of tazobactam results in a synergistic combination with piperacillin against Enterobacteriaceae species, N. gonorrhoeae, P. mirabilis, Bacteroides fragilis, and other susceptible anaerobes.

- Tazobactam may reduce the serum levels of certain agents with a short serum half-life, such as gentamicin. 
  - Tazobactam has been shown to reduce serum levels of aminoglycosides, including gentamicin, tobramycin, and amikacin.