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Internal Medicine

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ABSTRACT & COMMENTARY

Treating Diabetes May Impact Thyroid Status

By Rahul Gupta, MD, MPH, FACP

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

SYNOPSIS: In a longitudinal population-based study, metformin use was associated with an increased incidence of low thyroid-stimulating hormone (TSH) levels in patients with treated hypothyroidism.

SOURCE: Fournier JP, et al. Metformin and low levels of thyroid-stimulating hormone in patients with type 2 diabetes mellitus. *CMAJ* 2014;186:1138-1145.

In clinical practice, type 2 diabetes mellitus and hypothyroidism are among the most prevalent medical conditions encountered. While thyroid-stimulating hormone (TSH) testing is commonly utilized in both the diagnosis and management of hypothyroidism, metformin is an oral hypoglycemic biguanide that is often the first choice for oral treatment of type 2 diabetes when no contraindications exist. In recent years, some data have suggested that metformin may affect the thyroid profile in patients with type 2 diabetes.[1,2] Specifically, studies suggest that the use of metformin may lower TSH levels in patients with diabetes and hypothyroidism. The reductions in TSH levels may even fall below the reference range, in which case, patients may develop risks associated with subclinical hyperthyroidism.[3] Since metformin is commonly utilized in type 2 diabetics with hypothyroidism, it is important to evaluate the extent of this problem in clinical practice to determine whether it is clinically relevant.

In their research, Fournier et al conducted a large population-based study to determine whether the use of metformin monotherapy, when compared with sulfonylurea monotherapy, is associated with an increased risk of low TSH levels (< 0.4 mIU/L) in patients with treated hypothyroidism or euthyroidism

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and type 2 diabetes. Utilizing a United Kingdom general practice database, investigators identified patients with type 2 diabetes who had begun receiving either metformin or sulfonylurea monotherapy between 1988 and 2012 and divided them in two cohorts of 5689 treated hypothyroid patients and 59,937 euthyroid patients. Adjusted Cox proportional hazard models were used to estimate the hazard ratio (HR) of the association of low TSH level (< 0.4 mIU/L) and initiation of metformin, compared to sulfonylureas.

Researchers found that over 1 year, low TSH levels were recorded 495 times in the treated hypothyroid group (incidence 119.7/1000 person-years), compared with 322 times in the euthyroid group (4.5/1000 person-years). There were 445 low-TSH events in the metformin group (125.2/1000) and 40 among those taking a sulfonylurea (79.5/1000). Therefore, compared with sulfonylurea monotherapy, metformin monotherapy was associated with a 55% increased risk of low TSH levels in patients with treated hypothyroidism (HR, 1.55; 95% confidence interval [CI], 1.09-2.20), with the highest risk in the 90-180 days after initiation (HR, 2.30; 95% CI, 1.00-5.29). No association was observed in euthyroid patients (HR, 0.97; 95% CI, 0.69-1.36).

This study supports the previous studies that the use of metformin is associated with an increased risk of low TSH levels in patients with treated hypothyroidism, with the highest risk observed in the first 180 days after treatment initiation. However, metformin did not appear to have any significant effects on TSH levels in euthyroid patients.

■ COMMENTARY

This study in a clinical practice setting not only found a relatively high incidence of low TSH levels in treated hypothyroid patients receiving metformin, but also found that this risk increases to 2.3 times when patients continue to be treated for type 2 diabetes with metformin beyond the first 3 months. While the exact biological mechanisms explaining the TSH-lowering properties may be unclear, experts hypothesize that the mechanism of action for metformin on the thyrotropin releasing hormone–TSH axis may be complex and multifactorial.[4, 5] Metformin may impact the affinity or the number of thyroid hormone receptors or both. It may also increase the central dopaminergic tone or may directly act on TSH regulation, thus enhancing the effect of thyroid hormones on the pituitary gland. Finally, metformin may also inhibit the adenosine 5'-monophosphate-activated kinase (AMPK) activity in the hypothalamus, leading to the inhibitory modulation of thyroid hormones on TSH secretion.

Certainly, further research needs to be conducted in this area as well to further assess the clinical consequences of low TSH levels induced by metformin.

Nevertheless, these findings raise a concern for the short- and long-term clinical consequences of these types of metabolic changes and perhaps may support additional monitoring of TSH levels when starting metformin. Until further research is conducted, this type of monitoring would allow more appropriate adjustments of the levothyroxine doses when lower TSH levels begin to be observed in clinical practice. ■

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ABSTRACT & COMMENTARY

Colchicine for Recurrent Pericarditis

By Michael H. Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology University of California, San Francisco

Dr. Crawford reports no financial relationships relevant to this field of study. This article originally appeared in the September 2014 issue of *Clinical Cardiology Alert*.

SOURCE: Imazio M, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): A multicenter, double-blind, placebo-controlled, randomised trial. *Lancet* 2014;383:2232-2237.

Although colchicine has been shown to be effective for the treatment of acute pericarditis and first recurrences, little information exists about its use in patients with multiple recurrences. Thus, Imazio et al reported on the results of the colchicine for recurrent pericarditis 2 (CORP-2) trial. CORP-2 was a randomized, controlled trial performed at four general hospitals in Italy. Recurrent pericarditis was defined as another episode after a 6-week or more symptom-free interval. Recurrence was diagnosed as recurrent pain and at least one of the following: a pericardial friction rub, typical ECG changes, pericardial effusion on echocardiography, or elevated inflammatory biomarkers (white blood cell count, erythrocyte sedimentation rate or C-reactive protein concentration). Two or more recurrences of pericarditis caused by idiopathic/viral, post-cardiac injury, or connective tissue disease were required for enrollment. Patients with purulent pericarditis, myopericarditis, or a contraindication to colchicine (e.g., liver disease) were excluded. Colchicine was given to half the subjects (randomized) at a dose of 0.5 or 1.0 mg daily for 6 months without a loading dose. Recurrences were also treated with non-steroidal anti-inflammatory drugs (NSAIDs) as needed. Corticosteroids were given to those already on them or those who could not take NSAIDs. All patients received a proton pump inhibitor. The primary endpoint was recurrent pericarditis during at least 18 months of follow-up.

Of the 260 patients screened, a total of 240 patients were enrolled, 120 in each group, over about 6 years. No one was lost to follow-up. Adherence to both treatments was 95%. Pericarditis recurred in 22% of the colchicine group vs 43% of the placebo group (relative risk, 0.49; 95% confidence interval [CI], 0.24-0.65; $P < 0.001$; number needed to treat = 5). The Kaplan-Meier curves of event-free survival separated at 2 months and stayed separated for the 18-month minimum follow-up. Colchicine also significantly improved the following secondary endpoints: the frequency of symptom persistence, the number of recurrences, hospital admissions, and recurrences within 1 week. In a multivariate analysis, pericardial effusion at presentation was the only independent risk factor for multiple recurrences (odds ratio, 3.1; 95% CI, 1.7-5.8; $P = 0.0001$). Adverse effects occurred in 12% of the colchicine group and 8% in the placebo group (P = NS). Gastrointestinal side effects were most common and occurred at the same frequency in both groups (7.5%). The authors concluded that colchicine added to conventional NSAID therapy reduces the frequency of pericarditis recurrence in patients with two or more recurrences.

■ COMMENTARY

This study completes the Imazio et al trilogy on the treatment of pericarditis and suggests that colchicine is the drug of first choice for acute pericarditis, first recurrences, and multiple recurrences.[1,2] In this study, its beneficial effects were not related to the type of underlying NSAID or corticosteroid therapy. It basically halves the rate of recurrent pericarditis in these challenging patients.

Why is colchicine so effective and conventional treatment not? The pathogenesis of recurrences is poorly understood, but most believe it is immune-mediated. Colchicine concentrates up to 16-fold in white blood cells and disrupts microtubules, even at the low does used in this trial. Often, multiple recurrent pericarditis patients are treated with more potent immune-suppressant drugs such as azathioprine, intravenous immunoglobulins, and interleukin antagonists. However, there is little evidence of their effectiveness. Also, they are expensive and have potentially worse adverse effects. Thus, this colchicine protocol is a welcome addition to the treatment of recurrent pericarditis patients.

For acute pericarditis, Imazio recommends a loading dose of 1 mg (1.2 U.S. formulation) every 12 hours for 1-2 days, then 0.5 mg (0.6 U.S. formulation) once a day for those < 70 kg, and 0.5 (0.6 U.S. formulation) twice a day for those > 70 kg for 3 months. Recurrent pericarditis is treated without a loading dose in the same fashion for 6 months. This only applies to immune-mediated pericarditis — e.g., viral, idiopathic

or post pericardiotomy, not bacterial, neoplastic or myopericarditis. Also excluded from these studies were children and pregnant or lactating women. Finally, the duration of therapy in these studies was arbitrary and we don't know if shorter or longer durations would be equally or even more effective. ■

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ABSTRACT & COMMENTARY

Angiotensin Receptor Blockers for Hypertension

By Michael H. Crawford, MD

This article originally appeared in the September 2014 issue of *Clinical Cardiology Alert*.

SOURCE: Makani H, et al. Antihypertensive efficacy of angiotensin receptor blockers as monotherapy as evaluated by ambulatory blood pressure monitoring: A meta-analysis. *Eur Heart J* 2014;35:1732-1742.

Angiotensin receptor blockers (ARBs) are often used as first-line therapy for the treatment of systemic hypertension because of their perceived efficacy and relatively low incidence of adverse effects. However, there are contradictory reports about the efficacy of individual agents in this class, especially losartan. Thus, these investigators from New York City performed a meta-analysis of studies of ARBs used as monotherapy that employed 24-hour ambulatory blood pressure (BP) monitoring to assess antihypertensive efficacy. The randomized clinical trials included had to have no uptitration of the drugs, so they could clearly compare maximum recommended doses to half-maximum and quarter maximum doses of the ARBs. Also, trial duration had to be at least 1 month and no other classes of antihypertensives could be given. Also, none of the subjects could have severe hypertension. They identified 62 trials that met these criteria that enrolled more than 15,000 patients with a mean treatment duration of 10 weeks.

Reduction in systolic BP averaged 10 mmHg and diastolic BP averaged 7 mmHg at 25% maximum doses. At 50% maximum doses, systolic BP decreased 12 mmHg and diastolic BP 8 mmHg. At maximum doses, systolic BP dropped 13 mmHg and diastolic BP dropped 8 mmHg. When 25% maximum dose was compared to 50% maximum dose, there was a significant further reduction of systolic BP ($P = 0.04$) but not diastolic BP ($P = 0.08$). When comparing 50% to maximum dose, there was no significant reduction in systolic or diastolic BP.

Studies that compared losartan to other ARBs showed that losartan at 50% maximum dose (50 mg/day) lowered BP less than other ARBs (differences 2.5 mmHg systolic and 1.8 mmHg diastolic). Also, maximum dose losartan (100 mg/day) lowered BP less than maximum doses of other ARBs (differences 3.9 mmHg systolic and 2.2 mmHg diastolic). Sensitivity analyses showed no evidence of publication bias and no differences in outcomes based on study duration or number of subjects. The authors concluded that this comprehensive analysis of 62 studies of monotherapy at a fixed dose of ARBs showed a shallow dose response curve and that losartan was consistently inferior to other ARBs.

■ COMMENTARY

This analysis shows that ARBS as monotherapy have a similar efficacy as most other antihypertensive drugs; a 10-15 mmHg reduction in systolic BP and 5-10 mmHg in diastolic BP. Surprisingly, uptitrating the dose four-fold had little further effect. This is also consistent with other studies that have shown that combining drugs from two different classes of agents is approximately five times more effective than doubling the dose of one drug. The only exception to this rule appears to be calcium channel blockers, which seem to be more potent than most other agents in comparison studies, with maximum systolic BP lowering effects of up to 20 mmHg. Another reason not to uptitrate antihypertensive agents is to avoid dose-related side effects. This is a particular concern with thiazide diuretics, calcium blockers, and beta-blockers, but not with ARBs. Thus, for all these reasons, combination therapy at well-tolerated doses seems to trump uptitration of monotherapy.

The conclusion that losartan is the least effective of the ARBs has been demonstrated in other clinical studies and in vitro studies of angiotensin II receptor blocking effects. However, the absolute differences shown in this study were modest. Until recently, losartan was the only ARB available as a generic. Now that generic versions of other ARBs are becoming available, I predict the use of losartan will decrease in the United States.

Although not an ideal study, it supports the shift toward using combination therapy in moderately severe hypertension and the marketing of drug combination pills for hypertension treatment. ■

PHARMACOLOGY UPDATE

Dulaglutide Injection (Trulicity™)

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

The FDA has approved a third long-acting, once-weekly, glucagon-like peptide (GLP-1) receptor agonist for the treatment of type 2 diabetes mellitus, joining exenetide ER and albiglutide. Dulaglutide is made up of two identical human-based GLP-1 analogs linked to a modified human IgG4 Fc fragment. This makes the molecule resistant to degradation by DPP-4, slows absorption, reduces renal clearance, and extends the elimination half-life to approximately 5 days. Dulaglutide is marketed by Eli Lilly as Trulicity.

INDICATIONS

Dulaglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1]

DOSAGE

The recommended starting dose is 0.75 mg given subcutaneously once weekly.[1] The dose can be increased to 1.5 mg if additional glycemic control is needed. The drug is administered in the abdomen, thigh, or upper arm. Dulaglutide is available as 0.75 mg and 1.5 mg single-dose pen or prefilled syringes.

POTENTIAL ADVANTAGES

The long elimination half-life allows for once-weekly administration.

POTENTIAL DISADVANTAGES

Dulaglutide is contraindicated in patients with personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasma syndrome type 2.[1] It is associated with an increase incidence of thyroid C-cell tumors in rats. Dulaglutide is associated with an increased risk of pancreatitis.[1] GLP-1 receptor agonists have been associated with acute renal failure and worsening of chronic renal failure in postmarketing reports.[1] Most commonly reported adverse events (% vs placebo) are nausea (12-21% vs 5%), diarrhea (9-13% vs 7%), and vomiting (6-13% vs 2%).[1]

COMMENTS

Dulaglutide has been evaluated in five pivotal trials as monotherapy as well as an add-on to a number of antidiabetic drugs and drug combinations, including metformin, metformin and sulfonylurea, metformin and pioglitazone, and glargine insulin with or without an oral medication.[1-7] Studies were 52 weeks in duration, with efficacy assessment at 26 weeks, 78 weeks, or 104 weeks, with 52-week endpoints. The primary endpoint was reduction in HbA1c from baseline. Non-inferiority and superiority were compared to active comparator across the two doses (0.75 mg and 1.5 mg), with a prespecified non-inferiority margin of 0.4%.[2] In the monotherapy study (n = 807), subjects inadequately controlled with diet and exercise or diet and exercise and one anti-diabetic drug at submaximal dose, with an average baseline HbA1c of 7.6%, were randomized to dulaglutide 0.75 mg, 1.5 mg, or metformin (1500 to 2000 mg/day).[5] Changes from baseline were -0.7, -0.8, and -0.6. Both doses were non-inferior, as well as superior to metformin. However, as one FDA reviewer pointed out, most subjects failed on a submaximal dose of metformin (median interquartile range, 1000 mg; 850-1250). This means that the active comparator arm had an increase in the dose of metformin, potentially biasing dulaglutide.[2] In the add-on studies, dulaglitide was reported to be more effective than sitagliptin 100 mg when added to metformin (52-week endpoint),[4] more effective than insulin glargine when added to metformin and glimepiride (52-week) (1.5 mg dose),[6] more effective than exenatide when added to metformin and pioglitazone (26 weeks),[3] more effective than insulin glargine added to insulin lispro (26 weeks).[7] Similarly, the FDA reviewer was concerned about claims of superiority due to selection bias and suboptimal dose titration of the comparator.[2] Dulaglutide was shown to be noninferior to once-daily liraglutide with similar side effects.[8] There are no comparative studies with the other once-weekly products; however, albiglutite did not meet noninferiority criteria compared to liraglutide.[9]

CLINICAL IMPLICATIONS

Duluglitide is the third long-acting GLP-1 receptor agonist on the market. The first, exenetide, uses an extended-release microsphere technology, while albiglutide is two tandem copies of a modified human GLP-1 fused to human albumin. Dulaglutide is effective; however, reports of superiority to comparators should be interpreted with caution. Duluglitide, as with other GLP-1 agonists, is not recommended for first-line treatment of type 2 diabetes mellitus. Dulaglutide is the most expensive of the once-weekly drugs with a monthly costs of $482 compared to $440 for exenatide ER and $326 for albiglutide. ■

continued on page 183

Clinical Briefs

By Louis Kuritzky, MD

COPD Patients on Triple Therapy: The Safety of Inhaled Steroid Discontinuation

SOURCE: Magnussen H, et al. *N Engl J Med* 2014;371:1285-1294.

Bronchodilators (long-acting beta-agonists and anticholinergics) form foundation therapy for COPD, and have been found not only to provide symptomatic relief, but also reduce the frequency of acute exacerbations. When chronic obstructive pulmonary disease (COPD) becomes severe, and especially in patients with frequent exacerbations, it is appropriate to also include inhaled corticosteroids. Often, COPD patients are treated with triple therapy: a long-acting beta-agonist (LABA), long-acting anticholinergic agent (LACA), and inhaled corticosteroid (ICS). However, some have questioned whether, once stable, continuation of the ICS exerts meaningful benefit.

To address this issue, Magnussen et al performed a double-blind trial among severe COPD patients (n = 2485). Patients on triple therapy (LABA + LACA + ICS) were randomized to either continue on that regimen or to receive LABA + LACA + placebo ICS. The primary outcome of the study was time to first moderate or severe COPD exacerbation.

ICS withdrawal did not lead to any significant change in time to COPD exacerbation, dyspnea, or other measures of health status at 1 year. Although there were measurable differences between ICS-maintained vs ICS-withdrawn groups in FEV_1 at study end (slightly improved FEV_1 in the former), the magnitude of difference was of questionable clinical significance. These data would suggest that ICS discontinuation in patients on triple therapy may generally be accomplished without worsening likelihood of exacerbations. ■

Reason #999 to Endorse Exercise: Mental Health Benefits

SOURCE: Rosenbaum S, et al. *J Clin Psych* 2014;75:964-974.

With rare exception, advocacy for exercise is warranted. Indeed, several of the most problematic public health issues our nation faces today (diabetes, metabolic syndrome, obesity, hypertension, osteoporosis) could be ameliorated by exercise. Although most often studied for its metabolic effects, this systematic review and meta-analysis by Rosenbaum et al has, instead, evaluated the impact of exercise on persons with mental health issues such as depression and schizophrenia.

Twenty different trials reported the impact of exercise on depression symptoms. None of the studies reported a detrimental effect, and the overall favorable effect size was large (effect size = 0.84, with > 0.8 being large). Similarly, the effect size of exercise upon schizophrenia symptoms was large, even though the effect size on anthropomorphic outcomes (e.g., BMI) was not large.

A variety of different exercise interventions were studied, with a slightly greater effect size among programs that employed aerobic training. Nonetheless, diverse exercise modalities (e.g., tai chi, dance therapy, yoga, aquatic exercise, resistance exercise) all showed at least a favorable trend toward benefit. Clinicians would be wise to more often incorporate an exercise component to the therapeutic regimen for mental health disorders. ■

Ultrasound vs CT for Diagnosis of Kidney Stones

SOURCE: Smith-Bindman R, et al. *N Engl J Med* 2014; 371:1100-1110.

There may be greater consequences attendant to our frequent use of CT examinations than readily meet the eye. Whenever I have queried resident physicians about the dose of X-ray produced by an abdominal CT, they consistently underestimate from the literature-documented burden: A single standard abdominal CT is equivalent to the radiation of 500 chest X-rays. Hence, springs forth our enthusiasm for more radiation-friendly tools.

Identification of nephrolithiasis is a commonplace emergency department scenario during which CT may be called upon. Smith-Bindman et al performed a multicenter study to compare the effectiveness of point-of-care ultrasound vs radiologist-performed ultrasound, vs abdominal CT. Patients who presented to emergency departments (n = 2759) were randomized to receive one of these three initial evaluations. The primary outcome of the study was the number of missed or delayed serious diagnoses.

Additional endpoints included cumulative radiation dose over 6 months (to take into account that some initially ultrasounded patients would require follow-up radiographic investigation) and pain.

Ultrasound compared very favorably with CT, demonstrating similar efficacy for not missing high-risk diagnoses, complications, and requirement for return visits to the emergency department. Of course, the radiation exposure incurred in the ultrasound groups was substantially less than the CT group. Clinicians skilled at performing ultrasound, or working at sites with skilled ultrasonographers, may wish to consider ultrasound as an attractive alternative to CT for diagnosis of suspected nephrolithiasis. ■

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CME QUESTIONS

1. In the study by Fournier et al, which of the following statements is NOT true regarding metformin use in treated hypothyroid patients?

a. Metformin use was associated with an increased incidence of low TSH levels in patients with treated hypothyroidism.

b. Metformin use was associated with an increased incidence of low TSH levels in patients with treated hyperthyroidism.

c. Compared with sulfonylurea monotherapy, metformin monotherapy was associated with a 55% increased risk of low TSH levels in patients with treated hypothyroidism.

d. When patients with treated hypothyroidism were placed on metformin, the highest risk of low TSH was found to be during the 90–180 days after initiation.

2. Recurrent pericarditis is best treated with:

a. aspirin.

b. NSAIDs.

c. colchicine.

d. corticosteroids.

3. Which of the following is *not* a characteristic of ARBs for treating hypertension?

a. Low incidence of adverse effects

b. All are highly effective as monotherapy

c. Shallow does response curve

d. Few drug interactions

[IN FUTURE ISSUES]

Steroids & Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

Persistent ST Depression

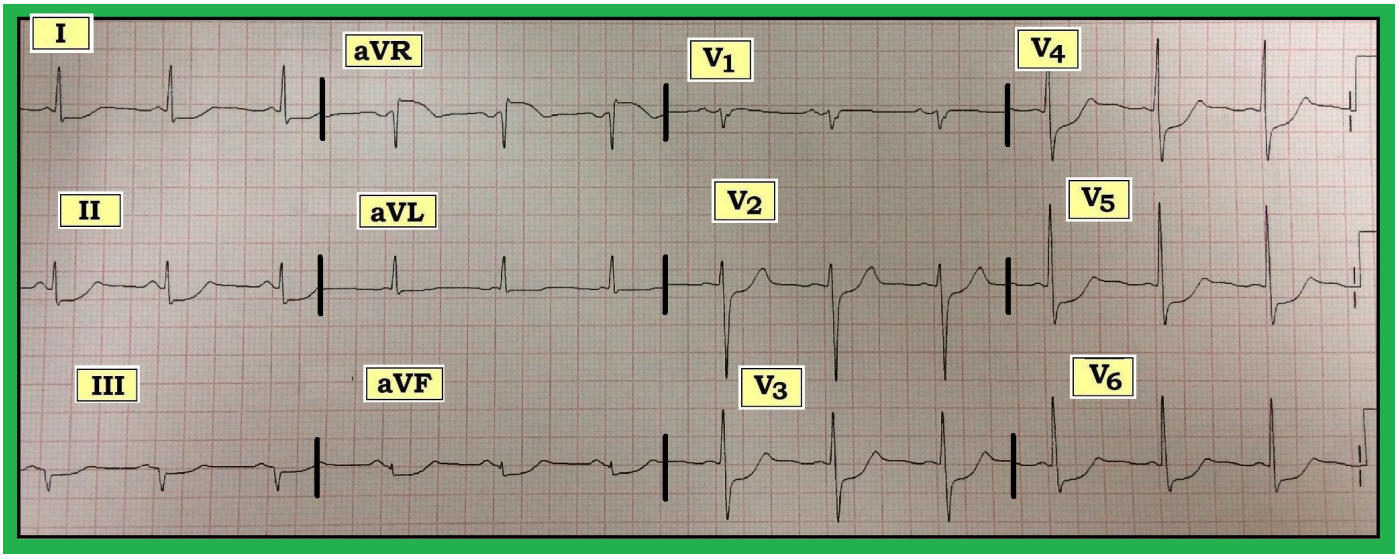

Figure: 12-lead ECG obtained 30 minutes after conversion of a sustained tachycardia to sinus rhythm.

Scenario: The ECG above was obtained from the 60-year-old man presented in last month's ECG Review. The patient had been in a sustained supraventricular tachycardia for a period of time. This ECG was taken 30 minutes after conversion to sinus rhythm. How would you interpret this ECG given the above clinical context?

Interpretation: Sinus rhythm is present at a rate of 75/minute. The PR and QRS intervals are normal. The QT interval is upper normal considering the heart rate. The axis is +20 degrees. There is no chamber enlargement.
• The most remarkable finding on this tracing is marked, and diffuse ST depression seen in virtually all leads (with exception of ST elevation in lead aVR). The amount of ST depression is at least 3 mm in leads II and V3-through-V6.

Impression: As a single tracing interpreted in light of the brief clinical context provided above, one would have to suspect severe coronary disease is likely. It is well to appreciate that the finding of diffuse ST flattening and depression in a majority of leads on a 12-lead tracing in association with ST elevation in lead aVR is highly suggestive of: 1) possible left main coronary artery narrowing; 2) LAD (left anterior descending) disease; or 3) other form of severe coronary disease.

Attention to lead aVR may be helpful. The unique perspective of this right-sided lead assesses the basal part of the interventricular septum. Predominant ST elevation in aVR compared to a lesser degree of ST elevation in leads aVL and V1 in association with diffuse ST depression suggests left main coronary disease. In contrast, ST elevation in lead V1 is more likely to equal or exceed the amount of ST elevation in aVR with proximal LAD disease.

Another potential cause of the marked ST depression in this case is that this may be a post-tachycardia phenomenon. Whereas ST-T wave changes associated with tachycardia typically resolve soon after conversion to sinus rhythm, sometimes such changes persist for hours, or even a few days.

Cardiac catheterization was performed in this patient and revealed insignificant coronary disease. ST-T wave depression resolved with time. ■

NOTE: Further discussion of this tracing is available on an ECG video found at this site:
https://www.youtube.com/watch?v=5E3_MKuvr9c&feature=youtu.be