HEALTHCARE GROUP

CENTRE FOR DIABETES & ENDOCRINOLOGY

CDE Academy - Diabetes Literature Review

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EASD 2022 - Diabetic foot ulcers: topical esmolol hydrochloride bests standard of care

The use of esmolol hydrochloride in adults with diabetic foot ulcer improves wound healing and may constitute a novel treatment option, suggests research reported at the 58th EASD Annual Meeting in Stockholm, Sweden.

Takeaway

Esmolol hydrochloride 14% topical gel, a novel therapy option, treated diabetic foot ulcers (DFU) much better than the standard of care (SoC) and did not cause any significant drug-related safety issues.

Esmolol hydrochloride is an intravenously administered β-1-selective (cardioselective) adrenergic receptor blocking agent that has been approved for the treatment of supraventricular tachycardia and heart failure with fast ventricular rate. Few studies have previously demonstrated the anti-inflammatory properties of esmolol, and the authors proposed that a topical formulation may induce nitric oxide production, leading to fibroblast migration and mobilisation of endothelial progenitor cells, thus hastening wound healing in diabetes.

The encouraging results from prior pre-clinical and phase 1 and 2 studies led to the design of this double-blind, multi-centre, phase 3 study, which evaluated the efficacy of topical esmolol hydrochloride gel for uninfected DFU. People with type 2 diabetes who had a DFU area of 2-15 cm^2 and an ≥6-week-old target ulcer were included in this trial. After a 1-week screening phase, 176 participants were randomly assigned to receive topical esmolol 14% gel + SoC, SoC only, or vehicle + SoC for 12 weeks. All were followed up until week 24. The recommendations made for SoC by the American Diabetes Association and the International Working Group for Diabetic Foot were implemented.

The primary efficacy outcome was the proportion of participants achieving target ulcer closure during the 12-week treatment phase. Target ulcer closure is defined as 100% re-epithelialisation without the need for drainage or dressing.

Interestingly, a significantly higher proportion of patients in the esmolol + SoC versus SoC-only treatment arm achieved target ulcer closure within 12 weeks (odds ratio [OR], 2.126; P=.0276), with the improvements maintained till the end of the study (week 24; OR, 2.708; P=.0126). Furthermore, the esmolol + SoC treatment arm demonstrated superiority over SoC alone in every sub-group regardless of the age of the ulcer, body mass index, haemoglobin levels, etc. (P<.05 for all). From the end of treatment (week 12) to the end of study (week 24), there was a 60.65% reduction in ulcer area with esmolol + SoC compared with a negligible reduction of 2.74% with SoC alone (P=.021), suggesting a "legacy effect" of topical esmolol on the migration of fibroblasts. Esmolol + SoC also reduced exudates much faster than SoC alone (P=.024). Dr Rastogi concluded the session by stating that none of the reported serious adverse events was related to esmolol hydrochloride.

Shrabasti Bhattacharya, EASD Annual Meeting; Stockholm, Sweden: Sept 19–23, 2022

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Prevalence of Statin Intolerance Is Approximately 9%

GUADALAJARA, Mexico — during his presentation at the Annual Congress of International Cardiology 2023, Francisco López-Jiménez, a Mayo Clinic cardiologist quoted the US FDA definition of statin intolerance as "the inability to tolerate at least two statins at the lowest approved doses due to musculoskeletal symptoms". He said that a recent meta-analysis, including data from 176 cohort studies, clinical trials, and case series with more than 4 million patients, showed that statin intolerance is present in approximately 9% of people treated with statins. The study-identified risk factors for statin intolerance, included female sex (47.9%), obesity (30.6%), hypothyroidism (37.6%), diabetes (26.6%), use of antiarrhythmics (31.2%), alcohol use (22%), exercise (23.2%), chronic liver disease (24.3%), chronic kidney failure (25.2%), use of calcium channel blockers (35.5%), and use of high-dose statins (37.5%). Factors not related to statin intolerance, included smoking, high blood pressure, duration of statin treatment, being White or Hispanic, and the use of warfarin.

López-Jiménez recalled that when statins first began to be used, the concept of intolerance to the drug did not exist. However, to clarify this situation, a study was conducted that compared statin intolerance in two phases of the same clinical trial. The first was a double-blind phase, where intolerance or muscle symptoms were present in 2% of people treated with statins and placebos. The second was an open-label phase. Participants treated with statins had a 40% greater risk of symptoms, versus those who took placebo. This suggests a 'nocebo effect', where the person believes and is convinced that a treatment will harm them. López-Jiménez noted that the most important study to demonstrate the existence of statin intolerance is the Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study, published in *Circulation*. This double-blind clinical trial of atorvastatin 80 mg versus placebo was specifically designed to assess the difference in muscle symptoms and muscle strength, as well as exercise capacity. In this 6-month follow-up study of only 420 participants, statin intolerance due to musculoskeletal symptoms occurred in 9% of participants taking atorvastatin versus 4% taking placebo. Meanwhile, in the GAUSS-3 study, all participants had a history of statin intolerance, and those who took atorvastatin had a higher incidence of muscle pain compared with those who took placebo. However, about 60% of the latter developed intolerance.

"avoid the initiation or increase of exercise exactly when a person starts or changes statin doses."

Lastly, to confirm the presence of intolerance and the proportions of people who are truly intolerant and tolerant, a meta-analysis of 123,000 patients was performed. This study included data from controlled clinical trials comparing statin or placebo or a high versus low dose. "They found that 27% of the participants developed intolerance at the 4-year follow-up, yet the absolute difference between those taking statins and those taking placebo was only one case per 1000 patient-years. In practical terms, it was concluded that only one in 15 cases reporting musculoskeletal symptoms attributed to statins was real," said López-Jiménez.

He said that some practical recommendations for the diagnosis of statin intolerance are measuring the enzyme creatine phosphokinase and evaluating the level of certainty that relates the symptoms to statins by means of causality rules. When symptoms start 5 years after taking statins, intolerance is unlikely "because usually when it is real it starts in the first few weeks, maybe even in 1 or 2 months. When the symptoms start the same day the statin was taken, surely there is no intolerance," he said.

Regarding the management of statin intolerance when there is evidence that the person has related symptoms, López-Jiménez recommended "asking oneself whether the drug is really necessary. Most of the time the answer will be positive, but in other cases not. In primary prevention, coronary calcium should be used not only to find patients at risk but also to move the needle to the other side. That is, if calcium is not found in people considered to be at moderate or high risk, it is advisable to lower their risk level, and they probably no longer need statins."

Another important aspect is the assessment of risk perceptions. "If we teach the patient that the risk of a serious event, death, hospitalization, or serious complications with statins is less than 1 in 3 million individuals on treatment, they can go away fearing the rare event and not focusing on the risk of the actual event. Thus, make it clear that the risk of not taking a statin is much higher, especially in patients with coronary disease," he noted.

López-Jiménez also recommended avoiding the initiation or increase of exercise exactly when a person starts or changes statin doses. "When the patient leaves the medical office with their statin prescription and is motivated to do exercise, it is inevitable that their muscles will ache, and they will not attribute it to the exercise they started to do, but to the statins," he concluded.

Medscape Medical News (2023) ***Prevalence of Statin Intolerance Is Approximately 9%*****. Available from https://www.medscape.com/viewarticle/989792**

NSAID Use in Diabetes May Worsen Risk for First HF Hospitalization

Among adults with diabetes but no history of heart failure (HF), taking a nonsteroidal anti-inflammatory agent (NSAID), even for only a month, sharply raises the risk of an HF hospitalization, suggests a prospective, controlled study. Certain subgroups may account for much of the excess risk, the results suggest, including people 80 years of age or older, people with uncontrolled diabetes, those prescribed an NSAID for the first time, and people already taking both a renin-angiotensin-system inhibitor (RASi) and a diuretic. Such clients with a firm indication for NSAIDs potentially could "be the ones benefiting most from closer follow-up, reduced dosage, or other mitigation strategies," Anders Holt, MD, told theheart.org | Medscape Cardiology.

Holt, of Copenhagen University Hospital, Denmark, is lead author on the analysis of Danish registry data published April 10 in the *Journal of the American College of Cardiology*. The report notes that heart failure hospitalizations linked to NSAIDs are often attributed to symptoms from temporary fluid overload, often without worsening cardiac function, that stem from the drugs' renal effects. "One could speculate," Holt said, that such HF events might be less severe and even associated with better outcomes compared with other forms of heart failure. But, the current analysis provides a hint to the contrary, he observed. The 5-year mortality was similar for clients with HF linked to NSAIDs and those with other forms of HF, "which could suggest that NSAID-associated heart failure is more than transient fluid overload." The drugs may promote HF through direct effects on the heart by any of several proposed mechanisms, including "induction of arrhythmias and heart fibrosis, vasoconstriction, subclinical inflammation, and blood pressure elevation," Holt said. The current study doesn't determine whether NSAID-associated HF stems from transient fluid overload or direct cardiac effects, but it's "most likely both."

"That NSAID use and diabetes are each associated with increased risk for HF is well established"

In other limitations, the analysis is unable to "reliably explore" whether promotion of HF is an NSAID class effect, a "clinically relevant" point given the drugs' varying effects on cardiovascular risk, states an accompanying editorial. Nor was it able to determine whether the drugs exert a dose-response effect on HF risk, note Hassan Khan, MD, PhD, Norton Healthcare, Louisville, Kentucky, and Setor K. Kunutsor, MD, PhD, University of Leicester, United Kingdom. Still, "Given the well-established relationship between the use of NSAIDs and increased HF, these findings are not unexpected because type-2 diabetes is also a major risk factor for HF." But it may be "premature to issue guideline recommendations based on a single observational study," the editorialists write. "Further robust clinical trial evidence is needed to replicate these results and investigate the relationship of the type and dose of NSAIDs with HF risk. However, it should be realized that short-term or long-term use of NSAIDs may be detrimental to cardiovascular health."

The analysis covered 23,308 people from throughout Denmark with a type-2 diabetes diagnosis and no HF history who experienced a first HF hospitalization; their age averaged 76 years and 39% were women. They served as their own controls; their NSAID exposures at two 28-day periods preceding the HF event, the one immediately before and the other preceding it by 56 days, were compared as the index and control periods, respectively.

Exposure to NSAIDs was defined as obtaining a prescription for celecoxib, diclofenac, ibuprofen, or naproxen, "as these are NSAIDs used primarily in Denmark," the report states. Odds ratios (OR) for HF hospitalization associated with NSAID exposure within 28 days preceding the event were:

- 1.43 (95% CI, 1.27 - 1.63) overall
- 1.41 (1.16 - 1.71) for an NSAID given on top of both RASi and diuretics
- 1.68 (95% CI, 1.00 - 2.88) for patients with elevated haemoglobin A1c
- 1.78 (95% CI, 1.39 - 2.28) for those 80 or older
- 2.71 (95% CI 1.78 - 4.23) for those with prior NSAID use

That NSAID use and diabetes are each associated with increased risk for HF is well established, Holt observed. Yet the drugs had been prescribed to 16% of patients in the study. "One of the more surprising findings, to me, was the quite substantial use of prescribed NSAIDs in a population of patients with diabetes, a patient group with a well-established cardiovascular risk," he said.

"This patient group is only growing, so emphasis on the possible associations between even short-term NSAID use and incident heart failure is probably timely and perhaps needed."

Medscape Medical News (2023). ***NSAID Use in Diabetes May Worsen Risk for First HF Hospitalization.*** **Available from https://www.medscape.com/viewarticle/990642**

New Recommendations for Weight Loss Drugs

Reuters - Novo Nordisk's Wegovy won U.S. approval in June 2021 with a label that says it can be used for chronic weight management in people with a body mass index (BMI) of 27 kg/m^2 or more who have at least one weight-related ailment, or in any person with a BMI of 30 kg/m^2 or greater.

Several leading international medical groups have since updated their recommendations on treating excess adiposity resulting in the classification of obesity while others are planning new guidance. Here are some of the new guidelines:

Obesity Canada

Updated its standards of care document in October 2022 to include use of semaglutide, the chemical name for Wegovy, and a related diabetes drug. These guidelines say doctors should tailor treatments to individuals using nutrition, physical activity, psychological interventions, medications, and surgery, and that BMI is not an accurate tool to identify obesity -related ailments. They also say drugs can be used to maintain weight loss that has been achieved by behavioural changes.

"Several leading international medical groups have since updated their recommendations on treating obesity"

The American Gastroenterological Association (AGA)

In November 2022, the AGA prioritized semaglutide over older medications in its new guidance but suggested that drugs should be used alongside diet and exercise changes in patients who had inadequate responses to lifestyle interventions alone. It also said patients would need to be on these drugs for life.

The American Academy of Pediatrics (AAP)

Published guidance in January recommending use of drugs in children ages 12 years or older in addition to lifestyle and behaviour changes for obesity treatment, drawing criticism over the lack of long-term data for how weight loss drugs affect children and teens.

The National Institute for Health and Care Excellence (NICE)

This year, the UK's national healthcare governance body, **NICE,** published guidance that says Wegovy should be reserved for patients with at least one weight-related health risk and a BMI of 35 kg/m^2 or more, or, exceptionally, a BMI of between 30 and 35 and a referral to specialist weight management care.

It also said Wegovy could only be used as a treatment for two years - the length of time it was tested in pivotal clinical trials.

Wingrove P (2023). ***New recommendations for weight-loss drugs*****. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/new-recommendations-weight-loss-drugs-2023-03-30/**