Selecting an A1C Point-of-Care Instrument

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ABSTRACT

A1C point-of-care (POC) instruments benefit patients with diabetes by facilitating clinician decision making that results in significant glycemic improvements. Three National Glycohemoglobin Standardization Program (NGSP)–certified POC products are available in the United States: the handheld A1CNow (formerly manufactured by Bayer Diabetes Care but now made by Chek Diagnostics) and two bench-top models called the Axis-Shield Afinion Analyzer and the Siemens DCA Vantage. This article compares the three available NGSP-certified POC products in terms of accuracy, precision, ease of use, cost, and additional features. Its goal is to aid health care facilities in conveniently identifying the A1C POC product that best meets their needs. It additionally reviews evidence that supports the continued use of A1C POC instruments in the clinical arena.

Technology has developed to assist health care providers with decision-making for diagnosing, treating, and managing patient care. When first introduced, point-of-care (POC) instruments were considered a supplementary feature to clinical laboratory testing (1). Today, they are used for a variety of diagnostic tests and therapeutic monitoring purposes (2). POC testing provides onsite, immediate results that minimize the delay associated with conventional laboratory measures and reduce the need for additional office visits to implement clinical decisions (3).

The provision of immediate results by A1C POC devices has demonstrated benefits for patient care encounters. Compared to traditional laboratory A1C testing, POC devices allow providers to more quickly evaluate the efficacy of diabetes treatment and influence health outcomes (4). Collectively, this aids efforts to lower patients' future A1C values, specifically for patients with poor glycemic control, by facilitating timely therapeutic modifications (4–6).

There are three National Glycohemoglobin Standardization Program (NGSP)-certified POC A1C devices available in the United States for use by health care facilities: the handheld A1CNow and two bench-top models called the Axis-Shield Afinion and the Siemens DCA Vantage (7). In September 2013, Bayer Diabetes Care announced that it was terminating production of the widely used A1CNow+ and A1CNow SELFCHECK At-Home (the only handheld A1C POC device available for personal use [8]), which were introduced to the market in 2005 (9); distribution was expected to end in late 2014 (10). However, Chek Diagnostics later acquired the A1CNow product family and has resumed production (11). In addition to the handheld device, the two bench-top models (Afinion Analyzer and DCA Vantage) remain on the market. This article compares the three NGSP-certified A1C POC options

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to help guide health care facilities in selecting the most appropriate product for their needs.

Performance

Accuracy and Precision

The ability of a POC instrument to most closely replicate the actual A1C of any given patient is paramount (12). Since its development in 1996 under the direction of the American Association for Clinical Chemistry, the NGSP has been the authority in establishing guidelines and protocols for standardizing A1C testing for both POC and laboratory instruments to Diabetes Control and Complications Trial (DCCT)-equivalent values (7,13). The DCCT, a primary-prevention cohort study, established the direct relationship between A1C and long-term complication risk in patients with type 1 diabetes (14). To ensure continued accuracy, the NGSP requires annual manufacturer certification, during which the A1C assay device must be tested in a 40-sample comparison against an NGSP secondary reference laboratory in a controlled environment. The 40 individual samples are distributed over an A1C range of 4–10%. Certification results when at least 37 of the 40 samples fall within 6% (lowered from ±15% in 2007) of the NGSP secondary reference laboratory values (7). This tight criterion provides practitioners confidence in the accuracy and precision of these devices under "optimal conditions" (9,15). Based on the stringent criterion set by the NGSP and its alignment with DCCT results, the American Diabetes Association (ADA) endorsed the NGSP and specifically recommends that laboratories use only methods that have passed NGSP certification (13,16,17). As of March 2014, the Bayer (now Chek Diagnostics) A1CNow, Siemens DCA Vantage, and Axis-Shield Afinion were the only three NGSP-certified A1C POC devices.

The College of American Pathologists (CAP) also conducts biannual proficiency testing of A1C instruments (18). Contrary to the NGSP annual certification, which demonstrates accuracy under optimal and standardized conditions, the CAP glycohemoglobin (GH2) survey provides information about accuracy and precision when assay methods are used in clinical and realistic environments, including potential influence caused by end-users. In the CAP program, three pooled, whole-blood reference samples consistent with a low, medium, and high A1C level are mailed to ~2,000 participating individual clinical laboratories, which then analyze them in the same manner they would patient samples and return the results to CAP (19). In the past 5 years (thus for 10 surveys), the low reference A1C range has been between 5.1 and 6.6%, the medium range between 5.65 and 7.6%, and the high range between 8.05 and 9.8%. As with the NSGP certification, two out of the three samples must demonstrate accuracy within 6% of the NGSP target values for any assay methods to pass the CAP survey. The survey reports each assay's mean A1C, mean bias (i.e., accuracy, the difference between the mean A1C and the NGSP reference value), and confidence of variance (CV) (i.e., imprecision) as it relates to inter-laboratory values. Although no device is ideal (i.e., with zero imprecision and perfect accuracy to the target value), the lower the CV and mean bias, the better. Although the NGSP has not set forth goals for precision and accuracy, it does recommend a mean bias of <0.2 (19) and CV <3% (preferably <2%) (19) while noting that less acceptable assay methods are those with a mean bias of >0.3 and CV >5% (18,19). Comparatively, the ADA recommends a CV <4%, and ideally <3% (17).

According to the CAP survey conducted in December 2013, the Bayer A1CNow, which was analyzed at 13 laboratories, performed with a higher-than-preferred mean bias and CV for all three reference values (Table 1). Although these data suggest lack of both accuracy and precision, EDTA (ethylenediaminetetraacetic acid) contained in all of the samples reportedly interferes with the assay methodology used in the device (18). Therefore, the CAP survey data specifically regarding mean bias of the A1CNow has little usefulness. However, an individual 2013 study using three reagent lots demonstrated improved CV (range 2.1–3.2%) and mean bias (approximately ±0.5%) for the A1CNow compared to CAP data (9).

The Afinion and DCA Vantage both performed to a much greater level of accuracy and precision through all three reference samples in the CAP survey (18). The Afinion demonstrated slightly better accuracy at the lower ranges and better precision at the higher target, whereas the DCA Vantage demonstrated slightly better precision at lower ranges and better accuracy at the higher target. Because the DCA Vantage and Afinion both closely replicated the true reference A1C values with reasonable precision as well, performance differences between the two bench-top POC instruments, according to this survey, are negligible and likely would not alter patient care.

A1C reporting ranges for the DCA Vantage (2.5–14.0%) (20) and Afinion (4.0–15.0%) (21) are wider than those of A1CNow (4–13.0%) (22), which expands their utility in patient care. However, NGSP certification verifies accuracy of instruments up to an A1C of 10% (7). Similarly, the CAP survey has not tested instrument performance at A1C values >9.8% in recent years (18). This seemingly undocumented performance above A1C values >10% should not raise concerns; manufacturers are required to periodically document their linearity and verify calibration to the upper limit of their reportable range.

TABLE 1. Performance Data for NGSP-Certified A1C POC Devices

Assay Method	Labs (*n*)	NGSP A1C Reference Value (95% CI)								
		5.30 (5.26–5.34)			6.14 (6.10–6.18)			8.05 (8.01–8.09)		
		Mean A1C (%)	Mean bias	CV (%)	Mean A1C (%)	Mean bias	CV (%)	Mean A1C (%)	Mean bias	CV (%)
Bayer A1CNow*	13	4.95	–0.35	4.6	5.70	–0.44	5.5	7.43	–0.62	5.7
Axis-Shield Afinion	34	5.25	–0.05	2.8	6.04	–0.10	3.1	7.64	–0.41	2.4
Siemens DCA Vantage	258	5.21	–0.09	2.3	6.03	–0.11	2.5	7.84	–0.21	2.7

Adapted from ref. 18.

**EDTA in the CAP sample has been shown by the manufacturer of A1CNow to cause artificially low results by this method. Routine samples for this method are from fingerstick and do not include EDTA. The manufacturer recommends the use of heparin anticoagulant instead of EDTA when testing venous samples.*

Assay Methodology

All three NGSP-certified POC devices quantify A1C based on structural differences (e.g., boronate affinity chromatography and immunoassays) rather than charge (e.g., cation-exchange chromatography and agar-gel electrophoresis) (13). The A1CNow and DCA Vantage use an immunoassay based on antibodies binding to glycated hemoglobin tetrapeptide or hexapeptide molecules. The Afinion uses borate affinity chromatography, which measures the total percentage of glycation (7,19). Neither assay method has demonstrated superiority (13); therefore, assay methodology should have no bearing on device selection decisions (23).

Sources of Interference

According to the NGSP, hemoglobin variants such as hemoglobin C (HbC), D (HbD), E (HbE), and S (HbS) cause assay interference in slightly more than half of laboratory and POC A1C instruments (24). Specific to NGSP-certified POC devices, neither the Afinion nor the DCA Vantage are affected by HbC, HbD, HbE, or HbS, but both are influenced by fetal hemoglobin (HbF). The Bayer A1CNow is unbiased by HbD and HbE, but is influenced by HbC, HbS, and HbF (24).

More than 300,000 Americans with diabetes carry the trait for HbC or HbS (25). Many are unaware of their carrier status, which is usually asymptomatic (12). The A1CNow exhibits a statistically and clinically significant positive bias in the presence of either HbC or HbS traits (12,25). This inaccuracy of interference could potentially result in unnecessary increased pharmacotherapy and hypoglycemic risks.

Normally, HbF levels are <1%. However, abnormal concentrations can remain elevated or increase in neonates, hereditary persistence of fetal hemoglobin (HPFH), thalassemias, late pregnancy, and patients with abnormal Hb variants (19). HbF is composed of two α and two γ chains, compared to two α and two β chains in normal HbA. This conformational change hinders the ability of antigenic sites on immunoassays to effectively recognize glycated HbF, although it has a slower glycation rate than HbA (19). During A1C analysis, nonglycated HbF contributes to the total hemoglobin assay estimate (19). Therefore, immunoassays used in patients with significantly elevated HbF (>10%) will receive falsely low results (19), which can result in unintentional clinical inertia. Samples analyzed by the DCA 2000, a Siemens floor-model product with similar immunoassay components to the DCA Vantage, are falsely elevated when HbF is >10% (26) and result in a clinically significant impact on patient care when it is >20% (27). Data are not available regarding interference caused by HbF on the Afinion or A1CNow analysis; the NGSP recommends assuming that both immunoassay and boronate affinity methods are influenced by HbF levels >10–15% (24).

Whereas an overestimation of A1C, which occurs in the A1CNow by HbC or HbS, could result in overly aggressive treatment, with a consequent increase in the risk of hypoglycemia (12), an underestimation caused by HbF with all three A1C POC assays can result in inadvertently under-treating hyperglycemia. Regardless of the direction of inference, it is important for end-users to be aware of potential influence by specific hemoglobin variants.

Device Size

Each device consists of a base unit and cartridge, including a capillary sampling device and a reagent cartridge. The two cartridge components are packaged separately for the A1CNow and the DCA Vantage, whereas they are integrated into one package for the Afinion. The A1CNow requires a 5-µL sample (22), whereas the DCA Vantage uses much smaller samples (1 and 1.5 µL, respectively [20,21]), which are more similar to volume requirements for blood glucose meters (0.8 µL). The reduced blood sam-

ple size requirements for the DCA Vantage and Afinion offer greater ease of use for office personnel, according to the manufacturer labels (20,21).

The handheld A1CNow base unit is easily transported to clinic exam rooms. Conversely, the Afinion and DCA Vantage are bench-top models with similar base unit profiles (Table 2) and are not convenient for room-to-room transportation. Blood samples collected in the DCA Vantage cartridge are stable for 5 minutes (20), compared to 3 minutes for the Afinion cartridge (21). Therefore, for logistical purposes of maintaining sample stability, physically larger or busier clinics may choose to collect patients' blood samples in the same room in which the base unit sits rather than collecting samples in exam rooms and quickly transferring them to the base unit for analysis. Alternatively, blood samples may be collected using a purple-top tube for later testing, or an additional base unit could be purchased to prevent sample degradation during wait time.

Ease of Use

Reagent stability varies among the POC A1C devices. Unopened Afinion and DCA Vantage test cartridges are stable for 3 months at room temperature (20,21), compared to 4 months with the A1CNow (22). Stability of all product cartridges can be extended to the package expiration date when refrigerated (20–22). Additionally, test cartridges have a brief shelf life once opened. Once exposed to room air, the reagent cartridge package must be used 10 minutes with the Afinion, 5 minutes with the DCA Vantage, and 2 minutes with the A1CNow (20–22).

For health care facilities, one A1CNow box contains a disposable handheld device, 20 test cartridges, and 20 sample dilution kits. The device turns on automatically when a cartridge is inserted into the handheld bases. A blood sample is then

TABLE 2. Comparison of NGSP-Certified A1C POC Devices

Characteristic	Bayer A1CNow (22)	Axis-Shield Afinion (21)	Siemens DCA Vantage (20)
Physical size	• Disposable, portable, handheld • Dimensions: ○ Depth: 6.35 cm (2.5 in) ○ Height: 1.0 cm (0.4 in) ○ Width: 5.1 cm (2.0 in) ○ 0.18 kg (0.4 lb)	• Bench-top unit • Dimensions: ○ Depth: 34 cm (13.4 in) ○ Height: 17 cm (6.7 in) ○ Width: 19 cm (7.4 in) ○ Weight: 5 kg (11 lb)	• Bench-top unit • Dimensions: ○ Depth: 27.7 cm (10.5 in) ○ Height: 25.4 cm (9.0 in) ○ Width: 28.7 cm (11.5 in) ○ Weight: 3.88 kg (9 lb)
Assay methodology	Immunoassay	Boronate affinity separation	Immunoassay (latex agglutination inhibition)
Blood sample size (µL)	5	1.5	1
Analysis time (min)	5	3	6
Reporting A1C range (%)	4.0–13.0	4.0–15.0	2.5–14.0
Sources of interference (24)	HbF (when level is 10–15%) HbC HbS	HbF (when level is 10–15%)	HbF (when level is >20%)
Other quantitative tests (moderate complexity requiring quarterly proficiency testing)	None	• Albumin:creatinine ratio • Creatinine • C-reactive protein and cholesterol (not available in the United States)	• Albumin:creatinine ratio • Creatinine • Microalbumin

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TABLE 2. Comparison of NGSP-Certified A1C POC Devices, *continued from p. 204*

Storage	• Store the test kit refrigerated (2–8°C) until the expiration date or at room temperature (15–25°C) for up to 4 months. • Use the test cartridge within 2 minutes after opening the foil pouch.	• Store the test kit refrigerated (2–8°C) until the expiration date or at room temperature (15–25°C) for up to 3 months. • Use the test cartridge within 10 minutes after opening the foil pouch.	• Store the test kit refrigerated (2–8°C) until the expiration date or at room temperature (15–25°C) for up to 3 months. • Use the test cartridge within 5 minutes after opening the foil pouch.
Features	• Memory capacity: none • Display: black and white, nontouch • Power supply: battery • Calibration: none • Separate test cartridge and sampling device • Data export: none • Accessories: one	• Memory capacity: 500 patient results and 500 control results • Display: color touch • Power supply: AC/DC adapter • Calibration: none • Integrated test cartridge and sampling device • Data export: ○ USB flash drive ○ Ethernet port ○ RS232 • Accessories: barcode scanner, purchased separately	• Memory capacity: 4,000 patient and control records • Color touch display • Power supply: AC/DC adapter • Calibration: lot specific calibration card • Separate test cartridge and sampling device • Data export ○ USB flash drive ○ Ethernet port ○ Accessories: barcode scanner, onboard printer
Approximate cost per unit (prices vary by distributor)	$40 for unit with 2 cartridges (for the home-use version) $170 for unit with 20 cartridges	$3,500 for base station $120 for 15 single-use testing kits $60 for 2 control sets	$2,100–3,600 for base station $75 for 10 single-use testing kits $60 for 2 control sets
Company Internet address	http://www.ptsdiagnostics.com	http://www.axis-shield.com	http://www.siemens.com

extracted from the patient using the capillary sampling device, inserted into the shaker, and inverted six to eight times to mix and dilute the blood sample with a reagent solution. When the visual display on the device base prompts accordingly, the diluted blood sample may be ejected from the shaker onto the cartridge sample site. The A1C result is available in 5 minutes. The cartridge, shaker, and sampling device should be discarded, whereas the base unit is retained until all 20 kits are used. Control testing is not needed. However, users should verify that lot numbers on the device, cartridge, and dilution kit match (22).

Physical manipulation of the DCA Vantage and Afinion devices is quite different from the A1CNow. Both base units remain plugged into an electric socket and enter a power-safe mode when not in use. Both offer user-friendly touchscreen interfaces that automatically prompt for the next required task to help reduce operator error. The DCA Vantage onboard scanner is used for calibrating and verifying authenticity and expiration date of the cartridge before and immediately after every sample collection. Conversely, the Afinion does not require package or product scanning before use; however, a scanner can be purchased separately ($120) that can facilitate adding patient identifiers. With both benchtop devices, users should collect the blood sample using the capillary sampling device, insert the filled sampling device into the reagent cartridge, and then insert the reagent cartridge into the base unit for analysis. The A1C results are available in 6 minutes using the DCA Vantage and in 3 minutes using the Afinion. The DCA Vantage houses an onboard printer that can provide the A1C results coordinated with the patient's medical record number (20,21).

All three units are termed "walkaway" devices, which means the sample does not need interaction from the technician during processing. This allows the technician to

leave and perform other clinic-related duties during sample analysis (20–23). It should be noted that the A1CNow has no long-term memory of previously analyzed sample results. Thus, although it is considered a walk-away unit, the technician must return within 60 minutes to retrieve the result before the machine automatically shuts off, resulting in loss of data. Conversely, the Afinion and DCA Vantage, respectively, store up to 500 (21) and 4,000 (20) results of past analyzed samples, allowing for later retrieval of data by the administering technician.

Cost

Devices and services must be profitable for continued use within a health care system. Factors that determine affordability include initial capital costs, individual testing supply costs, reimbursement fees, and personnel operating time (28). Initial capital costs for the base unit are similar between the Afinion and DCA Vantage, depending on distributor (20,21). Some distributors, however, participate in a placement program, through which a base unit is provided at no cost in exchange for using their company to purchase test cartridges and controls. Controls, which are purchased separately at ~$60 per two sets, should be conducted on every cartridge shipment or otherwise monthly. Once opened, they are stable for 60 days and, thus, if used strategically, can last for three testing cycles. Although some claim that high base-unit costs combined with required control testing limit these devices to high-traffic clinical settings (23), the availability of a placement program negates this issue. It is important to note that costs vary depending on supplier, region, and volume of use within a health care facility (because pricing is commonly tiered). In general, individual tests cost between $7 and $9 (Table 2).

The cost of personnel time devoted to administering the POC test is driven by the responsible practitioner. Although any health care provider can be trained to appropriately administer the POC A1C test regardless of the product selected, selecting a nurse in the health care setting or a technician in the pharmacy setting may be most financially sound. Of note, specific health care settings may decide whether the practitioners designated to administer the POC A1C tests should demonstrate periodic performance proficiency to ensure the integrity of test results and reduce testing errors; NGSP certification does not account for end-user proficiency (9). Ultimately, a health care practitioner should assess and interpret the test results in the context of each patient-specific encounter to support treatment recommendations.

Additional Features

The DCA Vantage and Afinion both offer analysis of microalbumin, creatinine, and albumin:creatinine ratio. Unlike the A1C, this moderately complex testing requires quarterly proficiency testing at each health care site. These tests require a separate patient sample and use of a different cartridge, purchased separately from the distributor (20,21). Both the DCA Vantage and Afinion have a color touch display and data export via USB flash drive or RS232 and ethernet port. The DCA Vantage also includes an onboard printer and barcode reader for organizational purposes, which may benefit clinics with higher patient volumes (20,21). In contrast, the simpler A1CNow does not offer any of these additional features (memory, data export ability, or additional quantitative tests).

Discussion

Diabetes affects 25.8 million Americans (8%) and is the seventh leading cause of death (29). A1C is widely accepted as a measure of glycemic control and a means of assessing the risk of long-term complications associated with diabetes, including end-organ damage and reduced quality of life (30). Improving glycemic control reduces the development and progression of microvascular complications (31,32).

Using a POC device has the potential to improve disease monitoring, therapeutic control, and clinical decision making during consultations (17,30). Patients who received immediate A1C feedback via a POC device were found to benefit from it, as evidenced by a 52% greater likelihood of receiving a medical/pharmaceutical intervention and an average A1C reduction of 1.03 ± 0.33 percentage points at 12 months in an endocrinology practice (6) and 0.57 ± 1.44 and 0.40 ± 1.65 percentage points at 6 and 12 months, respectively, at an academic diabetes center (P <0.01) (4). Comparatively, patients who use commercial laboratory testing had an intervention rate of 27% and an average A1C reduction of 0.33 percentage points (6). Thus, the incorporation of a POC A1C device potentially improves patient care by contributing to a clinically meaningful decline in A1C.

In addition to improving glycemic control, incorporating A1C POC devices also lowers health care system costs. Even within the first year of treatment, the economic impact of tighter glycemic control on overall health care expenditures is evident in the resultant prevention of complications and reduction in the need for specialty care (33). For every 1 percentage-point increase beyond an A1C of 6%, subsequent increases in overall medical charges follow by 4, 10, 20, and 30% (34). In 3 years, patients with long-term diabetes complications were found to have paid $33,958 more than patients without complications (34). Patients with tighter glycemic control (A1C <8%) experienced lower hospital admission rates compared to those with an A1C >10% (13 vs. 31 admissions per 100 patients, P <0.05) (35). The mean adjusted charges per admission were $2,000 greater for patients with an A1C >10% (35). Therefore, using A1C POC devices potentially low-

ers health care costs through several mechanisms.

As new A1C POC devices have been developed and marketed, standardization has become increasingly necessary to ensure integrity and equivalence to conventional laboratory procedures (7). All devices must meet quality measures set by the NGSP for clinical results to be considered reliable and accurate (7). Currently, the DCA Vantage, Afinion, and A1CNow devices have met NSGP criteria for analytical performance, which makes them acceptable options for POC A1C testing (15). Furthermore, the Afinion and DCA Vantage have documented accuracy and precision as measured in recent CAP GH2 surveys (18).

Conclusion

A1C POC devices have improved the quality of diabetes management (30) by offering health care providers a method for timely assessment of diabetes control, which facilitates informed decision making during consultations (6,30). Furthermore, A1C POC devices may improve patient adherence by lessening transportation and cost barriers associated with extra office and laboratory visits (4,6). The selection of a POC A1C device should be based on accuracy, precision, ease of use, and price, among other considerations.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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