Clinical Briefs in Primary Care

Evidence-based updates in primary care medicine

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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, detemir) 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. So, 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 the risk of stroke by as much as 66%, but warfarin requires close follow-up and has a narrow therapeutic range. Although 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 cardiovascular 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, angiotensin II receptor blockers, 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 inclusive of 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

those who had 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 these data are observational in nature, they cannot definitively establish whether beta-blocker treatment reduces mortality in d-CHF, but they provide strong impetus to perform a large randomized trial to ultimately answer the question. ■

Delay in Diagnosis of Hepatocellular Carcinoma

SOURCE: Patel N, et al. Diagnostic delays are common among patients with hepatocellular carcinoma. *J Natl Compr Canc Netw* 2015;13:543-549.

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer mortality worldwide. It is increasing in the United States, paralleling the rise in non-alcoholic fatty liver disease and hepatitis C. When diagnosed early, 5-year survival is as high as 70%, but diminishes to less than 1-year survival when diagnosed at an advanced stage.

Cirrhosis patients have been suggested to undergo ultrasound screening twice yearly, but not only does this process have only modest sensitivity (32%) it often is not followed by clinicians (or patients). Since 40% of HCC cases present with no previously recognized signs of liver disease, it becomes easier to understand how cases go "under the radar."

Patel et al studied cases of HCC (n = 457) that presented to a large hospital and its affiliated primary care clinics in Dallas, TX, between 2005 and 2012. Almost half of the patients had received the HCC diagnosis as inpatients, which was associated with a very short lag time between presentation and diagnosis (< 1 week).

For those diagnosed as outpatients (n = 226), the delay from presentation to diagnosis was substantial. For instance, almost 40% of HCC diagnosed among outpatients incurred a 3-month delay from time of presentation, an interval that has been associated with meaningful disease progression. Healthcare sites that employed an electronic medical record showed less diagnostic delay. There was also a patient-dependent role in diagnostic delay, wherein some patients did not follow up recommended return visits, an occurrence more common among patients with hepatic encephalopathy. The authors encourage timely identification and follow-up of persons at-risk for HCC. ■

Initial Orthostatic Hypotension: An Under-Recognized Form of Orthostatic Hypotension

SOURCE: McJunkin B, et al. Detecting initial orthostatic hypotension: A novel approach. *J Am Soc Hypertens* 2015;9:365-369.

Orthostatic hypotension (OH) is typically defined as a decline in blood pressure (BP) > 20/10 mmHg within 3 minutes of standing. OH is consequential not only because of adverse symptoms, such as dizziness, blurred vision, or so-called "coat-hanger" headache, but also because it is associated with falls. Fall risk leads to life-changing consequences, such as hip fracture and loss of autonomy due to non-independent living.

A less familiar form of orthostasis is termed initial orthostatic hypotension (IOH). IOH is characterized by a dramatic decline in BP (> 40/20 mmHg) presenting within the first 15 seconds of standing, which self corrects within 30-60 seconds. IOH differs from the normal physiologic experience many of us have had of a transient decrease in BP, which recovers by 30 seconds. IOH, then, is a prolongation of recovery time, during which patients might experience hypotensive symptoms or even falls.

One of the limitations of prior investigations about IOH has been the delay in BP measurement incurred by simply using 5-10 seconds or more to inflate the BP cuff to measure the BP in the first place! McJunkin et al suggest that this obstacle can be obviated by fully inflating the cuff while a patient is supine, allowing immediate deflation and BP measurement upon standing.

Among a population of elderly patients (n = 115), 12% were found to have OH, and 3.5% to have IOH. IOH represents a population at risk for falls, which may be missed with "traditional" methods of orthostatic BP measurement. ■

Beta-blocker, Shmeta-blocker…Or Are There Important Differences?

SOURCE: Aparicio LS, et al. Comparison of atenolol versus bisoprolol with noninvasive hemodynamic and pulse wave assessment. *J Am Society Hypertens* 2015;9:390-396.

Aside from beta-receptor selectivity (beta-1 receptors for cardiac function, beta-2 for pulmonary function), clinicians do not often distinguish major differences within the class of beta-blockers. Of course, alpha-beta-blockers (e.g., carvedilol, labetalol) are not really beta-blockers in the traditional sense, because they also provide alpha-receptor blockade. There's also nebivolol, the nitric-oxide enhancing beta-blocker associated with — in contrast to most other beta-blockers — peripheral vasodilation (traditional beta-blockers being associated with peripheral vasoconstriction that may result in complaints, for instance, of cold extremities).

In 2006, it was brought to the attention of clinicians that while various drugs may lower BP equivalently, they may not always reduce cardiovascular (CV) endpoints to the same degree. In the ASCOT trial, which compared amlodipine to atenolol, CV outcomes were more favorable with amlodipine, despite similar BP results. The CAFÉ trial (Conduit Artery Function Evaluation) determined that even though arm BP (sometimes called peripheral BP) was similar with either drug (amlodipine or atenolol), central BP (measured at the level of the aorta) decreased substantially better with amlodipine. Such differences might explain the advantageous outcomes results in favor of amlodipine.

Aparicio et al compared central BP effects of bisoprolol and atenolol, and found them to be comparable. Whether clinicians should choose pharmacotherapy based on central BP effects has not been confirmed, although hypertension guidelines throughout the world have increasingly recognized the inadequacy of traditional beta-blockers in comparison to most other classes of agents and relegated them to a lower position on the therapeutic ladder. ■

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