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ABSTRACT & COMMENTARY

More Mediterranean Diet Benefits: Diverse Microbiomes, Better Health Among Seniors

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Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: A randomized, multicenter study showed that eating a Mediterranean diet for one year improved the diversity of the gut microbiome in older subjects and was associated with reduced frailty and better health.

SOURCE: Ghosh TS, Rampelli S, Jeffery IB, et al. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut* 2020; Feb 17. pii: gutjnl-2019-319654. doi: 10.1136/gutjnl-2019-319654. [Epub ahead of print].

This study was based at a Microbiome Institute in Cork, Ireland. The authors profiled the gut microbiota of 612 non-frail or pre-frail elderly subjects from five European countries: the United Kingdom, France, Netherlands, Italy, and Poland. The randomized study group was placed on a standardized Mediterranean diet that has been used in other European studies.[1,2]

The microbiota initially reflected both the diets of the participants and the countries where they lived. After one year, the microbiota of those on the Mediterranean diet became more diverse among the intervention group on the diet, regardless of country. The control group remained on their standard diet.

Besides improving the diversity of the microbiome, the study group showed improvements in markers of frailty, including hand strength, walking speed, and cognitive function. The more diverse microbiome also was associated with fewer inflammatory markers, including C-reactive protein and interleukin-17. The more diverse microbiota in the intervention group produced more short-chain fatty acids that have been associated with better health. Conversely, the microbiome diversity decreased in the control group, with an increase

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in detrimental effects such as insulin resistance and fatty liver disease.

■ COMMENTARY

Microbiome science still is in its infancy, and this observational study is compelling. However, this work does not establish cause and effect. The expression "we are what we eat" has been conveyed in different ways for centuries. A revision of this concept would be "we are what we feed our microbiome."

Recently, Mark Hyman, MD, has explored the many problems of the modern Western diet, loaded with sugary carbs and overly processed foods.[3] Too many Americans (and plenty of others around the world) carry excess body fat; there's a good chance many in this group are at least prediabetic. We have been poisoning ourselves, including the "gut bugs" that protect us. There are healthy culinary alternatives, and the Mediterranean diet is a clear winner. Every clinician should consume a healthy diet and be able to recommend one to all patients. That way, we become agents for good health, including among the frail elderly. ■

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ABSTRACT & COMMENTARY

The Cascade Effect: Calcium Channel Blockers and High Blood Pressure

By Martin Lipsky, MD

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Dr. Lipsky reports no financial relationships relevant to this field of study.

SYNOPSIS: Many older adults who are prescribed calcium channel blockers subsequently receive a loop diuretic. Awareness of this common cascade may reduce unnecessary prescribing and potential harm.

SOURCE: Savage RD, Visentin JD, Bronskill SE, et al. Evaluation of a common prescribing cascade of calcium channel blockers and diuretics in older adults with hypertension. *JAMA Intern Med* 2020; Feb 24. doi: 10.1001/jamainternmed.2019.7087. [Epub ahead of print].

Calcium channel blockers (CCBs) often are prescribed as first-line medications for treating hypertension.[1] This occurs, in part, because of a perceived low incidence of adverse events and a limited need for routine lab monitoring.[2]

However, depending on the CCB type, dosage, and duration of therapy, the incidence of peripheral edema ranges from 2% to 25%. Using health administrative databases of community dwelling adults age 66 years and older, Savage et al compared the incidence of subsequent diuretic prescriptions in individuals newly prescribed CCBs to those newly dispensed an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) and individuals newly prescribed an unrelated medication.

The study cohort included 41,046 individuals (older than age 66 years) with hypertension who were newly prescribed a CCB, 66,494 newly prescribed another hypertensive medication, and 231,439

newly prescribed another medication. Individuals prescribed a CCB were more likely to receive a subsequent loop diuretic prescription (1.4%) vs. those prescribed an ACEI (0.7%) or ARB (0.5%). After adjustment, individuals who were newly dispensed a CCB were more likely to receive a loop diuretic vs. individuals who were newly dispensed an ACEI or ARB: hazard ratio (HR), 1.68; 95% confidence interval (CI), 1.38-2.05 in the first 30 days after index (days 1-30); HR, 2.26; 95% CI, 1.76-2.92 in the subsequent 30 days (days 31-60); and HR, 2.40; 95% CI, 1.84-3.13 in the third month of follow-up (days 61-90). For patients who were newly dispensed unrelated medications: HR, 2.51; 95% CI, 2.13-2.96 for days 1-30 after index; HR, 2.99; 95% CI, 2.43-3.69 for days 31-60 after index; and HR, 3.89; 95% CI, 3.11-4.87 for days 61-90 after index.

Considering how widely CCBs are prescribed, the authors noted clinicians should be aware of this common prescribing cascade to reduce the potential of prescribing an unnecessary medication that may cause harm.

■ COMMENTARY

A key concept when caring for older patients is to use the fewest and lowest doses of medications to achieve a desired result. Each additional medicine synergistically increases the risk of adverse events, highlighting the importance of avoiding the cascading use of medications. This study highlights an example of a cascade effect. Using CCBs increases the likelihood of receiving another prescription for a diuretic by more than 60% when compared to other hypertensive medications.[3] Potential risks from reflexively adding a diuretic to a CCB for peripheral edema include increasing the number of falls, triggering incontinence, overdiuresis in euvolemic patients, and more diagnostic testing. While the percentages revealed in this study seem small, prescribing a diuretic to 3.5% of those taking a CCB represents as many as 500,000 to 1.3 million individuals potentially taking an unnecessary medication.

Typically, peripheral edema occurs more frequently in dihydropyridine CCBs compared with non-dihydropyridine CCBs (e.g., verapamil and diltiazem),[2] Savage et al did not find this association in their study. One explanation might be related to the prescribing indication (e.g., atrial fibrillation rather than hypertension) or to differences in how the edema was managed.

In an accompanying editorial, Anderson and Steinman noted CCBs are not alone among antihypertensives for causing a pharmacologic cascade.[4] Other examples include ACEIs and antitussives, diuretics and bladder antispasmodics for urinary frequency, and antihistamines for dizziness related to antihypertensive treatment. Also, they noted prescribing an antihypertensive may represent a cascade-induced effect from medications such as nonsteroidal anti-inflammatory drugs, which might elevate blood pressure.

CCBs remain an effective antihypertensive therapy, and still should be considered a part of a primary care clinician's toolbox for treating high blood pressure. However, before prescribing a diuretic to treat CCB-related edema, options should include nonpharmacologic management such as elevation and support stockings, considering if the CCB can be cut off, or whether the patient can be switched to another therapy. ■

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ABSTRACT & COMMENTARY

Cannabis for Mental Health Disorders: Follow the Evidence

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: In a review of 83 eligible studies, researchers found little evidence to support the efficacy of cannabinoids to treat depressive disorders, anxiety disorders, or several other mental health disorders.

SOURCE: Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: A systematic review and meta-analysis. *Lancet Psychiatry* 2019;6:995-1010.

One of the most common reasons given for seeking medicinal cannabinoid use is for treatment of a mental health disorder. Medicinal cannabis is legal in 33 states; quality research regarding this substance is necessary to provide individuals with full clinical guidelines and risk profiles.[1]

Recognizing this need, Black et al conducted a meta-analysis of 83 eligible studies regarding medical cannabinoids and mental health disorders. The authors used "medicinal cannabinoids" to cover all plant-based and synthetic derivatives of the cannabis plant; "medicinal cannabis" refers to any part of the cannabis plant; "pharmaceutical cannabinoids" are extracts with defined tetrahydrocannabinol (THC) with or without cannabidiol (CBD); and "pharmaceutical CBD" refers to extractions of CBD alone.

Eligibility criteria included studies that used medicinal cannabinoids of any type and remission or change in symptoms in at least one of the following disorders: depression, anxiety, post-traumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, and psychosis. In all studies, the mental health disorder was either primary or secondary to another medical problem. Adverse effects and study withdrawals were included in the analysis.

Using standard tools — the Cochrane risk-of-bias tool[2] and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[3] — researchers put the evidence from the controlled trials into one of four categories, ranging from "very low quality" to "high quality." Within the 83 eligible studies, there were 50 randomized, controlled trials (RCTs). The median sample size across all diagnoses for RCTs ranged from 10 to 39 participants. Median length of the trials was four to five weeks. The most common substance investigated was pharmaceutical THC; the next most common was pharmaceutical CBD. The eligible studies that were not RCTs were observational and included prospective studies, chart reviews, and case studies.

Pharmaceutical THC (with or without CBD) was used in all but one RCT involving depression. In all studies, depression was not a stand-alone diagnosis but was secondary to a chronic medical problem (mainly chronic noncancer pain or multiple sclerosis [MS]). The pooled standardized mean difference (SMD) for a change in depressive symptoms associated with the use of pharmaceutical THC with or without CBD was 0.00 to 0.05 (95% confidence interval [CI], -0.20 to 0.17). Black et al explained that an SMD of 0.2 represents a small effect, 0.5 represents a medium effect, and 0.8 represents a large effect, meaning that pharmaceutical THC with or without CBD did not affect users with depression very much at all. The one RCT that concerned medicinal cannabis revealed no change in depressive symptoms in patients with chronic noncancer pain when compared to treatment with placebo.

Pharmaceutical THC with CBD beat placebo in a significant lowering of anxiety symptoms in seven studies involving patients with either chronic noncancer pain or MS. The SMD was -0.25 (95% CI, -0.49 to -0.01). However, the evidence GRADE was very low because of several factors, including reporting bias, and none of the respondents had received a primary diagnosis of anxiety. Two studies concerned CBD alone vs. placebo in the treatment of social anxiety; there was no significant improvement in symptoms.

Symptoms of ADHD did not show a significant change in one RCT of pharmaceutical THC with CBD vs. placebo. Two small RCTs compared pharmaceutical THC with CBD to placebo in treatment of Tourette syndrome and showed no significant effect on symptoms. One small study of 10

individuals with PTSD revealed pharmaceutical THC with CBD vs. placebo was associated with improved global functioning and reduced nightmares (SMD = -1.3; 95% CI, -1.48 to -0.77). One RCT of 24 individuals showed no change in positive symptoms of psychosis (such as hallucinations) with the use of pharmaceutical THC with CBD vs. placebo, but a worsening of negative symptoms, such as social isolation and withdrawal (SMD 0.36; 95% CI, 0.10-0.62). The remaining five RCTs of psychosis used CBD vs. placebo. There was no significant improvement noted in any primary outcomes, but the authors of one study involving 86 individuals reported an improvement in global functioning with an SMD of -0.62 (95% CI, -1.14 to -0.09).

Pooled results from all RCTs indicate pharmaceutical THC with CBD was associated with significantly more adverse effects in 10 studies (odds ratio [OR], 1.99; 95% CI, 1.20-3.29) vs. placebo and significantly more study withdrawals in 11 studies vs. placebo (OR, 2.78; 95% CI, 1.59-4.86). Adverse events were not recorded in this meta-analysis, but are known (from other literature) to increase the occurrence of depression, anxiety, and psychotic symptoms. The evidence GRADE for these findings was low to moderate. There were fewer studies of adverse effects and study withdrawal when CBD (one study) or medicinal cannabis (three studies) was compared with placebo, but none of these resulted in a significant difference. The researchers also did not state whether cannabis was the only treatment participants were using for their conditions.

■ COMMENTARY

The most striking conclusion emerging from this comprehensive review and meta-analysis regarding cannabinoids for the treatment of mental health disorders is how little we know. Standing in contrast to the lack of quality medical studies regarding mental health disorders and medical cannabinoids are high-quality, rigorous investigations regarding the use of this agent for chronic pain, neuropathic pain, and nausea and vomiting associated with chemotherapy, and spasticity associated with MS.[4]

In 2017, the National Academies of Sciences, Engineering, and Medicine released a comprehensive report reviewing and summarizing research since 1999 regarding recreational and medicinal cannabis use. The report summarized the relevant medical literature and ranked evidence for efficacy as well as adverse effects when using medicinal cannabinoids for a specific medical condition. Regarding mental health, the authors concluded there is "no evidence to support or refute a statistical association between cannabis use and changes in the course or symptoms of depressive disorder," and there is moderate evidence of increased social anxiety disorder associated with regular cannabis use.[5] In addition, the report noted substantial evidence of development of schizophrenia with heavy cannabis use and moderate evidence of more suicidal thoughts and attempts associated with heavy cannabis use.[5]

The work of Black et al strongly supports the idea that there remains no strong evidence for medicinal cannabis to treat depression, anxiety, ADHD, Tourette syndrome, or psychosis. Of note, with the exception of PTSD and Tourette syndrome, most of these conditions are not on a list of conditions qualifying for medicinal cannabinoid use in any state. However, 23 states currently specify PTSD as an approved condition for medicinal cannabinoids, and only five specify Tourette syndrome. In addition, in what appears to be a growing trend, at least six states allow physicians to certify a need for a dispensary card at the "discretion" of the provider.[6,7]

Considering the strong probability patients looking for alternative treatments will ask providers about medicinal cannabinoid use, it is useful to be armed with facts. There is no evidence showing medicinal cannabinoid use helps mental health disorders, and there are concerns that heavy use can cause mental health problems. There is weak evidence showing medicinal cannabinoid use is associated with a decrease in anxiety associated with a chronic health condition. Many states have preemptively approved medicinal use of cannabinoids for specific diagnosis without waiting for rigorous studies or medical evidence to prove their efficacy.

Medicinal cannabinoid efficacy is well-studied and established for specific disorders, but there is no convincing evidence this works for treating mental health disorders. The downside to using medicinal cannabinoids for a mental health disorder may be considerable. The primary care provider is well-situated to aid patients in understanding the current state of knowledge regarding medicinal cannabinoid use in disorders of mental health. However, it is important to urge caution and patience until enough evidence is gathered to reach firm conclusions. ■

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PHARMACOLOGY UPDATE

Ozanimod Capsules (Zeposia)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The Food and Drug Administration has approved the third sphingosine-1-phosphate (S1P) receptor modulator, following fingolimod and siponimod, to treat relapsing multiple sclerosis (MS). Ozanimod selectively binds to S1P subtypes 1 and 5 (S1PR1/S1PR5). Ozanimod will be marketed as Zeposia.

INDICATIONS

Ozanimod should be prescribed to treat relapsing MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.[1]

DOSAGE

Ozanimod is taken orally and is initiated with a titration schedule: 0.23 mg once daily (days 1-4), 0.44 mg once daily (days 5-7), and 0.92 mg once daily (day 8 and thereafter).[1] Before drug initiation, conduct a complete blood count; electrocardiogram (ECG); liver function tests; ophthalmic assessment; antibodies to varicella zoster virus; and current or prior treatment with immunosuppressives, antineoplastics, and drugs that slow heart rate or atrioventricular (AV) conduction. Ozanimod is available as 0.23 mg, 0.44 mg, and 0.92 mg capsules.

POTENTIAL ADVANTAGES

Ozanimod is a selective S1P modulator similar to siponimod. Fingolimod is nonselective, with binding to receptor subtypes 1, 3, 4, and 5 (S1PR1, S1PR3, S1PR4, and S1PR5). S1PR3 is associated with AV conduction slowing.[2] Ozanimod has a longer elimination than siponimod (mean 21 hrs vs. 4 hrs), permitting once-daily dosing.[1,3]

POTENTIAL DISADVANTAGES

Ozanimod is contraindicated in patients who have experienced a cardiovascular or cerebrovascular event (e.g., myocardial infarction, unstable angina, stroke, transient ischemic attack, class III or IV heart failure) or severe, untreated sleep apnea.[1] Ozanimod may increase the risk of infection caused by significant reduction in blood lymphocyte count. In addition, a slower heart rate and AV conduction delays, macular edema, reduction in pulmonary function, and elevation of liver transaminases may occur. Progressive multifocal leukoencephalopathy, a rare but serious viral brain infection, has been reported with S1P receptors modulators and other MS drugs.[1] Due to potential fetal risk, women of child-bearing age should use effective contraception during treatment and for three months after stopping treatment. Concomitant use with strong CYP2C8 inhibitors, strong CYP2C8 inducers, breast cancer resistance protein inhibitors, and monoamine oxidase inhibitors is either not recommended or should be avoided.[2]

COMMENTS

The efficacy of ozanimod was evaluated in two randomized, double-blind, active comparator-controlled clinical trials.[1,4,5] Study participants were mainly white females with a relapsing form of MS. At baseline, the mean age was 35.5 years, mean time to onset of symptoms was 6.6 to 6.9 years, there had been a mean of 1.3 relapses in the prior year, there were a mean of 1.8 Gadolinium-enhancing (i.e., active) lesions, and the median Expanded Disability Status Scale (EDSS) score was 2.5 (the severity ranged from 0-10). Subjects were randomized to ozanimod (0.92 mg once daily) or interferon beta-1a (30 mcg intramuscularly once weekly).[1] The primary endpoint was the annualized relapse rate (ARR) over 12 months in study 1 and 24 months in study 2. Additional outcomes included new and or enlarged magnetic resonance imaging (MRI)-detected lesions and the time to confirmed disability progression (one point increase from baseline EDSS score).

Ozanimod showed a relative reduction in ARR compared to interferon (48% in study 1, 38% in study 2). A relative reduction (48% and 42%,

respectively) also was observed in new or enlarging lesions. However, there was no difference in three-month or six-month confirmed disability regression. The primary difference in adverse reactions between ozanimod and interferon beta-1a was hepatic transaminase elevation (10% vs. 5%).[1] There are no comparative studies between ozanimod and fingolimod. A post hoc analysis of a matched cohort from data from ozanimod or fingolimod vs. interferon beta-1a provided an indirect comparison between ozanimod and fingolimod.[6] The findings suggest similar efficacy (i.e., ARR reduction) but fewer adverse reactions with ozanimod (e.g., slower heart rate, ECG findings, change in blood pressure).

CLINICAL IMPLICATIONS

MS is a chronic, immune-mediated, inflammatory, demyelinating disease of the central nervous system. Most patients are diagnosed with relapsing-remitting disease. MS is incurable, but the relapsing-remitting form is considered treatable. There are now 19 approved drugs for MS with the goal of reducing the number of relapses, delaying the progression of disability, and limiting new disease activity (e.g., MRI-detected lesions). Individual differences in characteristics of the disease, variability in response to treatment (effectiveness and tolerability), and disease breakthrough welcome new treatment options. Ozanimod is the second selective S1P receptor modulator to be approved with the convenience of once-daily dosing. The release of ozanimod may be delayed because of the COVID-19 pandemic. Cost information is unavailable. ■

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CME QUESTIONS

1. **According to the study by Black et al, which is true about medicinal cannabinoids?**
   a. There is evidence confirming efficacy in chronic pain, nausea, and vomiting associated with chemotherapy, anxiety, and post-traumatic stress disorder, but not in any other mental health disorder.
   b. There is no evidence confirming efficacy in chronic pain, nausea, or vomiting associated with chemotherapy.
   c. They are well-investigated for a range of disorders, including multiple disorders of mental health.
   d. They are approved for use in 33 U.S. states, despite no clear evidence of efficacy for any diagnosis.

2. **In the study by Ghosh et al, when elderly patients consumed a Mediterranean diet, what change did the authors observe among those subjects?**
   a. More c-reactive proteins
   b. Additional episodes of fatty liver disease
   c. Improved walking speed
   d. No cognitive change

3. **According to the Savage et al study, peripheral edema was seen in about what percentage of individuals taking a calcium channel blocker?**
   a. 2% to 25%
   b. 25% to 35%
   c. 35% to 45%
   d. > 45%

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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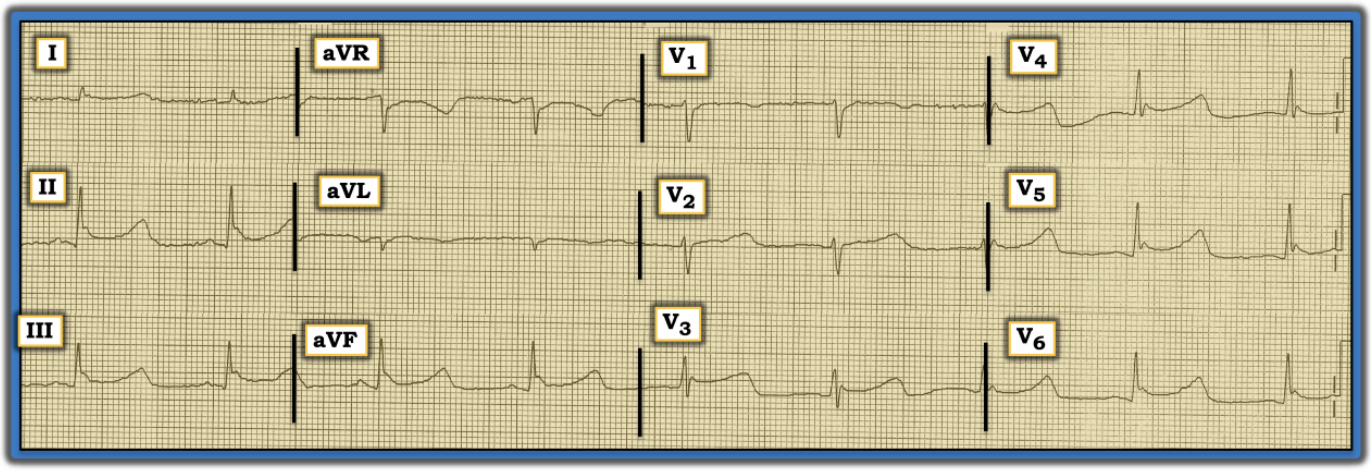
Dr. Grauer reports no financial relationships relevant to this field of study.

Acute Myocardial Infarction, or Acute Pericarditis?

The ECG in the figure below was obtained from a middle-aged man. Is this tracing most consistent with acute myocardial infarction or acute pericarditis?



The rhythm is slow and regular (sinus bradycardia). The PR interval is normal, and the QRS complex is narrow. However, the QT interval clearly is prolonged. The frontal plane axis is normal. There is no chamber enlargement. The most remarkable findings on this tracing are the prominent J-point notching (best seen in leads V3, V4, and V5) and upward-sloping ST segment elevation in the inferior leads (and in most of the chest leads).

The described ECG findings need to be interpreted in light of the clinical situation. I intentionally omitted the history in this case. It turns out this middle-aged man was found outside during the winter months. His core temperature on arrival in the hospital was 83°F. This ECG demonstrates typical findings of hypothermia. These include bradycardia, QTc prolongation, prominent J-point notching (Osborn waves), and upward-sloping ST elevation in several leads. Considering this constellation of findings in association with the markedly reduced core temperature, the chances are that all ECG findings are the result of hypothermia. The lack of significant Q waves, lack of any reciprocal ST depression, and the prominent J-point notching all suggest this may not be an acute infarction. Acute pericarditis is far less common than is generally appreciated. Usually, it is not associated with bradycardia, a long QTc, or such prominent J waves.

Even if this patient did suffer superimposed acute infarction (in addition to hypothermia), the highest priority in treatment still would be treating the hypothermia. After core temperature normalizes, one can repeat the ECG and question a much more alert patient to determine if there was any chest pain. Chances are that virtually all the ECG findings discussed in this article will have normalized.

For more information about and further discussion on this case, please visit: https://bit.ly/2XcUpvB.