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Abstract:

The GlycoMark® test measures 1,5-anhydroglucitol (1,5-AG), which is an indicator of hyperglycemic excursions over the prior 1-2 weeks in patients with diabetes. Circulating serum levels of 1,5-AG decrease in response to significant hyperglycemia because glycosuria interferes with 1,5-AG reabsorption in the kidney tubules. Significant hyperglycemia and resultant glycosuria causes 1,5-AG levels to fall below the normal range (~10 µg/mL), and persistent glycosuria is associated with very low 1,5-AG levels, less than or equal to 2 µg/mL. SGLT2 inhibitors elicit their effect by blocking glucose reabsorption, causing persistent glycosuria. A survey of clinical laboratory results by GlycoMark, Inc. in 2014 indicated that 13% of the GlycoMark 1,5-AG tests produced results of 2 µg/mL or less (unpublished, data on file). We hypothesized that the use of SGLT2 inhibitors (SGLT2i) would produce a high frequency of GlycoMark 1,5-AG results less than 2 µg/mL. A review of GlycoMark 1,5-AG measurements performed between January 2015 - December 2018 from 292 patients that were prescribed SGLT2i was performed. 52 patients were found to not be taking an SGLT2i at the time of the 1,5-AG measurement. From the 240 patients taking SGLT2i, the average GlycoMark 1,5-AG level was 1.2 µg/mL and 92% of patients had GlycoMark 1,5-AG values less than or equal to 2 µg/mL. From the 52 patients not taking SGLT2i, the average GlycoMark 1,5-AG level was 6.4 µg/mL and only 12% of patients had GlycoMark 1,5-AG values less than or equal to 2 µg/mL. The results of this analysis indicate that the majority of patients with diabetes that are taking SGLT2i have very low GlycoMark 1,5-AG results, which reflects the persistent glycosuria caused by the SGLT2i. In patients taking SGLT2i, a GlycoMark 1,5-AG result of 2 µg/mL may be useful as an indicator of the SGLT2i effect, particularly in patients with moderate to good glycemic control (HbA1c ≤ 8%). Additionally, the results suggest that GlycoMark test measurements above 2 µg/mL should be investigated for non-compliance, interference with, or reduced effectiveness of SGLT2i.

Background:

1,5-AG is a marker of glycosuria associated with hyperglycemic excursions above the renal threshold

- Specific for hyperglycemic excursions within the prior 1-2 weeks
- Changes more rapidly than A1C in response to changes in glycemic control

1,5-AG levels are widely considered to be a useful indicator of post-prandial hyperglycemia

- Post-prandial hyperglycemia is the major influencer of HbA1c levels when HbA1c ≤ 8%
- 1,5-AG levels are typically very low when HbA1c is very high, due to persistent hyperglycemia

SGLT2 inhibitors (SGLT2i) function by blocking glucose reabsorption in the kidney, which causes glycosuria

Very low GlycoMark 1,5-AG levels (anecdotally, ≤ 2.0 µg/mL) have been routinely observed in patients taking SGLT2i, and may be a useful indicator of SGLT2i effect and compliance

Hypothesis:

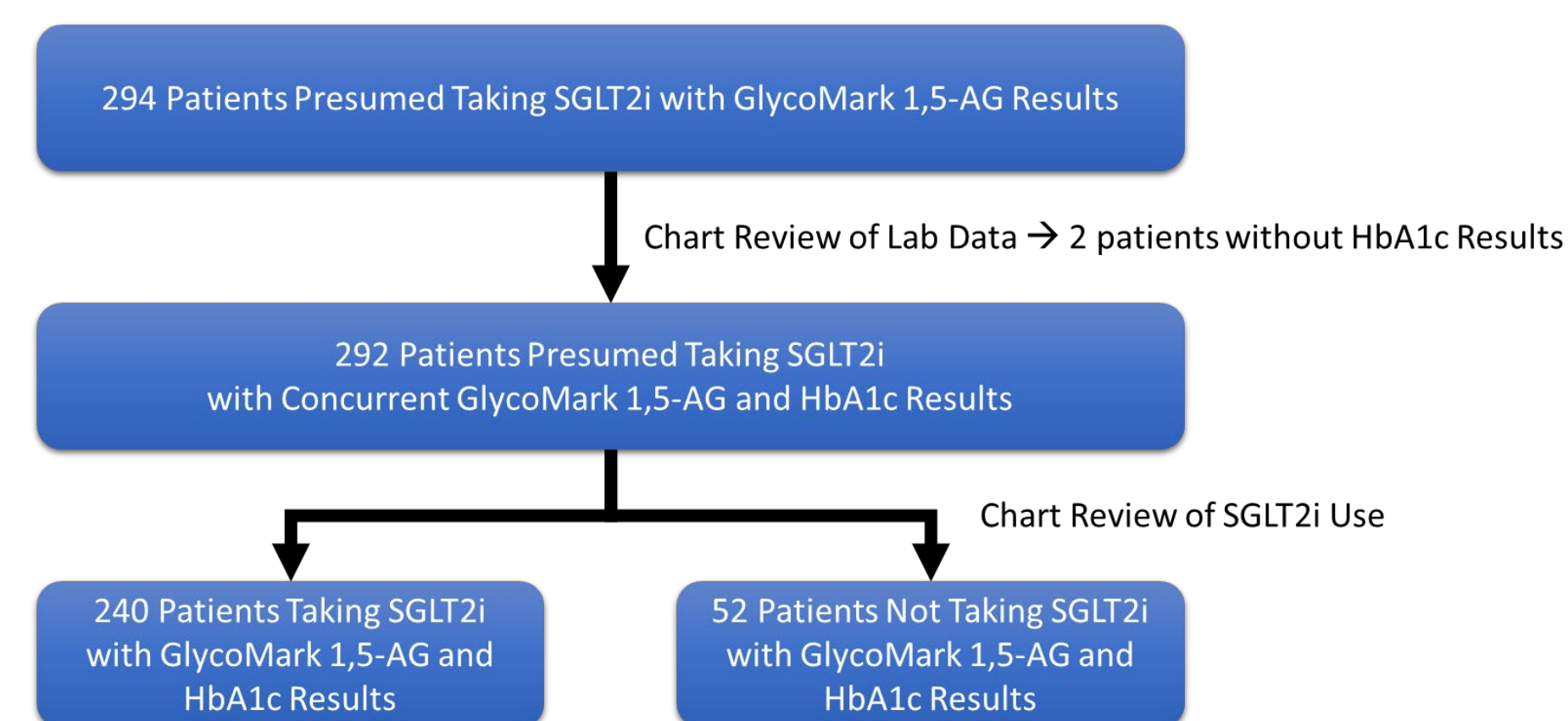
If very low GlycoMark 1,5-AG levels are predictive of SGLT2i use (independent of A1C levels), the following must be true:

- GlycoMark 1,5-AG levels ≤ 2.0 µg/mL are highly sensitive and specific for SGLT2i use
- GlycoMark 1,5-AG levels are more predictive of SGLT2i use than HbA1c
- GlycoMark 1,5-AG levels ≤ 2.0 µg/mL are more specific for SGLT2i use in patients whose HbA1c is ≤ 8%, compared to patients whose HbA1c > 8%

Methods:

- Male and female patients with diabetes that were prescribed SGLT2i with concurrent GlycoMark 1,5-AG measurements between January 2015 – December 2018 were selected for analysis
- Chart review was performed to confirm SGLT2i use at the time of the 1,5-AG measurement
 - Subjects were stratified as SGLT2i users or non-users at the time of the 1,5-AG measurement
 - Subjects with 1,5-AG measurements before initiating SGLT2i that had a later, on-treatment 1,5-AG measurement had the later, on-treatment measurements used.
- Basic demographic information, eGFR, BMI, and HbA1c measurements concurrent with 1,5-AG measurements were also recorded

Patient Selection:



Data Analysis:

292 subjects were included in the analysis

- 240 using SGLT2i at the time of their 1,5-AG and HbA1c measurements
- 52 not using SGLT2i at the time of their 1,5-AG and HbA1c measurements

All analyses were performed using Analyse-it for Microsoft Excel version 5.11

ROC curve analysis was performed to characterize discriminatory ability of 1,5-AG to detect SGLT2i use (overall and stratified by HbA1c levels)

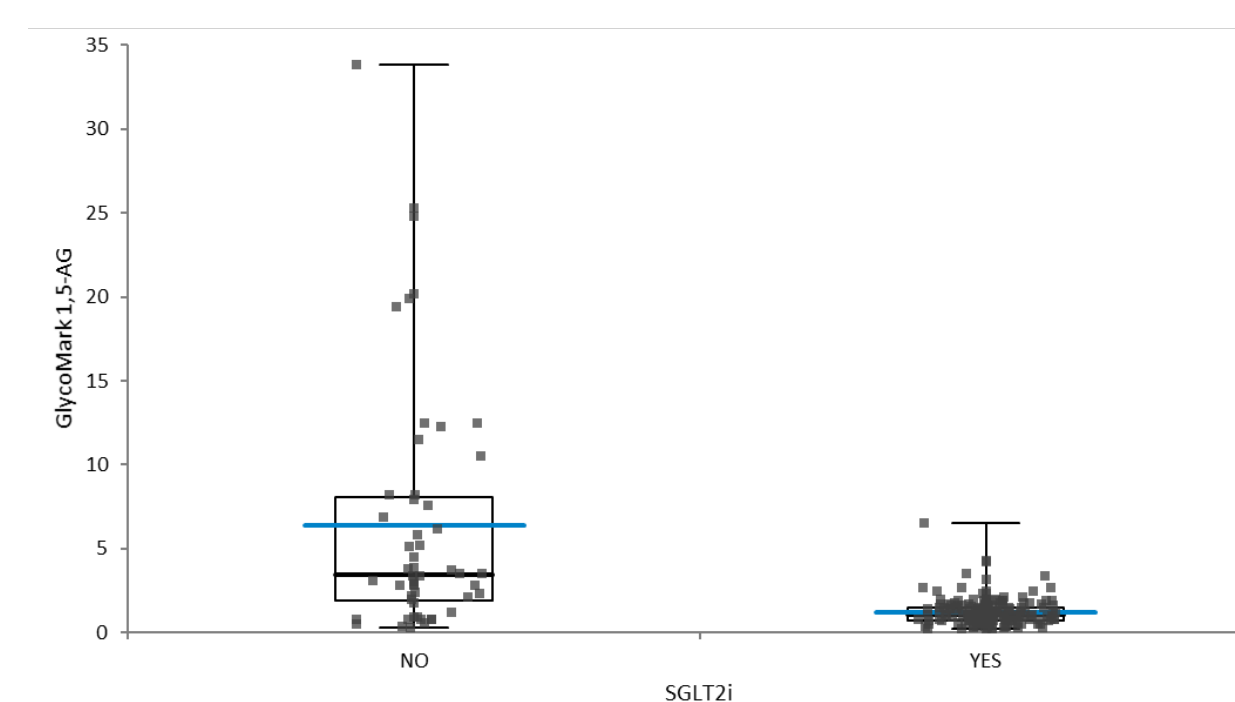
Optimal cutoff was determined by calculating the highest Youden J-statistic

Diagnostic performance of 1,5-AG ≤ 2.0 µg/mL was performed by calculating sensitivity, specificity, positive predictive value, negative predictive value, J-statistic, and odds ratio

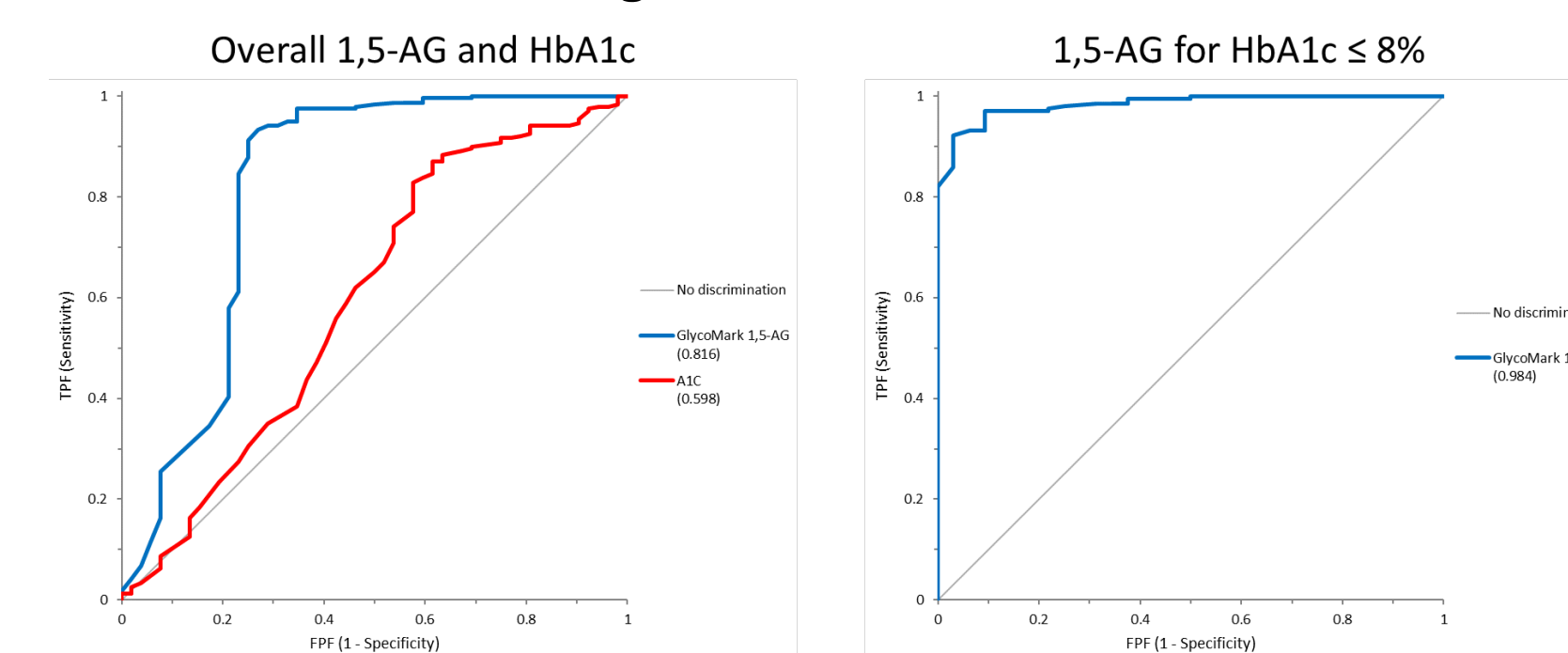
Results:

Variable	SGLT2i Users	SGLT2i Non-users	P-value
Age	57.1 ± 11.5	55.3 ± 13.2	0.3464
% Female	35.4	30.7	0.5230
eGFR (mL/min; mean ± SD)	85.9 ± 17.7	86.8 ± 20.5	0.7878
BMI (kg/m ² ; mean ± SD)	32.1 ± 6.3	33.2 ± 7.2	0.1725
HbA1c (%; mean ± SD)	7.0 ± 1.5	7.8 ± 2.3	0.0267
1,5-AG (µg/mL; mean ± SD)	1.2 ± 0.7	6.4 ± 7.4	< 0.0001

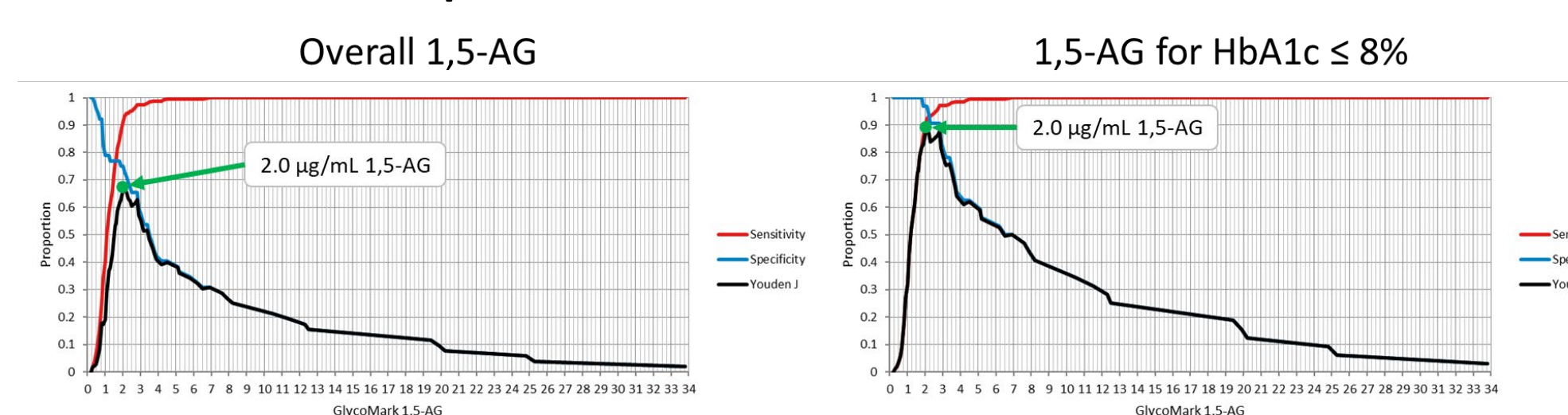
1,5-AG Levels by SGLT2i Use



ROC Curves for Discriminating SGLT2i Use



Determination of Optimal 1,5-AG Cutoff:



The optimal cutoff in both cases is 1,5-AG ≤ 2.0 µg/mL

Diagnostic Performance for 1,5-AG ≤ 2.0 µg/mL to Identify SGLT2i Use, Stratified by HbA1c Level

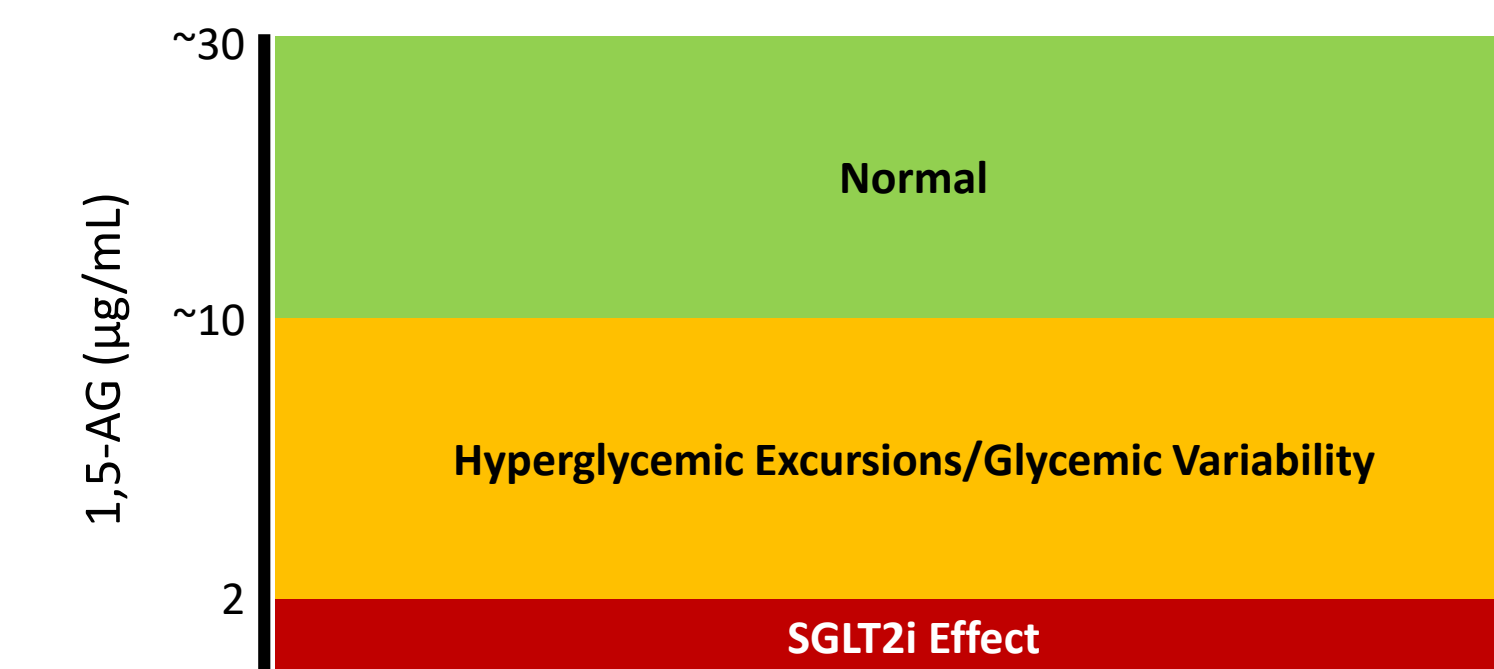
HbA1c Level	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	J-Statistic (95% CI)	Odds Ratio (95% CI)
HbA1c ≤ 10% (N = 268)	0.929 (0.888-0.956)	0.881 (0.750-0.948)	0.973 (0.941-0.988)	0.729 (0.624-0.814)	0.810 (0.638-0.904)	97.1 (34.2-273.4)
HbA1c ≤ 9% (N = 259)	0.927 (0.885-0.955)	0.923 (0.797-0.973)	0.982 (0.949-0.994)	0.733 (0.630-0.816)	0.850 (0.682-0.928)	153.0 (44.4-518.6)
HbA1c ≤ 8% (N = 238)	0.922 (0.878-0.952)	0.969 (0.843-0.994)	0.993 (0.952-0.999)	0.730 (0.627-0.813)	0.891 (0.721-0.946)	368.1 (58.4-2245.9)
HbA1c ≤ 7% (N = 182)	0.904 (0.847-0.941)	0.962 (0.811-0.993)	0.991 (0.941-0.999)	0.684 (0.571-0.779)	0.865 (0.658-0.934)	83.0 (12.4-531.8)
HbA1c ≤ 6.5% (N = 133)	0.885 (0.813-0.932)	0.950 (0.764-0.991)	0.988 (0.924-0.998)	0.641 (0.515-0.751)	0.835 (0.577-0.923)	60.4 (16.4-217.4)

ROC Curves for Discriminating SGLT2i Use: Overall and Stratified by HbA1c

Condition	AUC	95% CI		Difference	
		Low	High	AUC	95% CI
1,5-AG (Overall, N = 292)	0.816	0.729	0.903	0.218*	0.058 – 0.379
HbA1c (Overall, N = 292)	0.598	0.503	0.693		
1,5-AG (HbA1c ≤ 10%, N = 268)	0.932	0.876	0.989	0.200	-0.015 – 0.416
1,5-AG (HbA1c > 10%, N = 24)	0.732	0.524	0.940		
1,5-AG (HbA1c ≤ 9%, N = 259)	0.963	0.924	1.001	0.274*	0.083 – 0.465
1,5-AG (HbA1c > 9%, N = 33)	0.688	0.502	0.875		
1,5-AG (HbA1c ≤ 8%, N = 238)	0.984	0.970	0.998	0.201*	0.066 – 0.335
1,5-AG (HbA1c > 8%, N = 54)	0.783	0.649	0.917		
1,5-AG (HbA1c ≤ 7%, N = 182)	0.976	0.957	0.996	0.260*	0.124 – 0.396
1,5-AG (HbA1c > 7%, N = 110)	0.716	0.581	0.851		
1,5-AG (HbA1c ≤ 6.5%, N = 133)	0.972	0.946	0.998	0.224*	0.100 – 0.349
1,5-AG (HbA1c > 6.5%, N = 159)	0.747	0.626	0.869		

Potential Interpretation of GlycoMark 1,5-AG in Patients with HbA1c ≤ 8%

- 1,5-AG levels in the normal range indicate good glycemic control and no SGLT2i use
- 1,5-AG levels below the normal range but above 2.0 µg/mL indicate the presence of recent hyperglycemic excursions and/or glycemic variability and no SGLT2i use
- 1,5-AG levels ≤ 2.0 µg/mL indicate SGLT2i use



Conclusions:

- 1,5-AG ≤ 2.0 µg/mL is better than HbA1c at identifying the effect of an SGLT2 inhibitor
 - As expected, because 1,5-AG levels are influenced by glycosuria, which is the mechanism of action of SGLT2i
- The diagnostic performance of 1,5-AG to identify SGLT2i use was best in patients with HbA1c ≤ 8%
- In patients with HbA1c ≤ 8%, a level of 1,5-AG ≤ 2.0 µg/mL strongly indicates the presence of SGLT2i
- 1,5-AG levels are abnormal to a greater extent than expected for post-prandial hyperglycemia without SGLT2i use.
- 1,5-AG levels may be useful for assessing SGLT2i effect and patient compliance