Diabetes and Hypertension Project ECHO* Clinic

*ECHO: Extension of Community Healthcare Outcomes

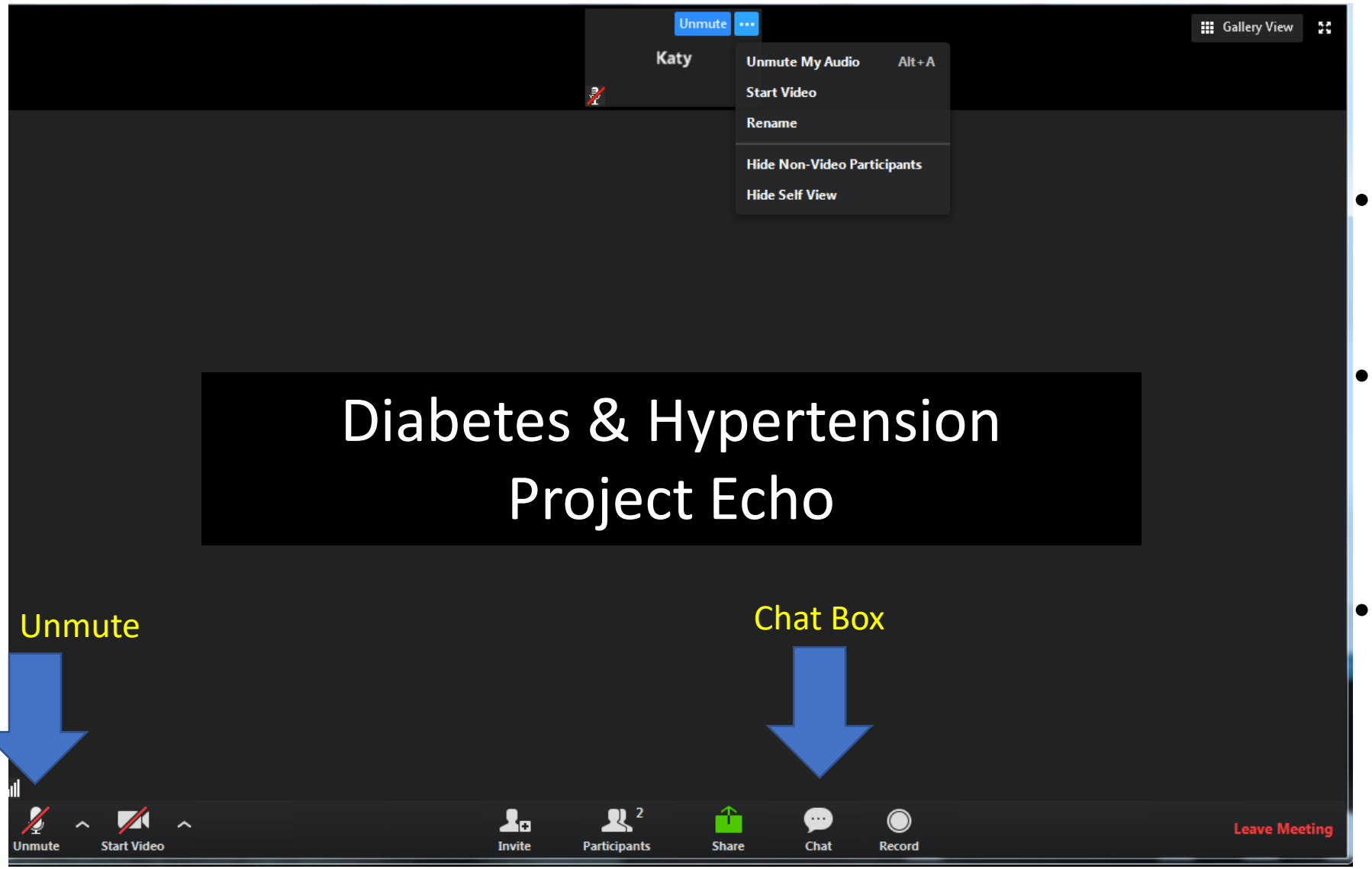
Sept. 23, 2021

Before we begin:

- Rename your Zoom screen with your name and organization
- Claim CE: text 19181-18817 to 804-625-4041
  - Go to **vcuhealth.org/echodmhtn** for instructions on creating your account

The Diabetes and Hypertension ECHO is made possible by funding through CDC Cooperative Agreement NU58DP006620-InnoVAte.

Zoom Reminders



- You are all on mute. Please unmute to talk.
- If joining by telephone audio only, press *6 to mute and unmute.
- Use the chat function to speak with our team or ask questions.

Helpful Reminders

- Please feel free to eat your lunch or step away briefly if needed
- We are recording and can share sessions upon request
  - Each session's slides are available on www.vcuhealth.org/echodmhtn
- Please **do not share any protected health information** in your discussion or the chat box
- Project ECHO operates on the "All Teach, All Learn" model
  - Feel free to ask questions in the chat or unmute to ask questions at designated times
  - We're all here to learn from each other and value each person's input and expertise!

VCU Health Diabetes & Hypertension ECHO Clinics

VCU Hub Team	
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Administrative Medical Director ECHO Hub	Vimal Mishra, MD, MMCi
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Project Coordinator/IT Support	Madeleine Wagner

- **NEW: *1-hour*** ECHO clinics on 2nd and 4th Thursdays
- Every ECHO clinic includes a didactic presentation followed by case discussions
- Website: www.vcuhealth.org/echodmhtn
  - Directions for claiming CE can be found here
  - You have up to six days after our session to claim CE by texting **19181-18817** to **804-625-4041**

Disclosures

Trang Le, M.D., has no financial conflicts of interest to disclose.

Niraj Kothari, M.D., has no financial conflicts of interest to disclose.

There is no commercial or in-kind support for this activity.

Diabetic Neuropathy

Objectives

- Review different types of diabetic neuropathies
- Describe best strategies for screening and prevention
- List treatment options for painful diabetic neuropathies

POSITION STATEMENT

Diabetic Neuropathy: A Position Statement by the American Diabetes Association

Rodica Pop-Busui,[1] Andrew J.M. Boulton,[2] Eva L. Feldman,[3] Vera Bril,[4] Roy Freeman,[5] Rayaz A. Malik,[6] Jay M. Sosenko,[7] and Dan Ziegler[8]

Diabetes Care 2017;40:136–154 | DOI: 10.2337/dc16-2042

Diabetic neuropathies are the most prevalent chronic complications of diabetes. This heterogeneous group of conditions affects different parts of the nervous system and presents with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons:

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable by specific measures.
2. A number of treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of diabetic peripheral neuropathies may be asymptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
4. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Among the various forms of diabetic neuropathy, distal symmetric polyneuropathy (DSPN) and diabetic autonomic neuropathies, particularly cardiovascular au-

Classification for Diabetic Neuropathies

A. Diffuse neuropathy

DSPN (Distal Symmetric polyneuropathy)

- Primarily small-fiber neuropathy
- Primarily large-fiber neuropathy
- Mixed small- and large-fiber neuropathy (most common)

Autonomic

Cardiovascular

- Reduced HRV
- Resting tachycardia
- Orthostatic hypotension
- Sudden death (malignant arrhythmia)

Gastrointestinal

- Diabetic gastroparesis (gastropathy)
- Diabetic enteropathy (diarrhea)
- Colonic hypomotility (constipation)

Urogenital

- Diabetic cystopathy (neurogenic bladder)
- Erectile dysfunction
- Female sexual dysfunction

Sudomotor dysfunction

- Distal hypohydrosis/anhidrosis,
- Gustatory sweating

Hypoglycemia unawareness

Abnormal pupillary function

Classification for Diabetic Neuropathies

B. Mononeuropathy (mononeuritis multiplex) (atypical forms)

Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal)

Mononeuritis multiplex (if confluent may resemble polyneuropathy)

C. Radiculopathy or polyradiculopathy (atypical forms)

Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy)

Thoracic radiculopathy

Diabetic Neuropathy

- Among the various forms of diabetic neuropathy, distal symmetric polyneuropathy (DSPN) and diabetic autonomic neuropathies, particularly cardiovascular autonomic neuropathy (CAN), are by far the most studied

DSPN

- Accounts for ~75% of the diabetic neuropathies
- Prevalence:
  - 20% of people with T1DM after 20 years of disease
  - 10-15% of newly diagnosed patients with T2DM, → 50% after 10 years of disease
- = > presence of symptoms and / or signs of peripheral nerve dysfunction in people with diabetes, after exclusion of other causes

Symptoms and Signs of DSPN

	Large myelinated nerve fibers	Small myelinated nerve fibers
Function	Pressure, balance	Nociception, protective sensation
Symptoms§	Numbness, tingling, poor balance	Pain: burning, electric shocks, stabbing
Examination (clinically diagnostic)**	Ankle reflexes: reduced/absent Vibration perception: reduced/absent 10-g monofilament: reduced/absent Proprioception: reduced/absent	Thermal (cold/hot) discrimination: reduced/absent** Pinprick sensation: reduced/absent**

§To document the presence of symptoms for diagnosis; **Documented in symmetrical, distal to proximal pattern.

DSPN

- Associated with:
  - Glycemia
  - Height (due to nerve length?)
  - Smoking
  - Blood pressure, weight, lipids
- May be present in 10-30% of subjects with prediabetes
- Most important cause of foot ulceration, Charcot neuroarthropathy

Screening and Diagnosis

- All patients should be assessed for DSPN starting at
  - diagnosis of type 2 diabetes
  - 5 years after the diagnosis of type 1 diabetes
  - at least annually thereafter
- Consider screening patients with prediabetes who have symptoms of peripheral neuropathy.
- Assessment should include a careful history and
  - **either** temperature **or** pinprick sensation (small-fiber function)
  - **and** vibration sensation using a 128-Hz tuning fork (large-fiber function).
- All patients should have an annual 10-g monofilament testing to assess for feet at risk for ulceration and amputation

True or False:

- Diabetic neuropathy is a diagnosis of exclusion.

True or False:

- Diabetic neuropathy is a diagnosis of exclusion.

TRUE

Differential Diagnosis of Diabetic Neuropathy

- Metabolic disease
  - Thyroid disease (common)
  - Renal disease
- Systemic disease
  - Systemic vasculitis
  - Nonsystemic vasculitis
  - Paraproteinemia (common)
  - Amyloidosis
- Infectious
  - HIV
  - Hepatitis B
  - Lyme
- Inflammatory
  - Chronic inflammatory demyelinating polyradiculoneuropathy
- Nutritional
  - B_{12}*
  - Postgastroplasty
  - Pyridoxine
  - Thiamine
  - Tocopherol
- Industrial agents, drugs, and metals
  - Industrial agents
    - Acrylamide
    - Organophosphorous agents
  - Drugs
    - Alcohol
    - Amiodarone
    - Colchicine
    - Dapsone
    - Vinka alkaloids
    - Platinum
    - Taxol
  - Metals
    - Arsenic
    - Mercury
- Hereditary
  - Hereditary motor, sensory, and autonomic neuropathies

When to refer to neurology?

- Electrophysiological testing or referral to a neurologist is rarely needed for screening, except in situations where
  - clinical features are atypical,
  - the diagnosis is unclear,
  - different etiology is suspected

- Atypical features include
  - motor greater than sensory neuropathy,
  - rapid onset, asymmetrical presentation

Diabetic Neuropathy

- Due to a lack of treatments that successfully target the underlying nerve damage, ***prevention*** is critical
- Screening for symptoms and signs of diabetic neuropathy may detect the earliest stages of neuropathy, enabling early intervention
- Although screening for rarer atypical forms of diabetic neuropathy may be warranted, DSPN and autonomic neuropathy are the most common forms encountered in practice.

Intensive glycemic control

A. Reduces incidence of DSPN in T1DM > T2DM

B. Is equally effective to reduce incidence of DSPN in T1 and T2DM

C. Reverses DSPN

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Intensive glycemic control

- Many people with type 2 diabetes develop DSPN despite adequate glucose control
- The presence of multiple comorbidities, polypharmacy, hypoglycemia, and weight gain might have attenuated the effects of glucose control in clinical trials and contributed to inconsistent findings
- Many patients have had asymptomatic hyperglycemia for many years prior to the diagnosis of type 2 diabetes → limitations to benefit of improved glycemia

Intensive glycemic control

- Enhanced glucose control in people with type 1 diabetes dramatically reduces the incidence of DSPN (**78% relative risk reduction**)(DCCT)
- In contrast, enhanced glucose control in people with type 2 diabetes reduces the risk of developing DSPN modestly (**5%–9% relative risk reduction**)(ACCORD)

Prevention

- Prevention of diabetic neuropathies focuses on ***glucose control*** and ***lifestyle modifications***.
- Available evidence pertains only to DSPN and CAN
  - most of the large trials that have evaluated the effect of glucose control on the risk of complications have included DSPN and CAN as secondary outcomes or as post hoc analyses rather than as primary outcomes.
  - In addition, in some of these trials, the outcome measures used to evaluate neuropathy may have limited ability to detect a benefit, if present.

Treatment

- Despite the recent major advances in understanding pathogenesis of diabetic neuropathy, there remains a lack of treatment options that effectively target the natural history of DSPN or reverse DSPN once established
- Consider either ***pregabalin*** or ***duloxetine*** as the initial approach in the symptomatic treatment for neuropathic pain in diabetes.
- Gabapentin may also be used as an effective initial approach, taking into account medication affordabilitiy, comorbidities, and potential drug interactions

Treatment

- Although not specifically approved by the U.S. Food and Drug Administration for painful diabetic neuropathy, tricyclic antidepressants may be effective for neuropathic pain
- Use with caution given the higher risk of serious side effects

Pregabalin (Lyrica)

- Binds to alpha-2-delta subunit of voltage-gated calcium channels within the CNS and modulates calcium influx at the nerve terminals, thereby inhibiting excitatory neurotransmitter release
- Majority of studies demonstrated proportion of responders with at least 30%–50% improvement in pain
- dose response effect, with a weaker effect with 300 vs. 600 mg/day
- However, not all trials with pregabalin have been positive, especially when treating advanced refractory pain

Duloxetine (Cymbalta)

- Selective norepinephrine and serotonin reuptake inhibitor
- Doses of 60 and 120 mg/day showed efficacy in the treatment of pain associated with DSPN in multicenter randomized trials (but some of these had a higher high drop-out rate)
- Duloxetine was also suggested to induce improvement in neuropathy-related quality of life
- In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo

Gabapentin

- Binds to alpha-2-delta subunit of voltage-gated calcium channels
- requires gradual titration
- doses up to 1,800–3,600 mg are generally needed to be clinically effective

Other agents

- Tricyclic antidepressants
- Selective serotonin/norepinephrine reuptake inhibitors
- Topical therapies (limited data)
  - Capsaicin→ analgesia through local depletion of substance P
  - Lidocaine patches
  - TENS (transcutaneous electical nerve stimulation)
  - Acupuncture
- Alpha lipoic acid – antioxidant effects?

Comorbidities to consider for drug selection

Drug Class	Comorbidities favoring use	Comorbidities favoring avoidance
SNRIs - Duloxetine* - Venlaxfaxine	Depression Anxiety	Restless legs syndrome Sexual dysfunction (venlafaxine) Angle-closure glaucoma
TCAs - Amitryptyline - Nortriptyline - Desipramine	Depression Anxiety Insomnia	Cardiac disease Prolonged QTc Orthostatic hypotension Sexual dysfunction Urinary retention Angle-closure glaucoma
Gabapentinoid anticonvulsants - Pregabalin* - Gabapentin	Restless legs syndrome Essential tremor Insomnia	Substance abuse Peripheral edema Chronic obstrucive pulmonary disease

*FDA approved for painful diabetic neuropathy

Cardiovascular Autonomic Neuropathy

- Prevalence increases with diabetes duration
- Independent risk factor for cardiovascular mortality, arrhythmia, silent ischemia, any major cardiovascular event, and myocardial dysfunction

Cardiovascular Autonomic Neuropathy: Signs / symptoms

- Resting Tachycardia
- Abnormal blood pressure regulation
- Orthostatic hypotension
  - Light-headedness
  - Weakness
  - Faintness
  - Visual impairment
  - Syncope
- Orthostatic tachycardia or bradycardia
- Exercise intolerance

Treatment-induced neuropathy

- “insulin neuritis”
- Small-fiber neuropathy caused by abrupt improvement in glycemic control after prolonged chronic severe hyperglycemia

Summary

- DSPN is extremely common
- Diabetic neuropathies can affect multiple organ systems, resulting in a wide variety of symptoms
- Screening and prevention are critical, as treatment options are few and may be of limited efficacy

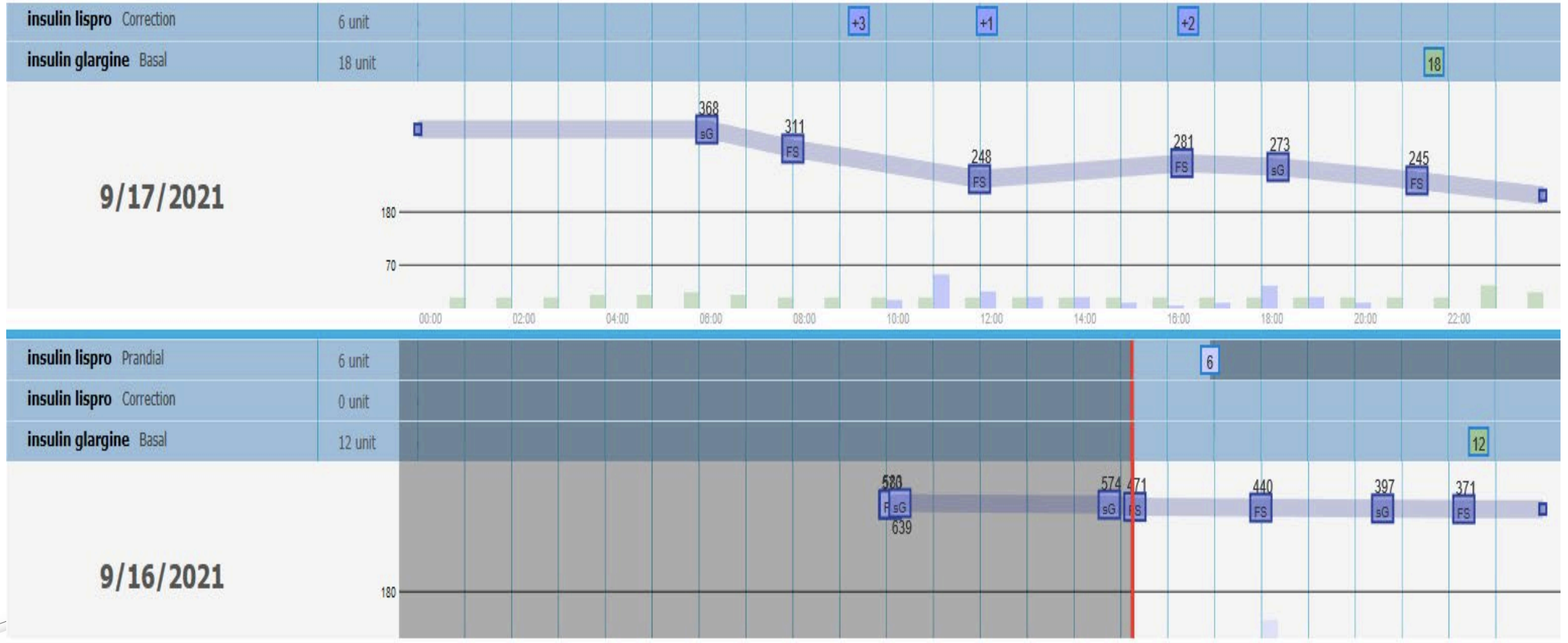
Case Study #1

72 yo M with EtOH use disorder and decompensated cirrhosis, psoriasis on immunomodulator therapy, HTN, hyperlipidemia

-presented to ED with polyuria and polydipsia, 10 pound weight loss over 4 months, current weight 60kg, BMI 22.1

-Labs: Na 124, Cr 2.43, glucose 639, CO2= 24, anion gap 12

Case Study #1


insulin lispro Correction
6 unit
insulin glargine Basal
18 unit
+3
+1
+2
18
9/17/2021
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311
FS
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FS
281
FS
273
sG
245
FS
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insulin lispro Correction
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440
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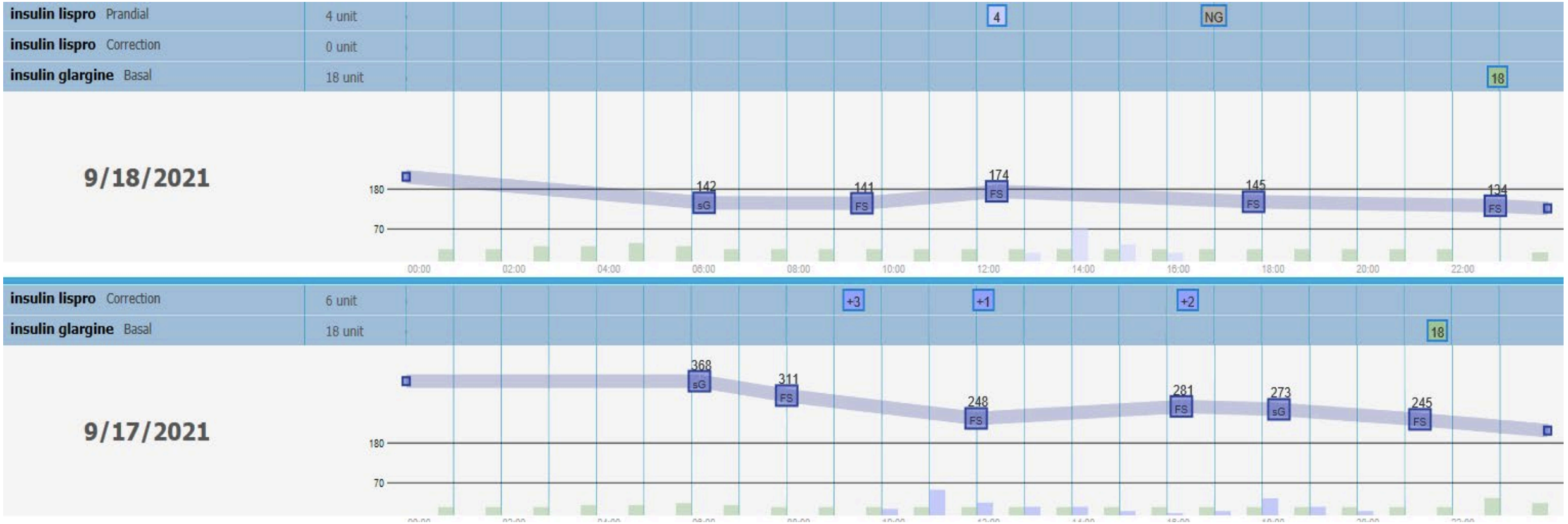
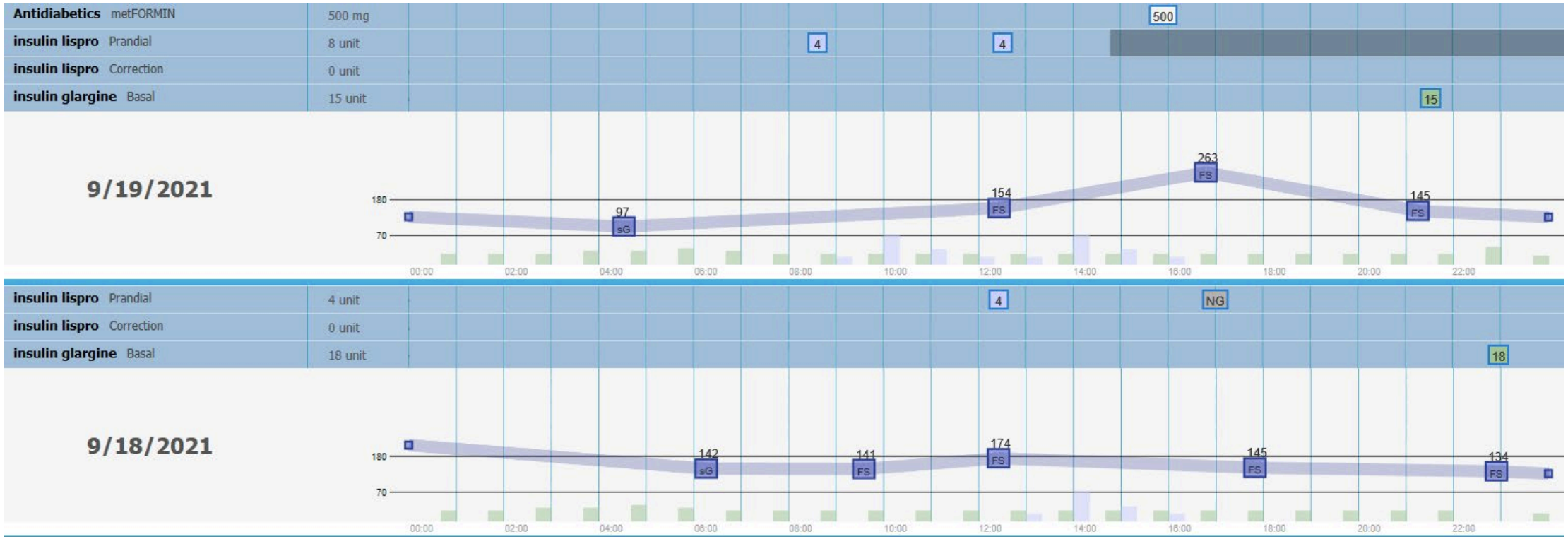
9/16/2021
180

Case Study #1



Cr 2.44 (GFR 29) in ER → improved to Cr 1.31 (GFR 62)

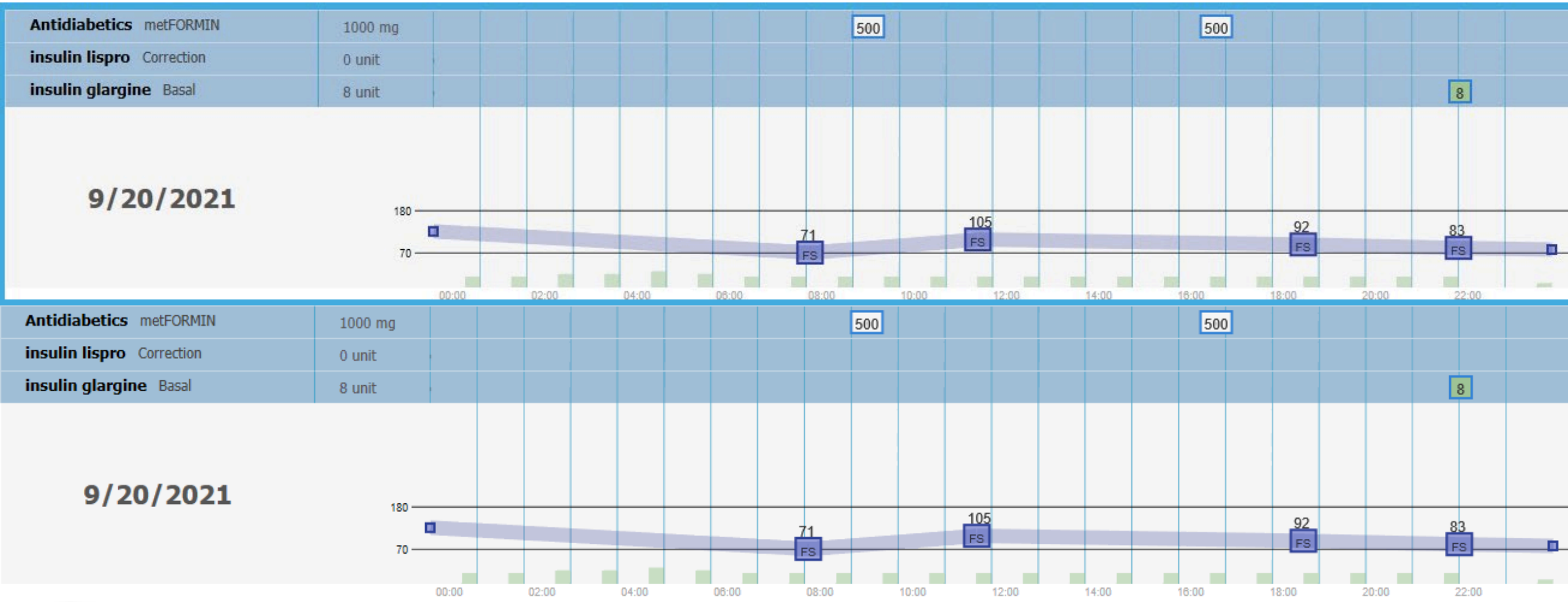
Case Study #1



Any clarifying questions?

Any suggestions?

Case Study #1



Antidiabetics metFORMIN
1000 mg
insulin lispro Correction
0 unit
insulin glargine Basal
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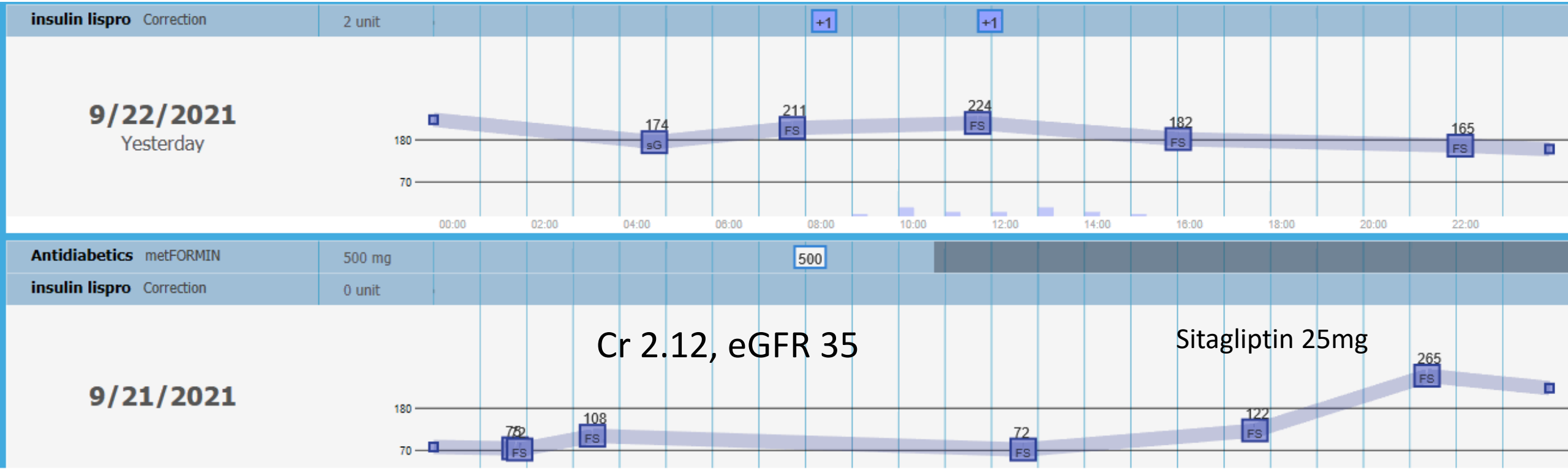
Case Study #1


insulin lispro Correction
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224
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Antidiabetics metFORMIN
500 mg
500
insulin lispro Correction
0 unit
Cr 2.12, eGFR 35
Sitagliptin 25mg
9/21/2021
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FS
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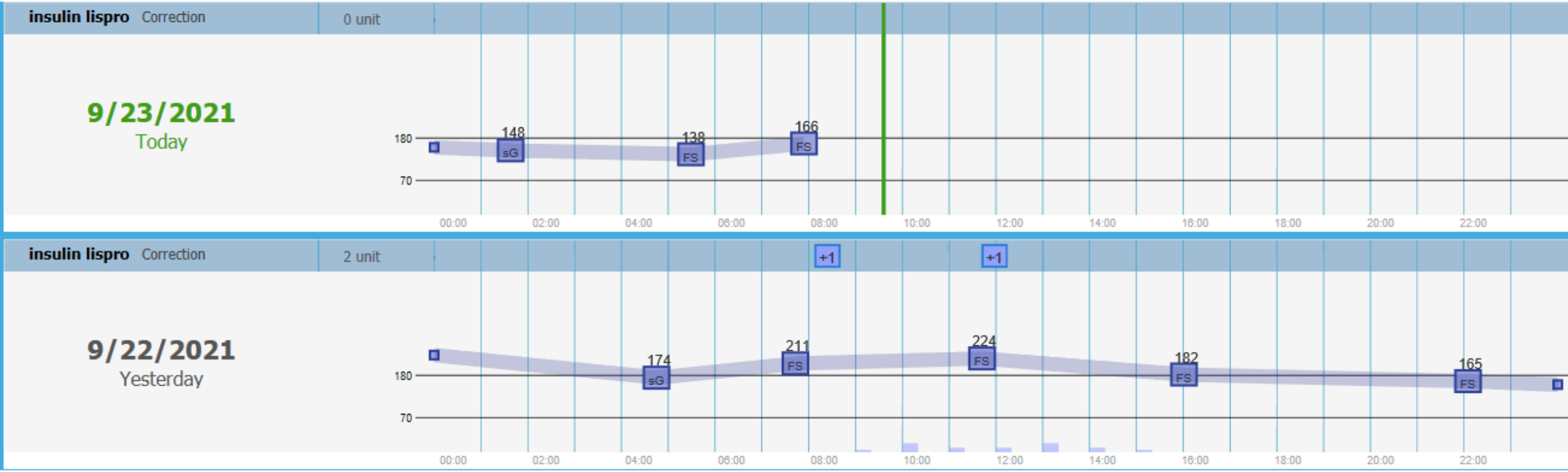
FS

Case study #1


insulin lispro Correction
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insulin lispro Correction
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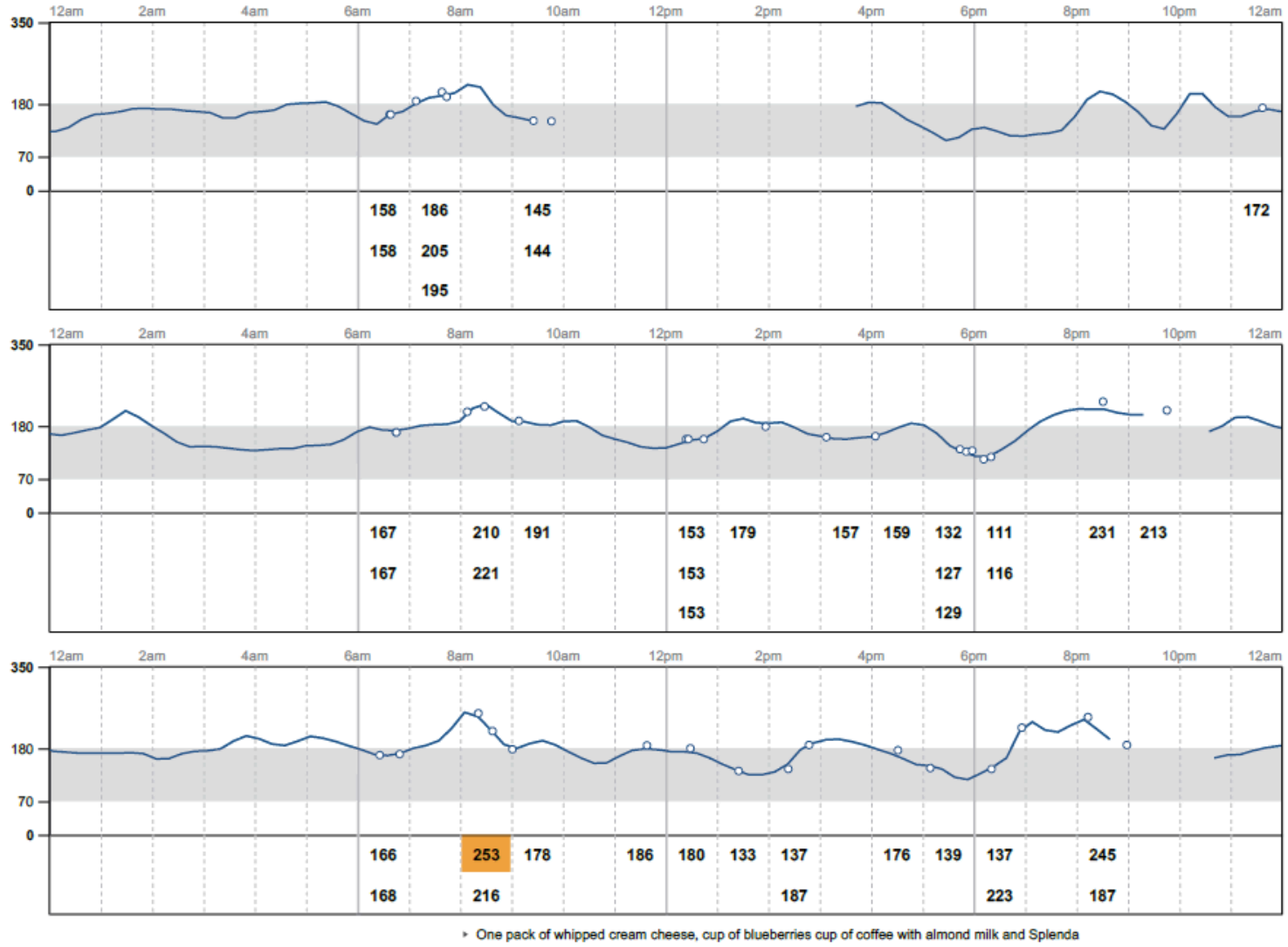
Case #2

61-year-old gentleman, with type 2 diabetes x 6 years, HTN, OSA, hyperlipidemia, BMI 35.57, today's A1c 8.1%, improved from > 10% 2 years ago when on metformin and glipizide.

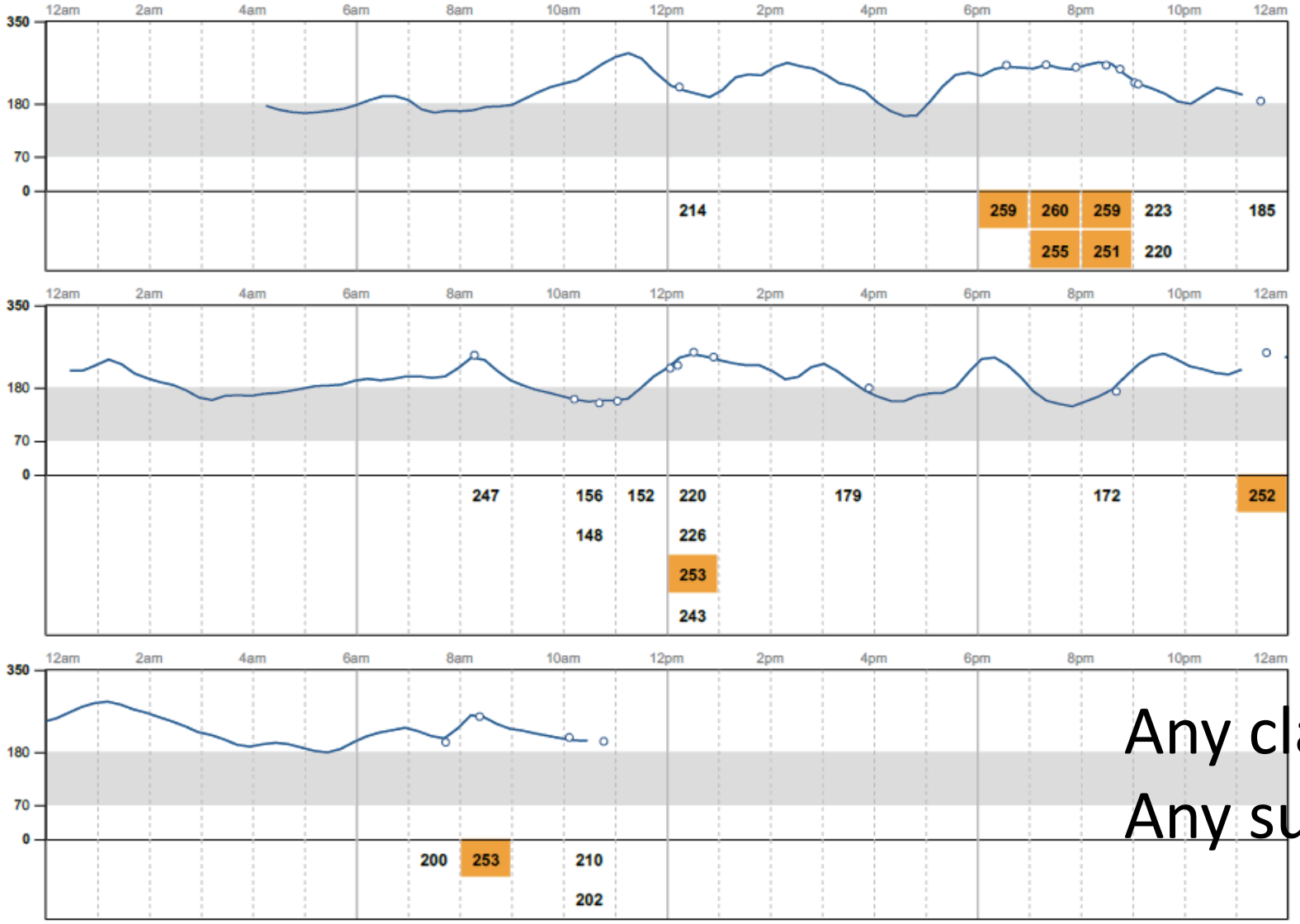
- Working very hard on healthy nutrition, some weight loss which has plateaued last 3 months, difficulty with increasing physical activity,
- Diabetes medications:
  - dulaglutide 4.5mg weekly
  - empagliflozin 25mg weekly
  - metformin ER 500mg daily, unable to tolerate higher doses

Case Study #2



▸ One pack of whipped cream cheese, cup of blueberries cup of coffee with almond milk and Splenda

Case Study #2



Any clarifying questions?
Any suggestions?

Case Studies

- Anyone can submit cases: www.vcuhealth.org/echodmhtn
- Receive feedback from participants and content experts
- Earn **$150** for submitting and presenting

Provide Feedback

www.vcuhealth.org/echodmhtn

- Feedback
  - Overall feedback related to session content and flow?
  - Ideas for guest speakers?

Access Your Evaluation

vcuhealth.org/services/telehealth/for-providers/education/diabetes-and-hypertension-project-echo

For Providers

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  - Virginia Opioid Addiction ECHO
  - Virginia Sickle Cell Disease ECHO

Diabetes and Hypertension Project ECHO

Welcome to the Diabetes and Hypertension Extension for Community Health Outcomes or ECHO, a virtual network of multidisciplinary diabetes and hypertension experts. An ECHO model connects professionals with each other in real-time collaborative virtual sessions on Zoom. Participants present de-identified cases to one another, share resources, connect to each other, and grow in their expertise. This ECHO will address practice level issues and solutions related to managing complex patients with difficult to control diabetes and hypertension. Register now for an ECHO Session!

Network, Participate and Present

- Engage in a collaborative community with your peers.
- Listen, learn and discuss informational and case presentations in real-time.
- Take the opportunity to submit your de-identified case study for feedback from a team of specialists for diabetes and hypertension.
- Provide valuable feedback.
- Claim CE credit by texting in attendance.

Benefits

VCU Diabetes & Hypertension Project ECHO Clinics

2nd and 4th Thursdays — ***NEW: 12 p.m. to 1 p.m.***

Mark Your Calendars — Upcoming Sessions

Oct. 14: Primary and Secondary Aldosteronism

Oct. 28: CGM Interpretation

Please register at www.vcuhealth.org/echodmhtn

Thank you for coming!

Text **19181-18817** to **804-625-4041** for CE credit

Reminder: Mute and Unmute to talk
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