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Internal Medicine

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ABSTRACT & COMMENTARY

Comparative Efficacy and Safety of Blood Pressure-lowering Agents in Adults with Diabetes and Kidney Disease

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

SYNOPSIS: Although no blood pressure-lowering strategy prolonged survival in adults with diabetes and kidney disease in this meta-analysis, angiotensin-converting enzyme and angiotensin-receptor blockers alone or in combination, were the most effective pharmacological strategies to prevent the development of end-stage renal disease.

SOURCE: Palmer SC, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: A network meta-analysis. *Lancet* 2015;385:2047-2056.

Diabetes mellitus effects 3-4% of adults worldwide, and chronic kidney disease occurs in 25-40% of patients with diabetes within 20-25 years of onset.[1] Diabetes is now the leading cause of end-stage renal disease,[2] and the combination of diabetes and renal disease is associated with a four-fold increase in the prevalence of atherosclerotic vascular disease and death.[3] Blood pressure lowering with pharmacological agents has been central to the treatment of diabetic kidney disease for decades and has contributed enormously to the decreased prevalence of end-stage renal disease over the past 10 years.[4] Surprisingly, the comparative efficacy and safety of available drugs is largely unknown, mainly because of an absence of published head-to-head clinical trials.[5]

In an attempt to assess the comparative effects of all blood pressure-lowering agents in adults with diabetes and renal disease, Palmer et al performed a worldwide network meta-analysis of randomized trials comparing blood pressure-lowering agents

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in adults with diabetic kidney disease.[6] They found and evaluated 157 studies comprised of 43,256 participants, most with type II diabetes and chronic kidney disease. No blood pressure-lowering strategy resulted in prolonged survival of adults with diabetes and kidney disease; however, compared with placebo, end-stage renal disease was significantly less likely to occur after dual treatment with an angiotensin-receptor blocker (ARB) and an angiotensin-converting-enzyme (ACE) inhibitor or after ARB monotherapy. ACE inhibitors and ARBs alone or in combination were the most effective strategies against the development of end-stage renal disease. In their analysis, the authors excluded all study participants who underwent renal transplantation and/or dialysis.

■ COMMENTARY

In clinical practice, the functional equivalence of ACE inhibitors and ARBs has been assumed; however, appropriate concerns exist regarding the risk of acute kidney injury and hyperkalemia with dual therapy. These concerns led to the premature termination of the Veterans Affairs Nephropathy in Diabetes trial.[7] The Palmer meta-analysis included clinical trials that compared the effect of any orally administered blood pressure lowering-agents (ACE inhibitors, ARBs, calcium channel blockers, beta-blockers, alpha-blockers, diuretics, renin inhibitors, aldosterone antagonists, or endothelin inhibitors) alone or in combination with a second blood pressure-lowering agent to placebo or control. They found little evidence that blood pressure-lowering in adults with diabetes and kidney disease increased survival. However, they did find that administration of ACE inhibitors and ARBs alone or in combination were the most effective hypertension treatment strategies for prevention of end-stage renal disease. Despite the proven clinical benefits of hypertensive drug therapy, clinicians should consider the potential harms of these treatments in individual patients. Constant surveillance for treatment-related acute kidney injury and/or hyperkalemia is mandatory.

Because of scant primary data, the effects of blood pressure treatment on cardiovascular events and related mortality were very uncertain in this very large meta-analysis,[6] which did not support the use of beta-blockers, calcium channel blockers, renin inhibitors, or diuretic monotherapy for treatment of hypertension in patients with diabetes and renal disease. However, the use of ACE inhibitors or ARBs alone or in combination proved to be the most effective treatment strategies for prevention of end-stage renal disease. When these drugs are administered, patients should be carefully followed to be certain that deteriorating renal function and/or hyperkalemia are promptly discovered and treated if either of these drug-related complications were to occur. Clinicians should continue to appropriately treat hypertension, whether a patient has diabetes or not, to reduce the incidence of coronary artery disease and its complications. However, as indicated above, careful clinical follow-up is indicated, especially in hypertensive patients who have associated diabetes and/or renal disease. ■

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ABSTRACT & COMMENTARY

Is It Time to Purge Full-Strength Aspirin from the Outpatient Armamentarium?

By Jeffrey Zimmet, MD, PhD

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

SOURCE: Xian Y, et al. The association of discharge aspirin dose with outcomes after acute myocardial infarction: Insights from the TRANSLATE-ACS Study. *Circulation* 2015. pii: CIRCULATIONAHA.114.014992. [Epub ahead of print].

Choosing an optimal maintenance dose of aspirin has been a matter of substantial debate for years. In the post-myocardial infarction (MI) setting, high-dose aspirin (325 mg/day) has been most commonly prescribed. This is despite data from observational and randomized trials suggesting a lack of benefit, the largest of which was the CURRENT-OASIS 7 trial, published in 2010. The American College of Cardiology/American Heart Association guidelines have changed in recent years to recommend low-dose rather than high-dose aspirin for maintenance therapy.

A recent analysis examined contemporary aspirin dosing in the TRANSLATE-ACS trial, which was a prospective, multicenter observational study of more than 12,000 ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction patients enrolled between 2010 and 2012 who were treated with percutaneous coronary intervention (PCI) and adenosine diphosphate (ADP) receptor inhibitors. Data, including discharge medications and outcomes, were tracked, and follow-up was performed at 6 weeks and at 6, 12, and 15 months post MI.

Of 10,213 patients eligible for analysis, 6387 (62.6%) received high-dose aspirin (325 mg) and 3826 (37.5%) received low-dose aspirin (81 mg) at discharge. Of those discharged on high-dose aspirin, nearly 35% were switched to low-dose by 6 months. In contrast, approximately 8% of patients discharged on low-dose aspirin were changed to high-dose by 6 months.

At 6 months post-discharge, the incidence of major adverse coronary events (MACE) was 8.2% in the high-dose aspirin group, compared with 9.2% in the low-dose group, which was not significantly different, even after multivariable adjustment. However, BARC-defined bleeding events, predominantly minor BARC type 1 or 2 bleeds not requiring hospitalization, were more frequent with high-dose aspirin. Results were unchanged after inverse probability-weighted propensity adjustment. MACE events generally were not different across subgroups defined by age, sex, home aspirin use, and type of ADP receptor antagonist used (clopidogrel vs prasugrel or ticagrelor) as part of the dual antiplatelet therapy regimen. However, the risk of bleeding associated with high-dose aspirin use was slightly increased in younger patients, men, those using aspirin before admission, and those prescribed higher-potency ADP receptor antagonists (prasugrel or ticagrelor, as opposed to clopidogrel) at discharge.

The authors concluded that high-dose aspirin is prescribed at discharge in a majority (nearly two-thirds) of U.S. MI patients treated with PCI, despite no apparent benefit in terms of MACE and a measurable increase in minor bleeding events by 6 months. They argue that their data support current guideline recommendations for low-dose as opposed to high-dose aspirin for maintenance therapy following MI.

■ COMMENTARY

Just a few short years ago, the dosing of aspirin for maintenance therapy in general, and after PCI specifically, was relatively complex. Official recommendations called for a higher dose of aspirin in the immediate post-PCI period, with conversion to a lower dose thereafter. Initial recommendations in the era of first-generation drug-eluting stents even called for differential periods of high-dose aspirin with sirolimus- vs paclitaxel-eluting stents. I can easily recall the discussion during our department cath conference after publication of the 2011 update to the ACCF/AHA/SCAI guidelines for percutaneous coronary intervention, which contained the following language as a IIa recommendation: "After PCI, it is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses." Would we as a department choose to follow this new

recommendation, or would we each make our own choices? A spirited debate ensued, with some arguing fervently for maintaining an initial period of high-dose aspirin.

What a long way we have come in only a few short years, at least on this one issue. The current study provides further evidence of a lack of benefit to high-dose maintenance aspirin, along with a suggestion of harm. The latest guidelines specifically recommend the use of low-dose aspirin for maintenance purposes, and for good reason. We should adopt low-dose aspirin for outpatient use in the United States, as much of the world has already done, and in doing so simplify treatment recommendations for ourselves and for our patients. ■

ABSTRACT & COMMENTARY

Prevalence of Rest Tremor in Essential Tremor

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Rest tremor is seen in patients with more advanced essential tremor, yet its prevalence varies significantly between patient groups.

SOURCE: Louis ED, et al. Prevalence and correlates of rest tremor in essential tremor: Cross-sectional survey of 831 patients across four distinct cohorts. *Europ J Neurol* 2015, 22:927-932.

Essential tremor (ET) is a common neurological disorder affecting approximately 4% of people age 40 years and older. It manifests as kinetic and postural tremor, but occasionally resting tremor is seen as well, contributing to diagnostic confusion with Parkinson's disease (PD). Few studies have looked at the prevalence of rest tremor in patients with ET, and the authors of this study aimed to estimate the prevalence of rest tremor in patients with ET and to assess the clinical correlations of that tremor. They used four different patient groups: a population-based study in northern Manhattan, a genetics study of movement disorders, a study of the environmental epidemiology of essential tremor, and a brain repository group of patients who were examined and signed consent for postmortem evaluation of their brains. The authors hypothesized that the prevalence of rest tremor could be related to the severity of the disease (ET). In total, 831 patients were analyzed from all four patient groups. Experienced movement disorder neurologists performed examinations, which included assessments of postural and kinetic tremors in the arms, as well as head, voice, and jaw tremors. Rest tremor was evaluated in seated and standing positions and while walking.

The results showed that the severity of arm tremor, duration of tremor, and the prevalence of head tremor were lowest in the population-based study and highest in the brain repository group. Rest tremor occurred in 1.9% of the population-based study, 9.6% of the family study group, 14.7% of the study of the environmental epidemiology of essential tremor, and 46.4% of patients in the brain repository group. No patient had tremor in the legs or feet. The patients with rest tremor were found to be significantly older than those without and they had their tremor for a longer period of time. Interestingly, patients with rest tremor also were more likely to have voice or head tremor. Rest tremor appeared to be asymmetric in approximately half of the patients who had it, and in those patients, action and postural tremor also were more pronounced in the same arm. The authors concluded that the prevalence of the rest tremor in ET patients varied greatly among the examined groups, ranging from 1.9% in the population-based setting to 50% in a brain repository group.

■ COMMENTARY

The authors of this study evaluated the prevalence of resting tremor in patients with essential tremor in four different patient groups and attempted to find clinical correlates of that tremor. The study was well-designed and the patients had similar demographic characteristics, except for the ET brain repository group, in which the patients were considerably older. It was astutely observed that the rest tremor was only noted in the arms, not the legs, which was a fundamental difference from what we see in PD, where leg tremor at rest can be common. The other observation was that the rest tremor emerged as the ET progressed later in life, and is consistent with what is usually seen in movement disorder clinics. The mechanisms underlying the resting tremor in ET

remain unclear, but the authors suggest cerebellar pathology as the potential cause based on the animal models with cerebellar lesions.

The results of this study were logically interpreted, but the certainty of the diagnosis is based on the clinical examination. It is well-known that patients with ET are at five-fold increased risk for developing PD later in life. In fact, it is quite common to see people with both conditions. The authors stated that none of the patients with ET had any parkinsonian features except for the rest tremor. It is possible, however, that some of the patients with longstanding ET developed Lewy body pathology in the brain, which did not yet result in any rigidity, bradykinesia, or reduced rapid alternating movements, suggestive of PD. DaT scans were not performed in this study to rule out dopamine deficiency, so we cannot exclude some patients with very early-stage PD who developed parkinsonian tremor superimposed on the existing action and postural tremor, except for some deceased patients from the brain repository group whose brains were examined pathologically. More prospective studies would be needed to follow the progression of rest tremor and find anatomical correlations that can help understand the pathophysiology of the disease and lead to more effective treatment. ■

PHARMACOLOGY UPDATE

Tedizolid Phosphate Injection and Tablets (Sivextro®)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

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

A new oxazolidinone-class antibacterial has been approved for the treatment of acute bacterial skin and skin structure infections. Tedizolid was designated a Qualified Infectious Disease Product (QIDPS). Tedizolid is chemically similar to linezolid and is marketed by Cubist Pharmaceuticals as Sivextro.

INDICATIONS

Tedizolid is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive bacteria.[1] These include *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis*.

DOSAGE

The recommended dose is 200 mg orally or intravenously (infused over 1 hour) once daily for 6 days.[1] Tedizolid is available as 200 mg tablets and as powder for injection.

POTENTIAL ADVANTAGES

Tedizolid is more active than linezolid against species of *Staphylococcus*, *Streptococcus*, and *Enterococcus*, including vancomycin-resistant enterococci and linezolid resistant genotypes.[2]

POTENTIAL DISADVANTAGES

The antibacterial activity decreases in the absence of granulocytes.[1] Alternative therapy should be considered in neutropenic patients.

COMMENTS

The efficacy and safety of tedizolid were evaluated in two randomized, double-blind, double-dummy, non-inferiority trials with linezolid as the active comparator.[1,3,4] Subjects had FDA-defined clinical syndrome for ABSSSI (cellulitis/erysipelas, wound infections, and major cutaneous abscess). They were randomized to receive tedizolid (200 mg x 6 days) or linezolid (1200 mg x 10 days). In one study, subjects could receive oral tedizolid after a minimum of 1 day of the intravenous drug. The primary endpoint, determined at 48 to 72 hours after treatment initiation was no increase in lesion surface area from baseline and oral temperature of ≤ 37.6° C, confirmed by a second temperature reading within 24 hours or at least a 20% decrease from baseline in lesion area. In the second trial the same endpoint was evaluated in patients randomized to tedizolid or linezolid.[1] A secondary endpoint was investigator-assessed clinical response post therapy (EOT) (7-14 days after the last dose). Response rates for the first endpoint were 79.5% vs 79.4% for study 1 and 86.1% vs 84.1% for study 2. For the other endpoint,

Continued on page 103

Clinical Briefs

By Louis Kuritzky, MD

Can You Make 'Flat' Basal Insulin 'Flatter'?

SOURCE: Yki-Järvinen H, et al. New insulin glargine 300 units/mL vs glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: Glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care* 2014;37:3235-3243.

One of the primary reasons for widespread clinician endorsement of newer basal insulins (i.e., glargine, determir) over NPH is the relative "flatness" of insulin levels with the former. The greater curve of NPH than newer basal insulins incurs greater risk for nocturnal hypoglycemia, which may become a limiting factor for insulin titration.

Glargine and detemir are generally regarded as "flat" basal insulins. Traditional glargine is supplied as 100 units/mL. Could there be an advantage to glargine 300 (300 units/mL)?

The EDITION 2 study was an open-label trial comparing traditional glargine (100 units/mL) with a new formulation of glargine (300 units/mL). The more concentrated insulin glargine-300 reportedly has smoother, more stable pharmacokinetics and pharmacodynamics than glargine-100, attributed to its extended release from the subcutaneous depot. Does glargine-300 offer any meaningful advantage?

In a 6-month trial comparing glargine-100 to glargine-300 in type 2 diabetes (n = 811), glargine-300 was similar in efficacy as far as A1c reduction goes, but there was a modest reduction in hypoglycemic events, including both severe hypoglycemia and any hypoglycemic event. Curiously, the dose of glargine-300 required for glycemic control was about 10% higher than that of glargine-100. A possible advantage of lesser hypoglycemia and smaller volume of injection with glargine-300 must be counterbalanced with the increased cost of the approximately 10% more glargine-300 needed to achieve the same degree of A1c reduction. For patients incurring problematic episodes of hypoglycemia, an insulin that provides even "flatter" plasma levels may provide an advantage. ■

Left Atrial Appendage Closure: Another Possible Interventional Fix for Atrial Fibrillation

SOURCE: Reddy VY, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: A randomized clinical trial. *JAMA* 2014;312:1988-1998.

The most feared consequence of atrial fibrillation is stroke, which most commonly results from a thrombus generated in the left atrial appendage (LAA). Warfarin and novel anticoagulant agents are highly efficacious, reducing risk of stroke by as much as 66%, but warfarin requires close follow-up, and has a narrow therapeutic range. Though novel anticoagulants do not require monitoring, bleeding risk is still an important obstacle. If most atrial fibrillation-related strokes are due to thrombus formed in the LAA, might mechanical closure of the LAA prevent stroke and diminish or eliminate the need for anticoagulation?

Reddy et al report on the results of the PROTECT AF clinical trial, which randomized atrial fibrillation patients (n = 707) to LAA closure or "traditional" warfarin treatment (LAA closure patients did not receive warfarin).

The primary endpoint of the study was a composite of stroke, systemic embolism, or CV death. At a mean of 3.8 years of follow-up, LAA closure was found to be non-inferior to warfarin treatment, and the warfarin treatment group had been well managed (time in therapeutic range = 70%). LAA closure may be another reasonable option for reduction of stroke risk in atrial fibrillation. ■

A Glimmer of Hope for Beta-blockers in Heart Failure from Diastolic Dysfunction

SOURCE: Lund LH, et al. Association between use of ß-blockers and outcomes in patients with heart failure and preserved ejection fraction. *JAMA* 2014;312:2008-2018.

Despite the consistent success of ACE inhibitors, ARBs, beta-blockers, and aldosterone antagonists in chronic heart failure from systolic dysfunction (s-CHF), trials of pharmacotherapy for chronic heart failure from diastolic dysfunction (d-CHF) have been disappointing. Modestly encouraging results for d-CHF were seen with candesartan (Atacand) in the CHARM-PRESERVED trial and nebivolol (Bystolic) in the SENIORS trial (for the d-CHF subgroup), but neither trial had strong enough outcomes to definitively establish a role in CHF.

Lund et al report on data obtained from national data registries in Sweden that included 19,083 patients with d-CHF (termed "heart failure with preserved ejection fraction" in this article). The registry (41,976 patients) allowed comparison of patients who had been treated with beta-blockers vs not by propensity scores. The primary outcome of the study was all-cause mortality.

Five-year survival in d-CHF was 7% higher in patients who were treated with beta-blockers. Because this data is observational in nature, it cannot definitively establish whether beta-blocker treatment reduces mortality in d-CHF, but it provides strong impetus to perform a large randomized trial to ultimately answer the question. ■

Continued from page 101

rates were 78% vs 76.1% and 85.2% vs 82.6%, respectively. EOT success rates were similar. The efficacy endpoint met the predetermined condition for non-inferiority to linezolid. Adverse events profiles were generally similar with a lower frequency of gastrointestinal disorders (e.g., nausea and vomiting) and platelet counts below the lower limit of normal (< 150,000 cells/mm^3).[3]

CLINICAL IMPLICATIONS

Tedizolid provides another option for the treatment of ABSSSI, particularly with multi-drug-resistant pathogen. The current Infectious Diseases Society of America guidelines on skin and soft tissue infections recommend treatment according to infection type (purulent [e.g. abscess] vs nonpurulent [e.g. cellulitis]) and suspected bacterial pathogen.[5] Vancomycin and linezolid are currently the preferred antibacterials for methicillin-resistant Staphylococcus aureus (MRSA) infections. The wholesale cost for a course of treatment is $3037 for linezolid and $1770 for tedizolid. ■

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CME QUESTIONS

1. For lowering blood pressure in adults with diabetes and kidney disease without development of end-stage kidney disease, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers:
a. were the most effective treatment strategies.
b. were only minimally effective.
c. did not produce hyperkalemia and/or acute renal injury.
d. should be utilized only after other drugs are tried.

2. High-dose aspirin (325 mg/day) after primary percutaneous coronary intervention for acute myocardial infarction (MI), results in which of the following vs low-dose aspirin (81 mg/day)?
a. Fewer strokes
b. Fewer recurrent MIs
c. More minor bleeding episodes
d. More major bleeding

3. Rest tremor associated with essential tremor has the following characteristic.
a. Rest tremor is accompanied by rigidity and bradykinesia.
b. Rest tremor occurs during sleep.
c. Rest tremor in the arm may be accompanied by tremor in the leg.
d. Rest tremor is often accompanied by head and voice tremor.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Can dietary intervention delay the onset of Alzheimer's disease?

Long-term weight loss rivals medications and ablation for AF rhythm control

Inferior vena cava filters and recurrent pulmonary embolism

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

Sinus Tachycardia with Tall, Peaked T Waves

Interpret the ECG shown in the figure below, which was obtained from a middle-aged adult. Are there DeWinter T waves in the chest leads shown in the figure? Is this patient about to occlude his proximal left anterior descending (LAD) coronary artery? Or does this patient have hyperkalemia? What is missing (that should never be missing)?

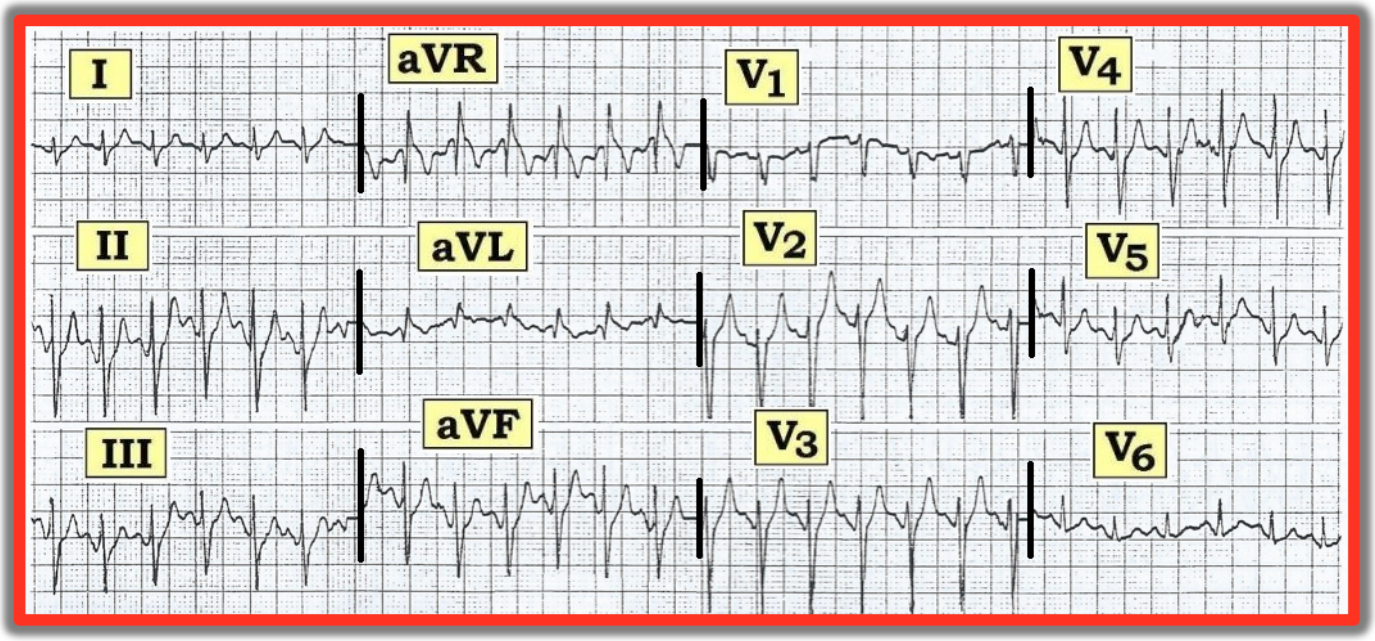

Figure: ECG obtained from a middle-aged man.

Interpretation: There is some baseline movement with slight artifact. The rhythm is sinus tachycardia at a rate of 160/minute. The PR interval is normal, and the QRS complex is narrow. All intervals appear to be normal. The axis is indeterminate, as QRS complexes are nearly isoelectric in virtually all limb leads. There is no chamber enlargement. Regarding Q-R-S-T Changes, there appears to be a Q wave in lead aVL, and transition is slightly delayed to between V4 to V5. The most remarkable findings on this tracing are the tall and peaked T waves, especially in leads V2 thru V4. In a patient with chest pain, this T wave appearance suggests ischemia or even impending proximal LAD occlusion (i.e., DeWinter T waves). There is even a suggestion of some J-point ST depression in leads V3, V4, and V5 prior to the steep rise in T wave ascent. On the other hand, in a patient predisposed to hyperkalemia, the T wave peaking seen here should prompt consideration of this electrolyte disturbance. That said, something is missing from this presentation!

Answer: No history was given. It turns out that this 12-lead ECG was recorded as part of an exercise stress test on an otherwise healthy and asymptomatic middle-aged man. The purpose of this test was to assess exercise capacity. There was no chest pain and no history of renal disease or other medical problems. Both peaked T waves and rapid-upslope ST segment depression are common normal findings during an exercise test.

Lesson To Be Learned: ECGs cannot be intelligently interpreted in a vacuum. If told that this patient was having new-onset chest pain we would wonder why his heart rate is so fast, and we would clearly be concerned that the prominent T wave peaking might be ischemic or a DeWinter T wave equivalent. We would check serum potassium values as part of our evaluation, especially if the patient had any factors potentially predisposing to hyperkalemia.

This patient had excellent exercise capacity for his age. His exercise test was entirely normal, and he was cleared to perform vigorous aerobic activity. No laboratory testing was done (as this was not necessary).