INTEGRATED HEALTHCARE
PRACTITIONERS
Integrated Healthcare Practitioners' Dietary and Nutritional Supplement, and Herbal Remedies Management Program

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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 1 CREDIT PHARMACOLOGY, 1 CREDIT NUTRITIONAL MEDICINE

Complementary medicine in secondary coronary prevention

The *American Heart Association* (AHA) provides guidelines for the prevention and treatment of heart disease. Primary coronary prevention (otherwise healthy people potentially presenting with undesirable cardiovascular risk factors) is differentiated from secondary coronary prevention (individuals with established heart disease, or who have survived a major coronary event) (Pearson 2002, Smith 2006). An aggressive pharmacological approach in conjunction with diet and lifestyle therapy is recommended in settings of secondary coronary prevention, while diet and lifestyle are generally considered first-line in settings of primary coronary prevention, with recommendations for pharmacotherapy if diet and lifestyle fail to normalize traditional cardiovascular risk factor values (Pearson 2002, Smith 2006).

This approach differs considerably from recommendations provided by the *Canadian Cardiovascular Society* (CCS). Specifically with regards to the management of dyslipidemia, the CCS has adopted an approach based on summation of cardiovascular risk factors. The model calculates a patient's risk score (a composite algorithm applying a value to the presence or absence or traditional cardiovascular disease risk factors). A patient's score determines desired LDL-cholesterol levels. Very often an otherwise healthy patient, possessing several cardiovascular risk factors, is labelled as "high-risk" according to the algorithm. Subsequently, the patient is instructed to strive for an LDL-C level not achievable through any means other than pharmacotherapy (statin therapy, typically) (McPherson 2006).

It is of interest to note that Scott Grundy, the individual who first developed the Framingham algorithm adopted by the CCS (Grundy 1999), is also a contributing author to the AHA position statements of management of primary and secondary coronary prevention (Pearson 2002, Smith 2006). The individual who created the algorithm does not use it as a tool to dictate pharmacotherapy. Such an application of the algorithm appears limited to the CCS.

Impact of "first line" therapies in secondary coronary prevention

Six pharmacotherapeutic classes are common first-line agents in secondary coronary preventon; statins, beta blockers, antiplatelet therapy, ACE inhibitors, thiazide diuretics, and cardioactive glycosides (Table 2). Of the six, only three were found to have sufficient evidence allowing for estimates to be made of impact on all cause mortality. Beta blockers reduce risk of all cause mortality 22% (Cucherat 2007). Antiplatelet therapy reduces risk of all cause mortality 13% (Berger 2008). Statins reduce risk of all cause mortality 12% (McPherson 2006). The remaining three drug classes, while lacking evidence of impact to all cause mortality, are utilized for their ability to control cardiovascular disease-related risk factors in this high-risk setting.

Three strategies falling under the heading of complementary medicine have also had sufficient evidence surface, allowing for estimates of impact on all cause mortality in secondary coronary prevention (Table 1). A Mediterranean dietary pattern reduces risk of all cause mortality 56% (de Lorgeril 1999, Singh 2002). Fish oil reduces risk of all cause mortality 20-25% (Marchioli 2002). Exercise reduces risk of all cause mortality 24% (Riedel 2004). CoEnzyme Q10, L- carnitine, and thiamine are complementary medicines capable of modifying important risk factors in this high-risk setting, although sufficient data allowing for estimates of impact on all cause mortality are yet to surface (Table 1).

"First- line" complementary therapeutic strategies

Mediterranean Dietary Pattern:

Two large, well-controlled clinical intervention trials have assessed the impact of a Mediterranean dietary pattern in settings of secondary coronary prevention (de Lorgeril 1999, Singh 2002). It is worth noting that in both settings, the intervention was added to a full-spectrum of conventional pharmacotherapeutic interventions and compared to control (pharmacotherapy with no diet/lifestyle counselling).

Therefore, outcomes described below are achieved in addition to what is achieved through pharmacotherapy alone.

Modelled after a Mediterranean dietary pattern, the Lyon Heart Study assigned 605 individuals who survived an MI to standard care or standard care plus dietary counselling. Subjects assigned to receive diet counselling successfully increased consumption of fruit, vegetables whole grains, alpha linolenic acid and oleic acid, and simultaneously decreased consumption of saturated fat and cholesterol. Four years of follow-up was available for the final analysis of the Lyon Heart Study (de Lorgeril 1999).

Subjects assigned to the diet counselling group experienced a 56% reduction in risk of all cause mortality, a 72% reduction in risk of cardiovascular death and non-fatal acute MI, and a 67% reduction in risk of major secondary endpoints (unstable angina, heart failure, stroke, embolism).

Has the Lyon Heart Study possibly underestimated the impact of diet and lifestyle intervention in secondary coronary prevention? Although the results reported above are impressive, they do not highlight the true ability of diet and lifestyle to modify disease risk in secondary coronary prevention. Three major shortcomings of the study can be sighted as a basis to conclude that the true impact of diet and lifestyle in secondary coronary prevention is significantly greater than that reported; A) Subjects were not instructed to lose weight through caloric restriction; B) Subjects were not instructed to exercise; C) A margarine was provided to subjects to help achieve increased consumption of oleic and alpha linolenic acid. While delivering these two health-promoting, plant- derived fats, the margarine also delivered 5.4% by volume trans fat.

The second major trial of a Mediterranean dietary pattern in secondary coronary prevention was the Indo-Mediterranean Diet Heart Study. A total of 1,000 high- risk patients (MI survivors, angina, or presence of multiple classic cardiovascular risk factors) were assigned to usual care or usual care plus counselling with regards to a Mediterranean dietary pattern (Singh 2002). Individuals assigned to the intervention group received counselling to increase consumption of fruit, vegetables, whole grains, mustard and/or soybean oil, almonds and walnuts. They were also instructed to engage in regular physical activity (3-4km per day of brisk walking).

Relative to the control group, individuals assigned to Mediterranean dietary pattern counselling experienced a 53% reduction in non-fatal MI, a 33% reduction in risk of fatal MI, a 67% reduction in risk of sudden coronary death, and a 52% reduction in total cardiac endpoints (Singh 2002).

Has the Indo-Mediterranean Diet Heart Study possibly underestimated the impact of diet and lifestyle in secondary coronary prevention? The control group in the current study was not a true control group. They did not receive usual care with little to no diet counselling. Instead, the control group also received extensive diet counselling, with instructions to follow a heart healthy diet. The control group was instructed to follow a *National Cholesterol Education Program* (NCEP) Step I diet, which recommends restrictions on total fat, cholesterol, and saturated fat intake, and also recommends increased fibre consumption. Subjects in the control group were also given identical exercise recommendations as the active treatment group. Had the control group not received such dietary and exercise counselling advice, the impact of the Mediterranean dietary counselling would have invariably been considerably superior to the reported results.

Exercise:
Regular exercise, of moderate or greater intensity, has reproducibly demonstrated an impressive magnitude of impact as a treatment strategy for patients in settings of secondary coronary prevention. A systematic review of cardiovascular rehabilitation programs included 14 RCT trials of exercise-based interventions. Exercise-based cardiovascular rehabilitation was shown to reduce risk of all cause mortality 24%, and cardiovascular mortality 27% (Riedel 2004).

Fish oil:
The GISSI-Prevenzione trial randomized 11,323 patients (all of whom were recent MI survivors) to placebo, vitamin E, fish oil, or vitamin E plus fish oil, in addition to standard care, for two years (Marchioli 2002). Vitamin E alone showed no significant impact, and vitamin E plus fish oil showed equivocal outcomes to fish oil alone. Therefore, the following discussion focuses on the impact of fish oil.

Patients received 850mg of combined EPA and DHA per day, in a 1.2:1 ratio of EPA: DHA. Patients were receiving the full-spectrum of conventional pharmaceutical medications, with 92% of patients at therapeutic INR through the use of either aspirin or warfarin. In addition to endpoints relating to risk of cardiovascular complications, subjects were evaluated for impact of the intervention on bleeding episodes relative to placebo (Marchioli 2002).

A protective effect of fish oil on “hard” clinical endpoints was observed very rapidly. Within three months of beginning the intervention, fish oil supplementation resulted in a 41% reduction in all cause mortality.

Table 1: Complementary therapeutic strategies in secondary coronary prevention

Intervention	Mechanism of Action	Adverse Effects	Outcomes	Reference
Mediterranean Dietary Pattern	Multiple	N/A	56% reduction in risk of all cause mortality. 67% reduction in risk of any major coronary event.	de Lorgeril 1999, Singh 2002
Fish Oil	Anti arrythmic, plaque stabilizing, anti thrombotic, improved lipoprotein spectrum	Fishy burp	20-25% reduction in risk of all cause mortality. 40-50% reduction in risk of sudden coronary death. 20-45% reduction in triglyceride levels. 5-10% increase in levels of HDL-C.	Kris- Etherton 2003, Marchioli 2002, Matsuzaki 2006, Yokoyama 2007
Exercise	Multiple	Muscle strain/sprain	24% reduction in risk of all cause mortality. 27% reduction in risk of cardiovascular mortality.	Riedel 2004
CoEnzyme Q10	Reversal of statin-induced depletion, hypotensive, obligatory member of the electron transport chain	N/A	Among patients who have experienced MI, reduction in risk of cardiovascular mortality and total cardiac events. Also reduced incidence of angina, total arrythmia, left ventricular dysfunction, and reversal of QT prolongation. Among patients with congestive heart failure, reduced number of hospitalizations, reduced myocardial thickness, reduced blood pressure.	Belardinelli 2005, Kuklinski 1994, Langsjoen 1993, Morisco 1993, Sarter 2002, Singh 1998.
L-Carnitine	Facilitates fatty acid entry into inner mitochondrial matrix	Gastro-intestinal discomfort	Among patients who have experienced MI, reduced risk of death, ischemic events, and congestive heart failure. Reduced left ventricular dilation, reduced end-diastolic and end-systolic volumes.	Ferrari 2004, Iliceto 1995, Rizos 2000, Tarantini 2006, Xue 2007.
Thiamine	Reversal of furosemide-induced thiamine deficiency	N/A	Among patients with congestive heart failure receiving long-term furosemide therapy, demonstrated to improve left ventricular ejection fraction and reverse refractory coronary heart failure.	Mendoza 2003, Seligmann 1991, Shimon 1995, Zenuk 2003

After one year, fish oil supplementation achieved a 28% reduction in all cause mortality. After 3.5 years of follow-up (1.5 years after cessation of the actual trial), patients initially assigned to receive fish oil had maintained a 21% reduction in risk of all cause mortality (Marchioli 2002).

After 3.5 years of follow-up, fish oil was shown to achieve the following outcomes in addition to above-outlined impact on all cause mortality; 30% reduction in risk of cardiovascular death, and 45% reduction in risk of sudden coronary death. Fish oil was safely combined with a full-spectrum of pharmaceutical medications used in secondary coronary prevention, and notably did not result in an increase in bleeding episodes among this population of patients at therapeutic INR (Marchioli 2002).

Table 2: Pharmacotherapeutic intervention strategies in secondary coronary prevention

Medication/Products	Mechanism of Action	Adverse Effects	Outcomes/Reference
Beta Blocker: Propranolol, Metoprolol Pindolol, Labetalol, Carvedilol	Inhibit normal epinephrine-mediated sympathetic actions, minimal effect on resting subjects. They reduce the effect of excitement/physical exertion on heart rate and force of contraction, dilation of blood vessels and opening of bronchi.	GI upset, bronchospasm, dyspnea, cold extremities, bradycardia, hypotension, heart failure, fatigue, dizziness, abnormal vision, hallucinations, insomnia, nightmares, depression, sexual dysfunction.	22% reduction in risk of all cause mortality. CPS 2008, Cucherat 2007.
Anti-platelet therapy: Aspirin, Coumadin Plavix, Heparin (IV or SC)	Warfarin blocks calcium-dependent clotting factors II, VII, IX and X; Plavix blocks ADP receptor on platelets thus inhibiting platelet aggregation and fibrin cross-linking; Heparin binds to anti-thrombin III (ATIII), causing inactivation of thrombin, and factors Xa and IXa. Aspirin is a non- selective inhibitor of cyclooxygenase.	Easy bruising, bleeding, internal hemorrhage Heparin-induced Thrombocytopenia (HIT). Coumadin reduces bone mineral density.	14% reduction in risk of all cause mortality Berger 2008, CPS 2008.
Statin: Atorvastatin, Cerivastatin Lovastatin, Pravastatin Simvastatin, Rosuvastatin	Inhibit HMG-CoA reductase, the enzyme controlling the first committed step of sterol (cholesterol) synthesis, in the liver. Mevalonate production is principally reduced.	Generally well tolerated. Myalgia, muscle cramps, elevated liver enzymes. Rare complications may include myositis and myopathy, with the potential for rhabdomyolysis.	12% reduction in risk of all cause mortality CPS 2008, McPherson 2006.
ACE inhibitor: Captopril, Benazepril Enlapril, Perindopril Quinapril	Block Angiotensin Converting Enzyme in the lungs, and conversion of angiotenin I to angiotensin II. ACE inhibitors lower arteriolar resistance and increase venous capacity; increase cardiac output and cardiac index, stroke work and volume, lower renovascular resistance, and lead to increased natriuresis.	"ACE Inhibitor cough", Orthostatic hypotension, hyperkalemia, headache, dizziness, fatigue, nausea, renal impairment.	Increases cardiac output and cardiac index, stroke work and volume CPS 2008.
Thiazide Diuretic: Lasix	Inhibits Na-K-2Cl symporter in the thick ascending limb of the loop of Henle, and blocks the corticomedullary osmotic gradient. It also blocks negative as well as positive free water clearance. Additionally, flasix is a noncompetitive subtype-specific blocker of GABA-A receptors.	Dehydration, electrolyte imbalance, may be ototoxic.	Decreases blood pressure, reduces edema. CPS 2008
Cardio-active Glycoside: Digoxin (Lanoxin)	Blocks Na/K ATPase on myocyte membrane, increasing intracellular Na+ and Ca2+ concentrations. Overall, positive ionotrope, negative chronotrope.	Hypokalemia Bradycardia Visual disturbances (yellow-green halos)	Decreased HR, increased contractility. Normalize atrial fibrillation/ atrial flutter. CPS 2008.

The JELIS trial (Japan EPA Lipid Intervention Study) randomized 18,654 patients to fish oil (1,800mg per day of EPA, no DHA) or placebo, and followed them for five years. Approximately 3,500 of the patients were in a setting of secondary coronary prevention. 1,050 of these patients were MI survivors. The remaining 15,000 patients were otherwise healthy, but were found to have hypercholesterolemia. All patients were receiving statin therapy, and patients in a setting of secondary coronary prevention received the full spectrum of standard pharmaceutical care (Matsuzaki 2006, Yokoyama 2007).

Patients in a setting of primary coronary prevention (hypercholesterolemic, otherwise healthy) assigned to fish oil achieved a 19% reduction in risk of combined major coronary events (MCE's) (Yokoyama 2007). Subjects in a setting of secondary coronary prevention at baseline achieved a 23% reduction in risk of MCE's. The subset of patients who had survived an MI prior to enrollment experienced a 27% reduction in MCE's (Matsuzaki 2006).

Contrary to the 45% reduction in sudden coronary death achieved in the GISSI- Prevenzione trial, JELIS failed to demonstrate any impact on risk of sudden coronary death. What is the explanation for this apparent discrepancy?

JELIS was conducted in Japan. The average intake of EPA and DHA among Japanese adults is approximately 900mg of combined EPA and DHA per day. The rate of sudden coronary death in subjects in the placebo group of the JELIS trial is as low as 1/9th the rate seen amongst subjects in the GISSI-Prevenzione trial. Therefore, low dose EPA and DHA (900mg of combined EPA and DHA per day, or less) powerfully reduces risk of sudden coronary death. Larger dosages of fish oil, above and beyond this low dose, do not further reduce the risk of sudden coronary death. Both the active group and the placebo group in the JELIS trial experienced maximal sudden coronary death risk reduction from fish oil through dietary intake of fish. What JELIS shows is the impact of adding almost two grams of EPA on top of this baseline intake of EPA and DHA. Low dose fish oil reduces risk of sudden coronary death. Larger dosages of fish oil do not further lower this risk, but rather, begin to lower risk of non-fatal, major coronary events.

"Second- line" complementary therapeutic strategies

The differentiation between first- and second-line treatment strategies has been made based on availability of sufficient evidence to make estimates of impact on "hard" cardiovascular endpoints; all cause mortality and cardiovascular mortality. The agents reviewed below have considerable evidence attesting to their application in settings of secondary coronary prevention. However, outcomes remain, for the most part, confined to surrogate markers of disease risk. Nonetheless, the rationale for their implementation appears to be sound.

L- Carnitine

We identified 26 clinical intervention trials of L-carnitine in settings of secondary coronary prevention. Although varying dosages have been utilized, 2,000mg per day (in divided doses) appears to be the most consistent dosing regime. Several trials studied reasonable patient numbers (100-500 subjects per trial), and were of reasonable duration (one year or greater) (Ferrari 2004, Iliceto 1995, Tarantini 2006).

Intervention trials have demonstrated reduced risk of death and ischemic events, but were not large enough to attach solid risk estimates to use of the intervention. Surrogate endpoints reproducibly demonstrated to be improved through L-carnitine administration include reduced ST segment depression, reduced left ventricular end-diastolic and end-systolic volumes, and reduced left ventricular dilation (Ferrari 2004, Iliceto 1995, Rizos 2000, Tarantini 2006, Xue 2007). Most trials utilize oral L-carnitine, while others use a combination of I.V. and oral delivery.

Mechanistically, L-carnitine increases the rate of fatty acid transport into mitochondria, and reduces the intramitochondrial ratio of acetyl- CoA to free CoA, thus stimulating the activity of pyruvate dehydrogenase and increasing the oxidation of pyruvate. Accumulation of long-chain acetyl-CoA has been shown to facilitate production of free radicals by damaged mitochondria and produces malignancy arrythmias. Both of these phenomena are reversed by L-carnitine's ability to reduce accumulation of acetyl-CoA (Ferrari 2004).

CoEnzyme Q10

Like L-carnitine, preliminary evidence has emerged suggesting an impact of CoEnzyme Q10 administration on reduced risk of cardiovascular mortality. More evidence is needed before solid estimates of risk reduction can be applied to hard cardiovascular endpoints and CoEnzyme Q10 therapy.

CoEnzyme Q10 is an obligatory member of the electron transport chain, and as such, is required for synthesis of ATP. It is also one of two endogenous antioxidant nutrients within LDL-cholesterol particles (the second being vitamin E) (Sarter 2002). Plasma CoEnzyme Q10 levels have been reproducibly demonstrated to be depressed by statin and/or fibrate therapy (Asano 2006, Berthold 2006, Lamperti 2005, Mabuchi 2005, Sarter 2002).

CoEnzyme Q10 can be administered at a dosage of 60-220mg per day, in divided doses. Among patients who have experienced MI, CoEnzyme Q10 therapy has demonstrated reduced incidence of angina, total arrythmia, left ventricular dysfunction and reversal of QT prolongation. Among patients with congestive heart failure, CoEnzyme Q10 therapy has achieved a reduced number of hospitalizations, reduced myocardial thickness, and reduced blood pressure (Belardinelli 2005, Kuklinski 1994, Langsjoen 1993, Morisco 1993, Sarter 2002, Singh 1998).

Thiamine

Thiamine is a required cofactor for ATP generation, acting as a component of the active arm of pyruvate dehydrogenase — a key regulating enzyme of the Krebs cycle. Furosemide, a common first-line diuretic class of medication, aggressively depletes body stores of thiamine (Zenuk 2003).

A modest number of intervention trials have examined supplemental thiamine in settings of secondary coronary prevention. Individuals receiving long-term furosemide therapy appear to be ideal candidates for the intervention. In studies of thiamine administration (100mg per day, I.V.) to patients who have been receiving long-term furosemide therapy, thiamine has been shown to improve left ventricular ejection fraction and reverse refractory coronary heart failure (Mendoza 2003, Seligmann 1991, Shimon 1995).

Conclusion

Diet and lifestyle-based intervention strategies remain recognized by leading global medical authorities as first-line therapy for management of cardiovascular risk factors in settings of primary coronary prevention, and as important adjunct therapy in settings of secondary coronary prevention. Such strategies impart an incredibly impressive magnitude of benefit to "hard" cardiovascular endpoints, including all cause mortality and cardiovascular mortality. A Mediterranean dietary pattern, exercise, and fish oil supplementation have an evidence-base in their support that is second to none.

An important list of nutritional supplements, although lacking sufficient evidence to make estimates of impact on all cause or cardiovascular mortality, have an impressive magnitude of efficacy in improvement of surrogate endpoint measures in cardiovascular care. L-carnitine, CoEnzyme Q10, and thiamine are important considerations for addition to standard treatment of patients in settings of secondary coronary prevention. ■

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Questions

1. Beta blockers, statins, antiplatelet therapy, diuretics, ACE inhibitors, and cardioactive glycosides comprise the standard medication classes utilized in secondary coronary prevention. All six of these medication classes have sufficient evidence allowing for estimates of their impact on all cause mortality.
   A) True
   B) False

2. Although exercise has been shown to improve a selection of surrogate markers in settings of secondary coronary prevention, there is insufficient evidence to establish impact of exercise on all cause mortality.
   A) True
   B) False

3. Thiamine administration in settings of secondary coronary prevention, among patients receiving long-term furosemide therapy, has been shown to reduce risk of all cause mortality by 18%.
   A) True
   B) False

4. Among patients who survived an MI, counselling regarding a Mediterranean dietary pattern has been shown to reduce risk of all cause mortality by 56% versus standard care alone.
   A) True
   B) False

5. Although fish oil supplementation has shown promise in the field of cardiovascular care, there is concern regarding its interaction with antiplatelet therapy. No study to date has combined fish oil with antiplatelet therapy to determine if there is adverse interaction between these two medications.
   A) True
   B) False

6. The outcomes produced by the Lyon Heart Study are impressive. However, the study may have in fact underestimated the true impact of diet and lifestyle in secondary coronary prevention. Choose the most appropriate selection of factors that may account for the study underestimating therapeutic potential.
   A) Participants were not discouraged to avoid fried foods, sweets and other processed foods.
   B) Participants were not encouraged to undertake meditation or eat fish.
   C) Participants were not encouraged to exercise, lose weight, and the supplemental margarine contained 5.4% trans fat.
   D) Recommendations to increase fruit, vegetable, and whole grain consumption did not include the importance of the produce being organic.

7. Choose the answer below that most accurately ranks the reduction in risk of all cause mortality achieved using the specified intervention strategies.
   A) Mediterranean diet pattern 56%, exercise 24%, fish oil 24%, beta blocker 22%, antiplatelet therapy 14%, statin 12%.
   B) Beta blocker 22%, Mediterranean diet pattern 20%, statin 18%, antiplatelet therapy 16%, exercise 10%, fish oil 9%.
   C) Mediterranean diet pattern 56%, beta blocker 22%, ACE inhibitor 18%, fish oil 14%, L-carnitine 11%.
   D) Beta blocker 22%, statin 20%, antiplatelet therapy 18%, no complementary intervention has sufficient evidence for estimates of all cause mortality.

8. The Indo-Mediterranean Diet Heart Study may have underestimated the risk of diet and lifestyle as a treatment for heart disease. Choose the statement that most accurately reflects why this may be true.
   A) Subjects in the treatment group were not advised to exercise.
   B) Subjects in the treatment group were advised to consume almonds and walnuts, foods known to increase cardiovascular disease risk.
   C) Subjects in the control group were advised to exercise, and were advised to follow a heart-healthy NCEP step I diet.
   D) None of the above provides a basis for suggesting the study underestimated the benefit of diet- and lifestyle-based intervention.

9. The mechanistic basis for considering inclusion of CoEnzyme Q10 supplementation in secondary coronary prevention includes:
   A) CoEnzyme Q10 reduces risk of all cause mortality.
   B) CoEnzyme Q10 is an obligate member of the electron transport chain, and is depleted by statin and fibrate therapy.
   C) CoEnzyme Q10 facilitates transport of long chain fatty acids into the inner mitochondrial matrix.
   D) CoEnzyme Q10 is a required cofactor of pyruvate dehydrogenase, a key regulatory enzyme of the Krebs cycle.

10. Based on estimates of impact on all cause mortality, select the most important pharmaceutical preparation in settings of secondary coronary prevention.
    A) Statins
    B) ACE inhibitors
    C) Antiplatelet therapy
    D) Beta blockers

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