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Letter to the Editor

Use of High-Intensity Statin in Patients with Ischemic Stroke: Observation and Opinion of a Clinical Pharmacist in the Inpatient Setting

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Letter to the Editor

Publication of the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [1] has spurred much controversy and discussion in the medical literature, such as but not limited to overestimation of risk, overemphasis of statin-based therapy, working panel ties to industry, and interpretation of data. As an academic clinical Pharm.D., I am a member of a neurology team rounding and providing pharmaceutical care recommendations for the neurology intensive care unit and floor patients admitted to our university-based hospital. From a pharmacist perspective, I am also attempting to define my use of these new guidelines and what I consider their limitations. But it is with great interest I observe and participate in physician prescribing practices of statin medications post-publication of the 2013 ACC/AHA Guidelines. Physician reluctance to utilize the new guidelines is from a different perspective than my own and a perspective I feel the need to counter. If I was to apply my anecdotal observations to a broader context of neurology physicians nationally, I would suspect the new guidelines are being overlooked or cautiously being applied to post-stroke patients in the inpatient setting, with deference to the older low-density lipoprotein cholesterol (LDL-C)-based goals established in 2011 by the AHA/ASAGuidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack [2].

HMG-CoA Reductase Inhibitors, commonly referred in clinical practice as "statins", have been prescribed for years across many acute and chronic diseases to lower cholesterol and ultimately reduce the incidence of stroke and MI, and more recent thought to potentially provide additional pleiotropic effects such as but not limited to anti-inflammatory properties. Statin cholesterol-lowering efficacy is tied to the various formulations available and dose resulting in an LDL-C level reduction of approximately 20% to 60%. Historically statins were known for more severe adverse effects of rhabdomyolysis and liver toxicity, side effects now considered to be rare.

The new 2013 ACC/AHA Treatment of Blood Cholesterol expert panel define stroke patients as a subset of patients who would most likely benefit from statin therapy and call for physicians to take a different and potentially more aggressive approach to the use of statins. The guidelines opine stroke patients, age >21 - ≤ 75 years of age, with no contraindications or intolerance to statins should be prescribed a "high-intensity" statin regardless of LDL-C level (Class of Recommendation 1, Level of Evidence A). A high-intensity statin is defined as the choice of statin medication at it's appropriate dose to achieve ≥ 50% reduction in LDL-C [atorvastatin (40) – 80 mg, rosuvastatin 20 – (40) mg)]. The older 2011 AHA/ASA Prevention of Stroke guidelines tied statin therapy to a more objective goal, an LDL-C level < 100 mg/dL (Class I, Level of Evidence B).

While there is always a learning-curve and a comfort level to be achieved with the release of new guidelines and a change of therapeutic goals, I'm listening with interest the barriers being presented by physicians as to why they are not using high-intensity statin therapy on stroke patients admitted to our university based hospital who meet the criteria as defined by the 2013 ACC/AHA guidelines. The most commonly voiced oppositions to high-intensity statin use are 1.) fear of future hemorrhagic stroke, 2.) the LDL-C is already< 100 mg/dL or the LDL-C is only slightly above 100 mg/dL, and 3.) fear of liver toxicity, rhabdomyolysis, and a statin naïve patient will experience myopathy or muscle pain. I'd like to address some of these physician concerns covered in the new guidelines.

Addressed in the new guidelines is the analysis of hemorrhagic stroke due to high intensity stain use derived from the SPARCL and CORONA studies combined with the Cholesterol Treatment Trialist (CTT) Collaboration [3]. The ACC/AHA expert panel point out the risk seems to be greatest in patients with a prior history of hemorrhagic stroke but also note the benefits in preventing an Atherosclerotic Cardiovascular Disease (ASCVD) event far outweighs the risk of hemorrhage. But with that said, there is a concession within the guidelines to allow clinicians to weigh the risks and benefits in patients with hemorrhagic stroke and defer to a lower intensity statin or no statin. 85% of strokes are typically ischemic and while they are not all atherosclerotic in origin, I feel this concession is being too broadly applied to all stroke patients. Seeing the devastating effects of hemorrhagic stroke on patients everyday as a part of my clinical service allows me to agree with a conservative approach in statin use in hemorrhagic stroke patients or those with a previous history of hemorrhage but I do not agree with this conservative approach to the ischemic stroke patients, in particular those < 75 years of age who still may derive many years of benefit from high intensity statin therapy.

By no longer having a pre-defined LDL-C goal but rather targeting a reduction of ≥ 50% regardless of baseline LDL-C is a simplification of the protocol. There no longer has to be a juggling of specific statin selection or calculation of what dose will drop the LDL-C by the needed percentage as required by the old guidelines to reach the

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predefined LDL-C goal. The ACC/AHA panel points out that there is no good data to support a specific goal and the main objective in secondary stroke prevention is significant reduction in the LDL-C level. But as with all recommendations, there is a concession that if two consecutive LDL-C goals are < 40 mg/dL, the clinician can consider decreasing the intensity of the statin. I'm not going to debate the pros or cons of achieving an LDL-C level < 100 mg/dL versus a LDL-C < 70 mg/dL or even lower. Interpretation of clinical trial data can be subjective and incomplete even in the best scenarios but I give pause to prescribing low or moderate intensity statins in a younger patient with an LDL-C level < 130 mg/dL who has just had an ischemic stroke of atherosclerotic origin. Our goal as clinicians is to give each patient the most optimal care available to us at the time. And at this time, aggressive reduction of LDL-C regardless of baseline levels is being defined as the best care we can give our patients.

Monitoring parameters for hepatic transaminase levels and rhabdomyolysis have decreased greatly since FDA approval of statins, as the incidence of occurrence is not as common as once thought and monitoring does not lead to additional prevention. As pointed out in the ACC/AHA guideline, elevations in hepatic transaminase levels only occurred in < 1.5 % of patients on high intensity statin therapy over 5 years. Utilizing pooled data, rhabdomyolysis and muscle symptoms occurred at similar rates in the statin groups as compared to placebo. The only exception was with simvastatin 80 mg which is no longer prescribed as per FDA guidelines. Any physician in clinical practice can attest to patient complaints of muscle pain with statin use. And as with every recommendation there is a concession within the guidelines to lower doses to moderate intensity in the setting of muscle pain or intolerance to statin therapy. But there is no data to preemptively assume all patients or which patients will develop an ADR nor that statin naïve patients are at greater risk. It is always a concern of mine from the perspective of the inpatient setting that when patients are started on a lower intensity stating that the dose will not be titrated up appropriately after discharge. By prescribing high intensity statin therapy prior to or at discharge, patient care can be at an optimal level sooner rather than later or not at all.

As a clinician, I need to find a balance between risk and benefit with every drug choice I recommend in patient care. I feel there is also a distinction to be made between statin use in primary prevention versus secondary prevention of ASCVD events. I would be more apt to initiate a moderate intensity statin in primary prevention than secondary prevention. In secondary prevention, I feel the benefits clearly outweigh the risks and an additional argument could be made that a higher intensity statin might be of greater use in the acute setting (such as used in the setting of MI). The new guidelines do give flexibility to make decisions for the individual patient, but there are times when conservative care is not the best choice. The scenarios I have detailed are most likely happening in the majority of hospitals, reflecting the inpatient standard of care. I am cognizant that physicians bear the weight of prescribing a drug that may or may not induce a hemorrhage or subsequent ADR, not the pharmacist. But I'd like to think that in a collaborative setting, the pros and cons of high intensity statin use can be debated to define the best care for each individual patient without placing up barriers that may have little or no weight in the discussion. I am fortunate to work with a group of physicians in which all members of the health care team are asked to weigh in on patient care and opinions are respected and valued. I'm hoping on this issue with repeated input from a pharmacist we may be over the learning curve.

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