

QPlus® Cartridge - Instructions for Use

For use with the Quantra® Hemostasis Analyzer

REF KT-0004

QPlus® Cartridge Kit

Contents: 10 cartridges per box

IVD

Rx ONLY

Intended Use/Indications for Use

The QPlus® Cartridge (Cartridge) is intended for *in vitro* diagnostic use to provide indications of the coagulation state of a venous or arterial whole blood sample. The QPlus Cartridge is a multi-channel cartridge to be used with the Quantra® Hemostasis Analyzer (Quantra). Tests performed with the QPlus Cartridge, described below, use citrated whole blood samples:

The QPlus Cartridge is intended for use by trained professionals at the point-of-care and in clinical laboratories to evaluate the viscoelastic properties of whole blood by means of the following functional parameters: Clot Time (CT), Clot Time with Heparinase (CTH), Clot Stiffness (CS), Fibrinogen Contribution to Clot Stiffness (FCS), Platelet Contribution to Clot Stiffness (PCS), and Clot Time Ratio (CTR).

The QPlus Cartridge is indicated for use with patients 18 years of age or older where an evaluation of their blood coagulation properties is desired. Coagulation evaluations are commonly used to assess clinical conditions in surgery (e.g., cardiovascular and orthopedic surgeries) to assess risk of hemorrhage and thrombosis before, during, and following the procedure.

Results obtained with the QPlus Cartridge should not be the sole basis for patient diagnosis.

Summary and Explanation

The QPlus Cartridge is a multi-channel cartridge used with the Quantra Hemostasis Analyzer (Quantra) to assess a patient's coagulation system. The Quantra is based on Sonic Estimation of Elasticity via Resonance (SEER) Sonorheometry, a patented technology that uses ultrasound to measure the shear modulus of whole blood during coagulation as a function of time¹.

The single-use plastic cartridge, shown in Figure 1, contains lyophilized reagents (beads) that enable four independent reactions/tests to be run simultaneously without the need for reagent or sample preparation. Sample testing involves placing a single cartridge into the Quantra and attaching a citrated venous or arterial whole blood sample tube into the cartridge's sample port. The blood sample is automatically pulled into the system by an inlet within the cartridge. The cartridge is the only component of the Quantra QPlus System that is in direct contact with blood.

Principle of the Procedure

SEER Sonorheometry uses ultrasound pulses to quantify the shear modulus (i.e., stiffness) of a blood sample during the process of coagulation¹. A focused ultrasound pulse is transmitted into the blood sample to generate a shear wave, causing the sample to resonate once the clot begins to form. The combination of clot time and clot stiffness parameters measured from the four channels of the cartridge provides information about the functional role of the coagulation factors, fibrinogen, and platelets in the sample.

The QPlus Cartridge performs four independent tests in parallel, one in each of its four channels. The test channels include a series of blood modifiers (reagents) as described below. The reagents are lyophilized and embedded into the cartridge which comes sealed in a foil pouch.

Clot Time (CT) Test

This test is a semi-quantitative test used to monitor the coagulation process via the intrinsic pathway. CT provides a measure of the functionality of the common coagulation factors. CT provides information about potential consumption or depletion of the clotting factors that lead to fibrin formation and fibrin polymerization.

Clot Time with Heparinase (CTH) Test

This test is a semi-quantitative test used to monitor the coagulation process via the intrinsic pathway in the presence of a heparin neutralizer. CTH inactivates heparin in samples from patients receiving unfractionated heparin and provides a measure of the functionality of the common coagulation factors.

Clot Stiffness (CS) Test

This test is a semi-quantitative test used to monitor the coagulation process via the extrinsic pathway after neutralizing heparin. CS provides a measure of the functional contribution of fibrinogen and platelets to clot formation.

Fibrinogen Contribution to Clot Stiffness (FCS) Test

This test is a semi-quantitative test used to monitor the coagulation process via the extrinsic pathway after neutralizing heparin and inhibiting platelets. FCS provides a measure of the contribution of functional fibrinogen to clot stiffness.

Two additional parameters are derived:

Clot Time Ratio (CTR)

This test is a qualitative test and is defined as the ratio of the Clot Time (CT) and Clot Time with Heparinase (CTH) tests. A CTR value above the threshold is indicative of prolongation of the intrinsic pathway clotting time due to the presence of heparin.

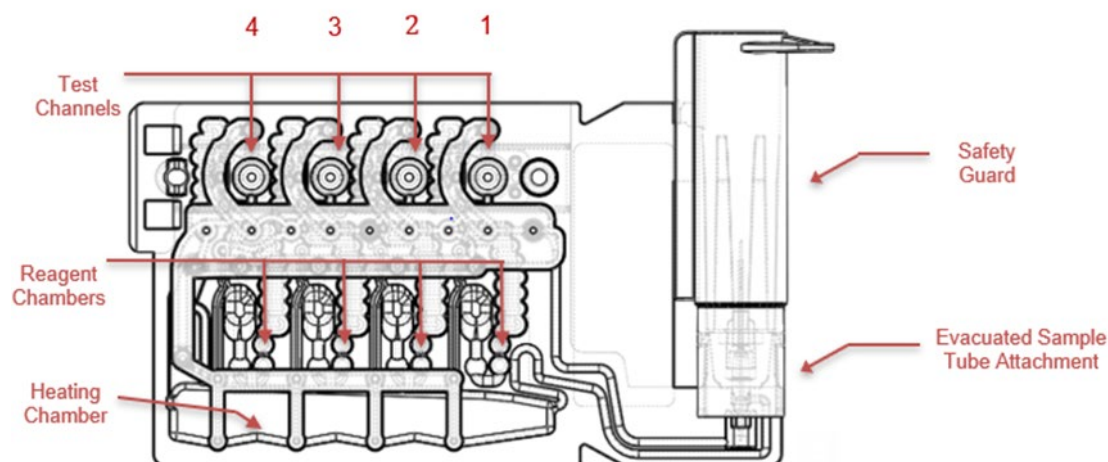
Platelet Contribution to Clot Stiffness (PCS)

This test is a semi-quantitative parameter that is calculated by comparing the Clot Stiffness results and the Fibrinogen Contribution results. PCS provides a measure of functional platelets and the portion of clot stiffness not attributable to Fibrinogen Contribution.

Results from the Quantra analysis should be interpreted in conjunction with other clinical and laboratory data available to the clinician.

The measurements are performed in four test channels of the disposable cartridge shown in Figure 1.

Figure 1. Disposable QPlus Cartridge



Reagents

The QPlus Cartridges are individually sealed in moisture proof pouches. Each test channel of the QPlus Cartridge contains the lyophilized reagents required to perform the QPlus assay. Table 1 summarizes the reagents utilized in each channel of the QPlus Cartridge.

Table 1: Reagents utilized in each QPlus Cartridge

Channel	Reagents	Measurement
1	Kaolin, buffers and stabilizers	Clot Time (seconds)
2	Kaolin, heparinase, buffers and stabilizers	Clot Time with Heparinase (seconds)
3	Thromboplastin, polybrene, buffers, and stabilizers	Clot Stiffness (hectoPascals)
4	Thromboplastin, polybrene, abciximab, buffers, and stabilizers	Fibrinogen Contribution to Clot Stiffness (hectoPascals)

The clot times obtained from Channels #1 and #2 provide an indication of the functional status of the coagulation system of the patient and the presence of residual heparin anticoagulation.

The clot stiffness values obtained from Channels #3 and #4 provide an indication of the overall clot strength as well as the relative contribution of platelets and fibrinogen. Clot stiffness is the result of fibrin polymerization, fibrin cross-linking, and platelet adhesion and contractility. The measurement of this parameter (in units of hectoPascals) from test Channel #3 provides information about fibrin/fibrinogen function as well as platelet activity.

Fibrinogen function is determined by assessing the fibrinogen contribution to clot stiffness. The fibrinogen clot stiffness (in units of hectoPascals) is measured in Channel #4 in the presence of a potent antagonist of the platelet GPIIb/IIIa receptor.

The functional contribution of platelets to clot stiffness is determined by subtracting the clot stiffness values measured in Channel #4 from the clot stiffness measured in Channel #3.

Materials Provided

- QPlus Cartridge Kit of 10: REF KT-0004

Materials Required (but not provided)

- Quantra Hemostasis Analyzer: REF HS-002
- Blood collection supplies (3.2% sodium citrate evacuated tubes)
- Refrigerator for storage of cartridges (optional) Also used with the Quantra Hemostasis Analyzer: QPlus Control Level 1 Kit: REF: KT-0023
- QPlus Control Level 2 Kit: REF: KT-0025
- Quantra Cleaning cartridge: REF: - KT-0012

Cartridge Storage and Handling

- The QPlus Cartridge should be stored in its pouch unopened until ready for use.
- The QPlus Cartridge may be stored refrigerated or at room temperature (up to 82°F/28°C) until the expiry date stated on the label.
- If stored refrigerated, remove from the refrigerator and place at room temperature unopened for a minimum of 30 minutes before use.
- Remove the cartridge from the pouch immediately before use.
- Visually inspect each cartridge before use. If the cartridge appears to be damaged in any way or is missing components or beads, do not use.
- Discard the cartridge if it sits at ambient temperature outside of its pouch for longer than 15 minutes.

Warnings and Precautions

- For *in vitro* diagnostic use only
- For professional use only
- The Quantra Hemostasis Analyzer and the QPlus Cartridge should only be used as directed in the Quantra Hemostasis Analyzer User Manual (Part # DMP-0254).
- Do not use the QPlus Cartridge beyond the expiration date.
- All patient samples should be handled with care, following the institution's policies and procedures pertaining to biohazardous material.

- The QPlus Cartridge should be handled as biohazardous material and as a potential sharps hazard after use with patient samples and as a potential sharps hazard and should be disposed of per institutional policies².
- The CTR parameter is not intended to be used to monitor the concentration of heparin in the patient sample.
- Studies evaluating the clinical performance of the QPlus Cartridge showed a 1.5% failure rate associated with the instrument/cartridge. Users should consider having an alternative method in place to use as a backup in case of a failure.

Sample Collection and Handling

- The QPlus Cartridge requires a sample of 3 mL or more of citrated venous or arterial whole blood collected in an evacuated tube containing 3.2% sodium citrate. Becton-Dickinson 13x75 mm 2.7 mL BD Vacutainer® Plus plastic citrate tubes were used in testing the QPlus Cartridge. Samples can be collected by venipuncture or from venous or arterial catheters.
- The blood collection tube must be filled to the minimum fill line. The entire blood sample will be used for analysis on the Quantra.
- Gently invert the blood collection tube 5 times before attaching it to the cartridge.
- Fresh blood kept at room temperature should be analyzed within 4 hours after collection.
- Samples should be collected and handled per the institution's policies and procedures pertaining to biohazardous material².
- Do not use a discard tube as the sample as it may affect results or cause incomplete filling of the cartridge.
- Store citrated blood at room temperature.

Test Procedure

- Refer to the Quantra Hemostasis Analyzer User Manual for complete operating instructions including instructions for instrument setup.
- Prior to testing, keep the QPlus Cartridge in its airtight pouch until ready to use. If kept refrigerated, remove pouch from the refrigerator and allow to sit at room temperature for a minimum of 30 minutes before opening and using.
- Prepare the Quantra Hemostasis Analyzer for testing. Scan or type in the Operator (User) ID to initialize the instrument.
- Once the analyzer is ready and a blood sample or QPlus Control is prepared to be loaded on the QPlus Cartridge, remove cartridge from its airtight pouch and inspect it. If the cartridge is damaged or missing components or beads do not use.
- Scan or type in the Cartridge ID on the label affixed to the cartridge. When prompted, insert the cartridge into the instrument.
- Hold the QPlus Cartridge on the end with the sample collection tube attachment. Insert the cartridge until resistance is felt, then gently push the cartridge until it clicks into place. The analyzer will position the cartridge slightly to the right and the shutter will close. The cartridge is now ready for the sample to be attached.

- Scan or type in the Patient ID on the sample tube and press “Continue”.
- Confirm that the blood collection tube is filled to the minimum fill line and that the tube is gently inverted 5 times.
- Attach the sample tube to the cartridge. Make sure the tube is pushed all the way down into the sample collection tube attachment so that the rubber cap is completely punctured.
- Press “Start” to initiate the test.

Reported Results

Test results are automatically calculated by the Quantra analyzer and are displayed upon test completion.

The clot times and clot stiffness values obtained from the four measurements performed by the QPlus Cartridge are combined to yield six (6) output parameters that describe the functional status of the patient’s coagulation system. The results reported are summarized in Table 4.

Table 4: Results reported using the QPlus Cartridge

QPlus Output Parameter	Units	Description	Reportable Ranges
Clot Time (CT)	Seconds	Clot time in citrated whole blood	60 - 480
Heparinase Clot Time (CTH)	Seconds	Clot time in citrated whole blood with heparin neutralization	60 - 480
Clot Time Ratio (CTR)	None	The CTR parameter may indicate the prolongation of the intrinsic pathway clotting time that is likely due to the influence of unfractionated heparin. CTR values are not directly correlated with heparin levels in the sample; if CTR is > 1.4, it is only indicative of heparin in the sample.	0.8 to 4
Clot Stiffness (CS)	hectoPascals	Stiffness of blood clot	2 to 65
Platelet Contribution to Clot Stiffness (PCS)	hectoPascals	Contribution of platelet activity to overall clot stiffness	2 to 50
Fibrinogen Contribution to Clot Stiffness (FCS)	hectoPascals	Contribution of functional fibrinogen to overall clot stiffness	0.2 to 30

QPlus Cartridge results are displayed on the Dials screen. During the testing process values are displayed on the screen in light gray and labeled “evolving” (CT, CTH, CS, FCS) or “in progress” (CTR, PCS) as the test develops in real time. Final test results are calculated by the Quantra analyzer and displayed in solid boldface characters upon test completion. The reportable range is indicated by

the value displayed at each end of the dial's semi-circle. On the semi-circle dial the reference range is shown in green, except for CTR which has no reference range. Colored symbols located on the lower right side of a dial signify a result that is either 1) outside the reference range, 2) outside the reportable range, or 3) a test error. Further information is available in the Quantra User Manual.

The Quantra outputs both numerical and non-numerical values for output parameters. Certain non-numerical test results are expected from samples with specific characteristics whereas other non-numerical test results may indicate an issue with a cartridge or the instrument. Table 5 provides a listing of the non-numerical test results that may be reported by the Quantra Analyzer.

Table 5: Non-numerical test results reported by the Quantra Analyzer

Test Result and Symbols	Description	Comment	Action Required	Symbols
"Not Computable"	Displayed in the following situations: 1) For CTR and PCS, when data is missing for one or both components used to calculate the parameter. 2) When the clot time plus the time required to calculate clot stiffness (7 min) exceeds the maximum measurement period (25 min).	In the case of 2), this behavior is observed with certain samples that form very weak clots or form clots very slowly. CS, FCS and PCS are not computed. Result is reflective of sample properties, not of an instrument/ cartridge issue.	None; Because result is due to sample properties and not the System, running a fresh sample on a new cartridge will give same result	None
"No Clot Detected"	Displayed when a cartridge ran successfully to completion, but a clot did not form in one of the channels within the assay measurement period.	Result is expected for CT for samples taken during cardiac bypass. Result is reflective of low coagulation function	Use result. Result reflects low coagulation function	
">Maximum reportable #"	Displayed when a cartridge ran successfully to completion and a clot was detected but result is above the reportable range for a given parameter.	>max reportable for CT and CTH reflects low coagulation function. >max reportable for CS, FCS, PCS reflects high coagulation function	Use result. Result reflects low or high coagulation function (see comments)	
"<Minimum reportable #"	Displayed when a cartridge ran successfully to completion and a clot was detected but result is below the reportable range for a given parameter.	<min reportable for CT and CTH reflects high coagulation function. <min reportable for CS, FCS, PCS reflects low coagulation function	Use result. Result reflects low or high coagulation function (see comments)	
"Test Error"	Displayed under the following conditions: 1) Cartridge or instrument error 2) Software identified an error in the relationship between parameters (e.g., FCS>CS). 3) Software quality checks identified an abnormal shear modulus curve and clot parameters could not be determined. 4) Clot formed before data acquisition began or clot retraction	These are potential instrument or cartridge failures	Repeat run with fresh sample on new cartridge	

When a result is outside of the reference range but within the reportable range, a yellow warning symbol is displayed.

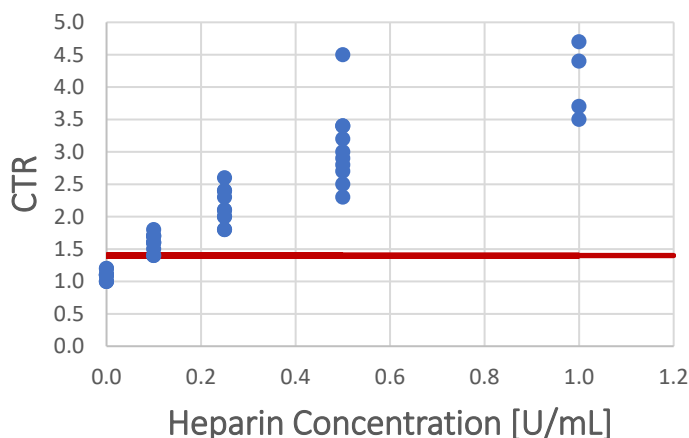


Clot Time Ratio (CTR)

The Clot Time Ratio (CTR) is a calculated parameter. CTR values of 0.8 – 1.2 are demonstrated to be typical of “normal” patient samples. Samples with CTR values >1.4 are indicative of prolongation of the intrinsic pathway clotting time, likely due to the influence of unfractionated heparin.

Dose-response experiments demonstrated the influence of heparin on CTR values. Unfractionated heparin was spiked into citrated whole blood from five normal healthy donors to give final concentrations in whole blood of 0.0, 0.1, 0.25, 0.5, 1.0, and 6.0 U/mL heparin. Duplicate samples were tested at each heparin level, thus yielding a total of 60 observations. Figure 2 shows the CTR values obtained versus heparin concentration. The highest CTR value obtained from these experiments was 4.7. The data in Figure 2 shows duplicate measurements for each of 5 normal subjects at each concentration. The red horizontal line represents a CTR value of 1.4. Although CTR values >1.4 were observed for heparin-containing samples, CTR values do not directly correlate with heparin levels in a sample.

Figure 2: QPlus CTR vs heparin concentration



Reference ranges

A reference range study was conducted by collecting whole blood samples from 129 healthy adult donors across three (3) sites in the United States. The data were evaluated as recommended in EP28-A3c “Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition.”³ The reference range determined from this study, expressed as the central 95% confidence interval of the mean, are summarized in Table 7.

Table 7: Reference Ranges

Output Parameter	Units	Reference Ranges
Clot Time (CT)	Seconds	104 - 166
Heparinase Clot Time (CTH)	Seconds	103 - 153
Clot Stiffness (CS)	hectoPascals	13.0 - 33.2
Fibrinogen Contribution to Clot Stiffness (FCS)	hectoPascals	1.0 - 3.7
Platelet Contribution to Clot Stiffness (PCS)	hectoPascals	11.9 – 29.8

Performance Characteristics

Precision

Two precision studies were conducted for the QPlus cartridge utilizing CLSI guidance.

The first was a single-site study that assessed the within-laboratory precision performance using two levels of lyophilized QPlus Controls (QC) in duplicate with two runs per day over 20 testing days. All testing was conducted using one Quantra instrument, one lot of QPlus Cartridges, and one operator. Results are summarized in Table 8. Analysis of the internal precision study data for the QPlus Cartridge on the Quantra demonstrated within-laboratory precision (total) of 1.6 – 6.7% for QPlus Level1 QC and from 5.8 - 14.3% for QPlus Level 2 QC.

Table 8: Single-site precision study results

QPlus Level 1 QC						
Parameter	N	Mean	Repeatability (Replicate) (SD, %CV)	Between-Day (SD, %CV)	Between- Run (SD, %CV)	Total (SD, %CV)
CT (sec)	80	157.79	4.75, 3.0	0.00, 0.0	1.62, 1.0	5.02, 3.2
CTH (sec)	80	155.74	3.75, 2.4	0.93, 0.6	0.00, 0.0	3.87, 2.5
CTR	80	1.00	0.02, 1.6	0.00, 0.0	0.00, 0.0	0.02, 1.6
CS (hPa)	80	13.97	0.64, 4.6	0.30, 2.1	0.00, 0.0	0.71, 5.1
FCS (hPa)	80	15.26	0.91, 5.9	0.00, 0.0	0.46, 3.0	1.01, 6.7
PCS (hPa)	80	<0.2	NA*	NA*	NA*	NA*
QPlus Level 2 QC						
Parameter	N	Mean	Repeatability (Replicate) (SD, %CV)	Between-Day (SD, %CV)	Between- Run (SD, %CV)	Total (SD, %CV)
CT (sec)	80	246.90	28.31, 11.5	9.99, 4.0	0.00, 0.0	30.03, 12.2
CTH (sec)	80	186.08	9.73, 5.2	4.50, 2.4	0.00, 0.0	10.72, 5.8
CTR	80	1.33	0.13, 9.6	0.03, 2.2	0.00, 0.0	0.13, 9.9
CS (hPa)	80	5.02	0.45, 8.9	0.21, 4.3	0.00, 0.0	0.50, 9.9
FCS (hPa)	80	5.58	0.74, 13.3	0.00, 0.0	0.29, 5.3	0.80, 14.3
PCS (hPa)	80	<0.2	NA*	NA*	NA*	NA*

* QPlus QC materials do not contain platelets

The second study was conducted to evaluate the precision of the QPlus Cartridge on the Quantra using whole blood samples across multiple instruments, operators, and cartridge lots. The study included samples from 15 native subjects (non-contrived normal and abnormal specimens) and 12

contrived samples that covered five different coagulation categories based on each test's measurement range and respective normal ranges including: Normal, Greatly Increased, Greatly Reduced, Moderately Increased, and Moderately Reduced coagulation function. Values for each QPlus Cartridge parameter were grouped into 2 or 3 categories based on whether they were below, within or above the respective reference range (above or below the threshold for CTR). Precision results are summarized in Table 9.

Table 9: Whole blood repeatability study results

Parameter	Range	n	Mean results	Between-Replicate		Between-(Analyzer/ Cartridge Lot)		Between- Operator		Total	
				SD	CV%	SD	CV%	SD	CV%	SD	CV%
CT (sec)	60 - 104	3	71.8 - 95.2	3.4 - 7.4	4.1 - 10.4	0.0 - 2.0	0.0 - 2.8	0.0 - 0.0	0.0 - 0.0	3.5 - 8.3	4.1 - 10.8
	104 - 166	12	111.3 - 147.3	3.8 - 7.0	2.7 - 5.3	0.0 - 5.7	0.0 - 4.7	0.0 - 5.9	0.0 - 4.2	4.9 - 10.4	4.0 - 8.8
	166 - 480	12	169.5 - 409.1	6.2 - 36.0	2.6 - 10.7	0.0 - 13.4	0.0 - 4.0	0.0 - 21.5	0.0 - 5.3	6.6 - 38.4	3.7 - 11.5
CTH (sec)	60 - 103	4	66.1 - 97.5	3.3 - 6.6	3.5 - 7.8	0.0 - 5.7	0.0 - 5.9	0.0 - 2.3	0.0 - 2.3	3.8 - 8.2	4.0 - 8.4
	103 - 153	20	111.2 - 150.8	1.9 - 10.2	1.3 - 7.0	0.0 - 5.3	0.0 - 3.8	0.0 - 3.7	0.0 - 2.6	3.5 - 11.2	2.4 - 7.5
	153 - 480	3	163.2 - 373.4	6.8 - 34.3	3.4 - 9.2	0.0 - 26.8	0.0 - 7.2	0.0 - 8.3	0.0 - 2.8	8.4 - 44.0	5.2 - 11.8
CTR	≤ 1.4	22	0.98 - 1.41	0.03 - 0.14	2.0 - 12.3	0.00 - 0.08	0.0 - 7.6	0.00 - 0.06	0.0 - 5.4	0.05 - 0.17	4.2 - 14.5
	> 1.4	4	1.46 - 2.87	0.10 - 0.18	4.7 - 9.0	0.00 - 0.09	0.0 - 4.8	0.00 - 0.05	0.0 - 2.0	0.10 - 0.18	5.0 - 9.2
CS (hPa)	2.0 - 13.0	6	2.03 - 12.13	0.11 - 0.64	3.0 - 5.6	0.00 - 0.22	0.0 - 2.9	0.00 - 0.12	0.0 - 1.0	0.12 - 0.84	3.4 - 7.5
	13.0 - 33.2	16	15.81 - 31.06	0.33 - 1.53	2.0 - 7.2	0.00 - 0.69	0.0 - 4.0	0.00 - 1.17	0.0 - 3.8	0.41 - 2.03	2.4 - 9.1
	33.2 - 65.0	4	34.19 - 64.21	0.98 - 4.91	2.8 - 10.0	0.80 - 2.77	1.6 - 8.1	0.00 - 0.77	0.0 - 2.3	2.80 - 4.98	5.0 - 10.1
FCS (hPa)	0.2 - 1.0	2	0.53 - 0.79	0.09 - 0.10	13.1 - 17.1	0.03 - 0.05	5.4 - 6.3	0.00 - 0.08	0.0 - 10.3	0.10 - 0.14*	17.9 - 18.0*
	1.0 - 3.7	16	1.28 - 3.56	0.03 - 0.23	2.2 - 10.3	0.00 - 0.20	0.0 - 9.0	0.00 - 0.19	0.0 - 8.7	0.06 - 0.30	3.9 - 13.6
	3.7 - 30.0	9	4.41 - 23.65	0.15 - 1.34	3.1 - 17.5	0.00 - 0.42	0.0 - 3.0	0.00 - 0.41	0.0 - 2.9	0.22 - 1.46	4.4 - 20.4**
PCS (hPa)	2.0 - 11.9	4	7.13 - 11.59	0.31 - 0.59	3.9 - 5.6	0.00 - 0.23	0.0 - 2.9	0.00 - 0.13	0.0 - 1.1	0.38 - 0.81	4.7 - 7.7
	11.9 - 29.8	17	14.46 - 26.62	0.39 - 2.22	2.3 - 9.1	0.00 - 1.39	0.0 - 5.7	0.00 - 1.29	0.0 - 5.3	0.42 - 2.71	2.9 - 11.1
	29.8 - 50.0	3	30.63 - 45.82	0.99 - 4.39	3.2 - 10.3	0.99 - 2.8	2.3 - 9.0	0.00 - 0.84	0.0 - 2.7	3.07 - 4.5	7.4 - 10.6

* For FCS below the reference range, results were compared to expected precision of CV%(total) ≤ 15% or SD(total) ≤ 0.2 hPa.

**Included 1 contrived sample (Clauss fibrinogen of 587 mg/dL) with CV%(total) = 20.4%. CV%(total) for the remaining 8 samples was 4.4 - 10.7%.

Clinical Performance

The clinical performance study of the QPlus Cartridge was a multi-center, prospective observational study involving patients 18 years of age or older undergoing major cardiac and/or vascular procedures or major orthopedic surgery (primarily complex spine surgeries). Two hundred seventy-seven (277) adult subjects were eligible for this study across four clinical sites in the US. This number also included abnormal samples from non-surgical subjects as well as up to 10% artificially contrived samples. Several types of analyses were performed which are summarized below.

Quantra instruments were located near patient, directly outside of the operating rooms (ORs), located in the OR STAT Lab or located in clinical research laboratories. From each subject venous blood was collected at three or four timepoints; preoperatively, during surgery and postoperatively for analysis on the Quantra with QPlus Cartridge, the ROTEM® delta Thromboelastometry System (Instrumentation Laboratory) and in standard laboratory tests.

A clinical concordance analysis was conducted to determine the agreement of each QPlus test output to a corresponding Clinical Composite Index (CCI) comprised of data from standard laboratory tests and the status of heparin use. The CCIs were developed solely to serve as laboratory-based comparators to the QPlus Cartridge parameters and were designed based on in-depth review of the clinical literature, clinical guidelines and consideration from multiple physicians. Table 10 provides the information used to define each of the CCIs.

Table 10: Information comprising the CCIs

QPlus parameter and corresponding CCI	Information comprising each CCI
Clot Time (CT) vs CCI1	aPTT, ACT, INR and presence of heparin
Clot Stiffness (CS) vs CCI2	Clauss fibrinogen, Platelet Count
Fibrinogen Contribution (FCS) vs CCI3	Clauss fibrinogen
Platelet Contribution (PCS) vs CCI4	Clauss fibrinogen, Platelet Count
Clot Time Ratio (CTR) vs CCI5	aPTT, ACT, and presence of heparin

For each CCI, specific criteria were defined to assign clinical samples as “High”, “Low”, or “Normal/Subclinical”, representing increased, decreased or normal/subclinical coagulation function, respectively (i.e., hypercoagulable, hypocoagulable, normal coagulation). For each QPlus parameter, similar categories were assigned to each clinical sample with respect to that parameter’s normal reference range except for CTR in which the threshold of 1.4 was used to assign samples. The overall agreement and agreement within sub-categories between each QPlus Cartridge parameter and the corresponding CCI is shown in Table 11.

Table 11: Summary of concordance analysis for QPlus Cartridge parameters vs CCI

QPlus Parameter vs CCI	Overall Agreement* (95% CI)	Low Agreement* (95% CI)	Normal/Subclinical Agreement* (95% CI)	High Agreement* (95% CI)
CT vs CCI1	0.72 (0.69) [605/840]	0.98 (0.96) [183/187]	0.62 (0.58) [376/603]	0.92 (0.83) [46/50]
CS vs CCI2	0.77 (0.73) [641/832]	0.83 (0.66) [24/29]	0.80 (0.77) [557/693]	0.55 (0.42) [60/110]
FCS vs CCI3	0.84 (0.81) [702/833]	0.77 (0.50) [10/13]	0.84 (0.80) [643/770]	0.98 (0.93) [49/50]
PCS vs CCI4	0.75 (0.72) [618/823]	0.86 (0.71) [25/29]	0.80 (0.76) [534/664]	0.45 (0.35) [59/130]
CTR** vs CCI5	0.98 (0.97) [821/838]	0.94 (0.90) [156/166]	0.99 (0.98) [665/672]	N/A

*Point estimates (lower bounds of the 95% confidence intervals) [number of observations vs total number of occurrences in the specific category].

**For CTR, clinical samples were categorized as Low if CTR > 1.4 or Not Low if CTR ≤ 1.4.

Validation of the CTR threshold was demonstrated through the 94% agreement in the Low category, 99% agreement in the Not Low category, and a 98% overall agreement (Table 11).

A clinical concordance analysis was also conducted to determine the agreement of each QPlus parameter with the corresponding ROTEM delta parameter. Clinical samples were assigned as “High”, “Low”, or “Normal/Subclinical”, based on the respective QPlus Cartridge or ROTEM normal reference ranges (Table 12).

Table 12: Summary of concordance analysis for QPlus Parameters vs ROTEM

QPlus Parameter vs ROTEM parameter	Overall Agreement* (95% CI)	Low Agreement* (95% CI)	Normal/Subclinical Agreement* (95% CI)	High Agreement* (95% CI)
CT vs INTEM CT	0.85 (0.82) [713/842]	0.90 (0.86) [195/217]	0.82 (0.79) [439/534]	0.87 (0.80) [79/91]
CS vs EXTEM A20	0.87 (0.84) [728/841]	0.89 (0.82) [75/84]	0.87 (0.84) [605/694]	0.76 (0.63) [48/63]
FCS vs FIBTEM A20	0.87 (0.85) [729/834]	0.50 (0.37) [34/68]	0.91 (0.88) [615/675]	0.88 (0.80) [80/91]

*Point estimates (lower bounds of the 95% confidence intervals) [number of observations vs total number of occurrences in the specific category].

Additional clinical concordance analyses were performed in which the “High” and “Normal/Subclinical” categories were combined to “Not Low” to demonstrate concordance in hypocoagulable samples (Table 13).

Table 13: Summary of concordance analysis for QPlus Parameters vs CCI or ROTEM, Overall and 2 categories

Comparison	Overall Agreement* (95% CI)	Low Agreement* (95% CI)	Not Low Agreement* (95% CI)
CT vs CCI1	0.98 (0.97) [821/840]	0.97 (0.95) [182/187]	0.98 (0.97) [639/653]
CS vs CCI2	0.86 (0.83) [719/832]	0.83 (0.66) [24/29]	0.87 (0.83) [695/803]
FCS vs CCI3	0.96 (0.94) [801/833]	0.77 (0.50) [10/13]	0.96 (0.95) [791/820]
PCS vs CCI4	0.85 (0.81) [698/823]	0.86 (0.71) [25/29]	0.85 (0.81) [673/794]
CTR** vs CCI5	0.98 (0.97) [821/838]	0.94 (0.90) [156/166]	0.99 (0.98) [665/672]
CT vs INTEM CT	0.96 (0.95) [811/842]	0.90 (0.86) [195/217]	0.99 (0.97) [616/625]
CS vs EXTEM A20	0.91 (0.89) [769/841]	0.89 (0.82) [75/84]	0.92 (0.89) [694/757]
FCS vs FIBTEM A20	0.95 (0.93) [793/834]	0.50 (0.37) [34/68]	0.99 (0.98) [759/766]

*Point estimates (lower bounds of the 95% confidence intervals) [number of observations vs total number of occurrences in the specific category].

**For CTR, clinical samples were categorized as Low if CTR > 1.4 or Not Low if CTR ≤ 1.4.

A Deming regression analysis was conducted to evaluate the correlation between QPlus output parameters and corresponding ROTEM delta assay parameters for all timepoints combined (overall). The Best Fit equations are provided in Table 14 below.

Table 14: Best Fit Deming Regression Analysis – Qantra vs ROTEM

			Intercept		Slope		
Comparison	N Samples	Best fit equation	Estimate	(95% CI)	Estimate	(95% CI)	R*
CT vs INTEM CT	681	CT = 13.42 + 0.69 * INTEM CT	13.42	(-16.647, 43.493)	0.69	(0.496, 0.887)	0.84
CTH vs HEPTTEM CT	846	CTH = 18.01 + 0.65 * HEPTTEM CT	18.01	(4.626, 31.389)	0.65	(0.568, 0.741)	0.84
CS vs EXTEM A20	835	CS = -6.65 + 17.22 * EXTEM A20 / (100 - EXTEM A20)	-6.65	(-8.212, -5.089)	17.22	(16.145, 18.288)	0.89
FCS vs FIBTEM A20	830	FCS = -0.89 + 17.04 * FIBTEM A20 / (100 - FIBTEM A20)	-0.89	(-1.240, -0.548)	17.04	(15.206, 18.884)	0.87

*Pearson Correlation

A sample matrix comparison study was performed at one external site to evaluate QPlus parameter results in venous and arterial blood samples. One hundred matched venous and arterial citrated whole blood samples were collected from patients undergoing cardiac surgery into evacuated collection tubes containing 3.2% sodium citrate and analyzed in singlicate on the QPlus Cartridge. Means were compared by paired t tests and none showed a statistically significant difference ($p < 0.05$) between venous and arterial sampling. In addition, the mean differences between the paired venous and arterial measurements were 3.64% or less demonstrating that venous and arterial whole blood samples provide equivalent results on the QPlus Cartridge.

A Reader Study was also conducted to assess the ability of potential Quantra users to correctly interpret results displayed on the Quantra Dials display screen. The study was prospectively conducted at three sites using a total of 14 readers who regularly assess the blood coagulation status of patients in the critical care setting. Participants viewed 15 Quantra Dials display screens, each containing results for six QPlus Cartridge parameters, and answered a total of 180 test questions. Participants correctly interpreted results for all QPlus Cartridge parameters >95% of the time.

Refer to the Quantra User Manual “Understanding the Dials Display” for detailed information on interpreting results on the dials display.

Limitations

Sources of potential reagent and procedural errors are outlined in Table 6 below.

Table 6. Assay limitations

Source	Limitations
Sample	Samples with severe hemolysis may interfere with results
Sample	Samples with hematocrits greater than 50% interfere with results
Sample	Use of discard tubes may interfere with results
Sample	Use of hemodiluted samples may interfere with results
Cartridge	Cartridge should be used within 15 minutes of opening the pouch.
Blood collection	Do not collect blood from a heparinized line or lock. Do not collect blood in a blood collection device coated with an anticoagulant.
Timing	Citrated whole blood samples should be analyzed within 4 hours from collection to prevent premature clotting.

Results obtained with the QPlus Cartridge should not be the sole basis for patient diagnosis. The QPlus Cartridge results should always be considered within the clinical context of the individual patient. In the event of inconsistencies with the patient’s clinical status, samples should be repeated or supplemented with additional clinical information and/or data.

The device has not been evaluated to guide blood product use or use of medication.

Known Interfering Factors

An interference study was performed following the CLSI EP07-A2 guidelines to evaluate the effect of potential endogenous, exogenous, and sample variable interferents on the QPlus Cartridge results. Testing was performed with normal and hypocoagulable whole blood samples (samples with and/or without heparin or reduction in platelet or fibrinogen levels/function).

Table 7 shows the highest concentration at which each substance showed no significant interference in whole blood samples collected in 3.2% sodium citrate anticoagulant collection tubes.

Table 7. Known Interfering Factors

Interferent	Concentration
Lipid	697 mg/dL (highest level tested)
Hemoglobin	Normal Whole blood;0.8 g/dL
Hemolysis	Normal Whole blood;0.09 g/dL
Clopidogrel	100 µM
Aspirin	4.34 mM (0.694 mg/mL) (highest level tested)
Tranexamic acid	60 µg/mL (highest level tested)
Epsilon-aminocaproic acid	600 µg/mL (highest level tested)

As expected and per design, the following substances showed significant effects on QPlus Cartridge parameters in testing:

- Heparin (6U/mL) demonstrated an effect on CT but had no effect on other QPlus Cartridge parameters.
- Protamine sulfate demonstrated an effect on CT and CTR in heparinized samples (5U/mL) with effects starting at 30 µg/mL.
- The direct oral anticoagulants rivaroxaban and dabigatran demonstrated a dose response effect starting at concentrations greater than 25 ng/mL.
- Hemodilution demonstrated a dose response effect at dilutions greater than 10%.
- Increasing hematocrit levels in the range of <20% to >40% generated a decrease in most QPlus results.

Specimen collection tubes filled at less than 80% of the required/specified volume may affect results or cause nonreported results due to incomplete filling of the QPlus Cartridge. Use of a discard tube may affect QPlus results.

Quality Control

The QPlus Cartridge has a comprehensive Quality Assurance Program that is based on a combination of labeling, internal controls, automated quality control checks and the use of external biological control materials to support the development of a local Individual Quality Control Plan.

The Quantra Analyzer performs internal quality checks of all system components at regular intervals and during each phase of a test run on a cartridge to verify that the instrument hardware and all subsystems are functioning properly.

External biological control materials test the performance of each of the QPlus Cartridge output parameters. Two levels of external QPlus Quality Controls (QC) are available and supplied separately (with an accompanying instruction for use) for testing on the QPlus Cartridge. The two levels of QPlus QC (Level 1 and Level 2) are designed to be used as part of a laboratory's Individual Quality Control Program. Each QPlus Control consists of A) a polyethylene transfer pipette; B) a stopped screw cap glass vial containing a lyophilized cake comprised of pooled animal plasma, fixed human red blood cells, and other components; and C) an HDPE vial with an extender containing a 3.4 mL diluent.

HemoSonics recommends running QC materials with the QPlus Cartridge when changing cartridge lots, changing control lots, or after significant changes are made to the Quantra instrument (e.g., software update). The QPlus Level 1 and Level 2 QC are designed to have non-overlapping ranges for CT, CTR, CS, and FCS. The QC materials do not include platelets therefore, values for PCS parameter are typically at or below the reportable range (≤ 2 hPa). However, limits for PCS will be provided from the lot specific value assignment range limits of the CS and FCS parameters. Value Assignment cards supplied with each individual lot of QPlus QC provide the lot-specific minimum and maximum values for the QPlus Cartridge output parameters.

To run QPlus QC materials on the QPlus Cartridge, follow the directions described for Test Procedure except that when prompted to enter the patient ID, scan the barcode on the vial of QPlus QC material to be tested. Vigorously mix each vial to resuspend the solution prior to loading the QPlus QC onto the cartridge. Attach the vial with extender to the sample tube attachment on the cartridge, making sure that the cap is completely punctured.

The results obtained during a QPlus QC run are compared to the values assigned to each output parameter for each QC lot. These values are entered from the Value Assignment Card provided with each box of QPlus QC material into the Lots tab on the Administrator section of the Quantra instrument. All QPlus Cartridge parameters must exhibit results within the lot-specific minimum and maximum values assigned for the control run to Pass. If the QPlus QC material does not Pass, repeat the procedure using a new QPlus Cartridge and new vial of QPlus QC material. If the result is still out of range, call HemoSonics Technical Support for further assistance.

If additional confirmation of the performance of the QPlus Cartridges and QPlus QC materials is desired, the performance can be tested using whole blood drawn from one or more normal healthy donors according to the following procedure.

- a) Identify a normal donor(s) that has (have) no known coagulation defects and is not taking any medications known to affect coagulation status.
- b) Collect whole blood from the donor(s) by venipuncture into a 2.7 mL evacuated tube containing 3.2% sodium citrate per standard phlebotomy practices.
- c) Run the whole blood sample on the QPlus Cartridge as patient samples (not as a QC sample). All test results should fall within the established reference ranges for each parameter.

If a user wishes to further evaluate the performance of the PCS parameter, optional testing can be conducted using “abnormal” whole blood samples prepared according to the following procedure.

- a) Collect whole blood from a normal donor by venipuncture into two 2.7 mL evacuated tubes containing 3.2% sodium citrate as indicated above.
- b) To create an “abnormal” sample, spike one of the whole blood samples with the platelet inhibitor abciximab (ReoPro®; Eli Lilly, VL7140, supplied as 10 mg/5 mL). Add 30.0 µL of the abciximab solution to each collection tube to achieve a final concentration of 20 µg/mL. Recap the tubes and gently mix. Vent the tubes by inserting a needle into the rubber septa to release positive pressure from the tube.
- c) Run samples on the QPlus Cartridge as patient samples (not as QC samples). For the sample treated with abciximab, the PCS value should fall below the sites’ established reference range for PCS and maybe below the PCS reportable range. The test result for PCS from the “normal” sample should fall within the site’s established reference range for PCS.

Further information regarding the Quality Control materials can be found in the respective instructions for use of these materials.

References

1. Corey, F. S., & Walker, W. F. (2016). Sonic estimation of elasticity via resonance: a new method of assessing hemostasis. *Annals of biomedical engineering*, 44(5), 1405-1424.
2. Ernst DJ, Martel AM, Arbique, JC, et al. (2017). *Collection of Diagnostic Venous Blood Specimens*. 7th ed. CLSI standard GP41. Wayne, Pa: Clinical and Laboratory Standards Institute.
3. Horowitz, G. L., Altaie, S., & Boyd, J. C. (2010). Defining, establishing, and verifying reference intervals in the clinical laboratory; approved guideline – third edition. CLSI EP28-A3c. Vol. 28, No. 30.

Glossary of Symbols

The following symbols may have been used in the labeling of this product.

	Lot Number
	Catalog Number
	Part Number
	<i>In Vitro</i> Diagnostic Use
	Manufacturer
	Biological risks
	Use By
	Temperature Limits
	Contains sufficient for <n> tests
	Do not re-use
	Consult instructions for use
	Date of Manufacture
	Caution US Federal Law restricts this device to sale by or on the order of a physician

Revision History

Date of Revision	Revision Number	Description of Technical Changes
APR 2019	00	Original US Release
APR 2020	01	Removed -238004- from part #. Updated Technical Support Number.
NOV 2020	02	Updated quality control information (lyophilized controls).
JUN 2021	03	Added clarification about venipuncture to “Sample Collection and Handling” section.
JAN 2023	04	Updated text to allow information for use of arterial blood samples. Updated Control performance characteristic data to better reflect current product. Updated manufacturing address.
JAN-2024	05	Added Information about the Extended Assay
JUL-2024	06	ECO-001084: Harmonize this IFU with the OUS Version of IFU.



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