MAYO CLINIC

Relationship between glucose meter error and glycemic control efficacy

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Learning objectives

- **List regulatory and clinical issues related to use of glucose meters for critically ill hospitalized patients**
- **Weigh the benefits of glycemic control vs. the risks of hospital-acquired hyoglycemia**
- **Discuss the impact of glucose meter accuracy on glycemic control effectiveness**
- **Review various recommendations for glucose meter accuracy**

Glucose meters in the hospital

- **Multiple uses for glucose meters in hospital**
  - **Dose subcutaneous insulin for diabetic mildly ill patients**
    - *Same accuracy requirements as home use*
  - **Screen for neonatal hypoglycemia**
  - **Screen for hypoglycemia or hyperglycemia in hospitalized patients**
  - **Manage intravenous insulin for critically ill patients on glycemic control**
    - *Hourly glucose measurement, hourly IV insulin adjustment*
    - *Narrower insulin dosing ranges, more opportunity for dosing errors*

Glycemic control vs. hypoglycemia

- Van den Berghe 2001
- 1500 ICU patients randomized into two groups:
  - Conventional treatment: maintain glucose 180-200 mg/dl, insulin infusion if glucose > 215 mg/dl
  - Intensive insulin therapy: Intravenous insulin if glucose > 110 mg/dl, maintain glucose 80-110 mg/dl
- Primary findings:
  - Among patients in ICU > 5 days, mortality reduced ~ 30% in intensive insulin group
  - Bloodstream infections, acute renal failure, RBC transfusions, polyneuropathy all reduced 40-50% in intensive insulin group
  - *Increased rate of hypoglycemia in intensive group (6x, 5% of intensive group)*

Glycemic control vs. hypoglycemia

- Leuven II (NEJM 2006)
  - Repeat of study in medical ICU
  - TGC only effective in patients with > 3 d ICU stay
  - Hypoglycemia significant limitation, increased mortality for patients < 3 d in ICU
  - *6-fold increased rate of hypoglycemia (18.7%)*
  - *Glucose meters instead of ABG*
- Subsequent studies
  - Mixed outcome results (more negative than positive)
  - Glucose targets varied
  - Average 5-fold increase in rate of hypoglycemia
  - Leuven I used arterial blood gas glucose
  - Most other studies used glucose meters or methods/sample types differed by location

Glycemic control vs. hypoglycemia

- Single episode of severe hypoglycemia (< 40 mg/dL) associated with increased mortality
  - OR 2.3 X for death (Krinsley, 2007)
- In same population patients glycemic control reduced mortality
- Sensitivity analysis performed to determine how much SH would offset TGC
  - 4X increase in SH (from 2.3% to 9.2%) predicted to completely offset survival benefit of glycemic control
  - Could glucose meter inaccuracy be leading to hypoglycemia?

Technologic limitations of glucose meters

- **Number of factors influence relationship of glucose meter to true (usually lab plasma) glucose**
  - **Whole blood vs. plasma (conversion factor)**
  - **Sample type (capillary vs. venous catheter vs. arterial catheter)**
    - *Physiologic and technologic limitations*
  - **Interferences (medications, pO2, others)**

Technologic limitations of glucose meters

- **Whole blood vs. plasma glucose**
  - **Whole blood glucose ~ 15% lower than plasma glucose**
  - **US Vendors now calibrate reagents to express "plasma-equivalent" units**

Technologic limitations of glucose meters

- **Conversion of WB to plasma equiv glucose**
  - **Function of water content of plasma (PW), water content of red cells (RW), and percent red cells in WB (Hematocrit)**
  - **Vendors used agreed upon standards for one conversion factor**
  - **Does patient acuity impact validity of PW, RW and Hct assumptions?**

Lyon ME and Lyon AW Clin Biochem 2011;44:412-7

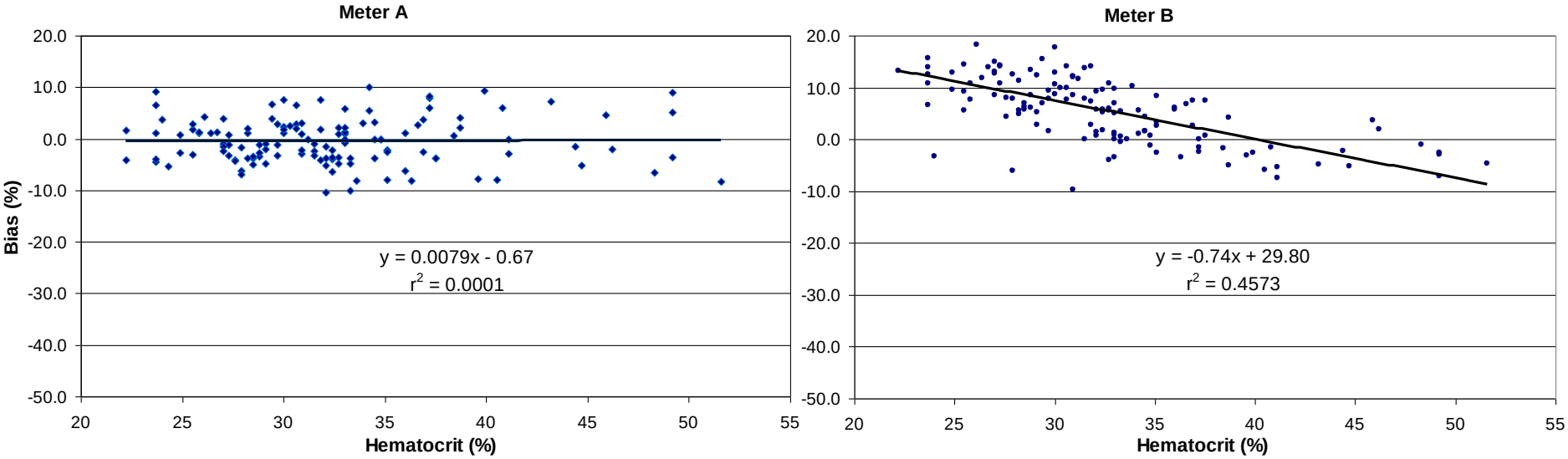
Technologic limitations of glucose meters

- **Conversion of WB to plasma equiv glucose**
  - **Compared PW, RW, Hct values among oupatients, inpatients, and adult ICU patients**
  - **Adult ICU patient mean and distribution PW, RW, and Hct values differed markedly from assumptions**
  - **Lower Hct and higher PW in adult ICU patients predicted to result in 8.3% of results with > 10% error at value of 10 mM (180 mg/dL)**

Lyon ME and Lyon AW Clin Biochem 2011;44:412-7

Technologic limitations of glucose meters

- **Hematocrit "interference"**



- **> 10% overestimation at low Hct**
- **> 10% underestimation at high Hct**

Karon et al Diabetes Tech Ther 2008;10:111-20.

Technologic limitations of glucose meters

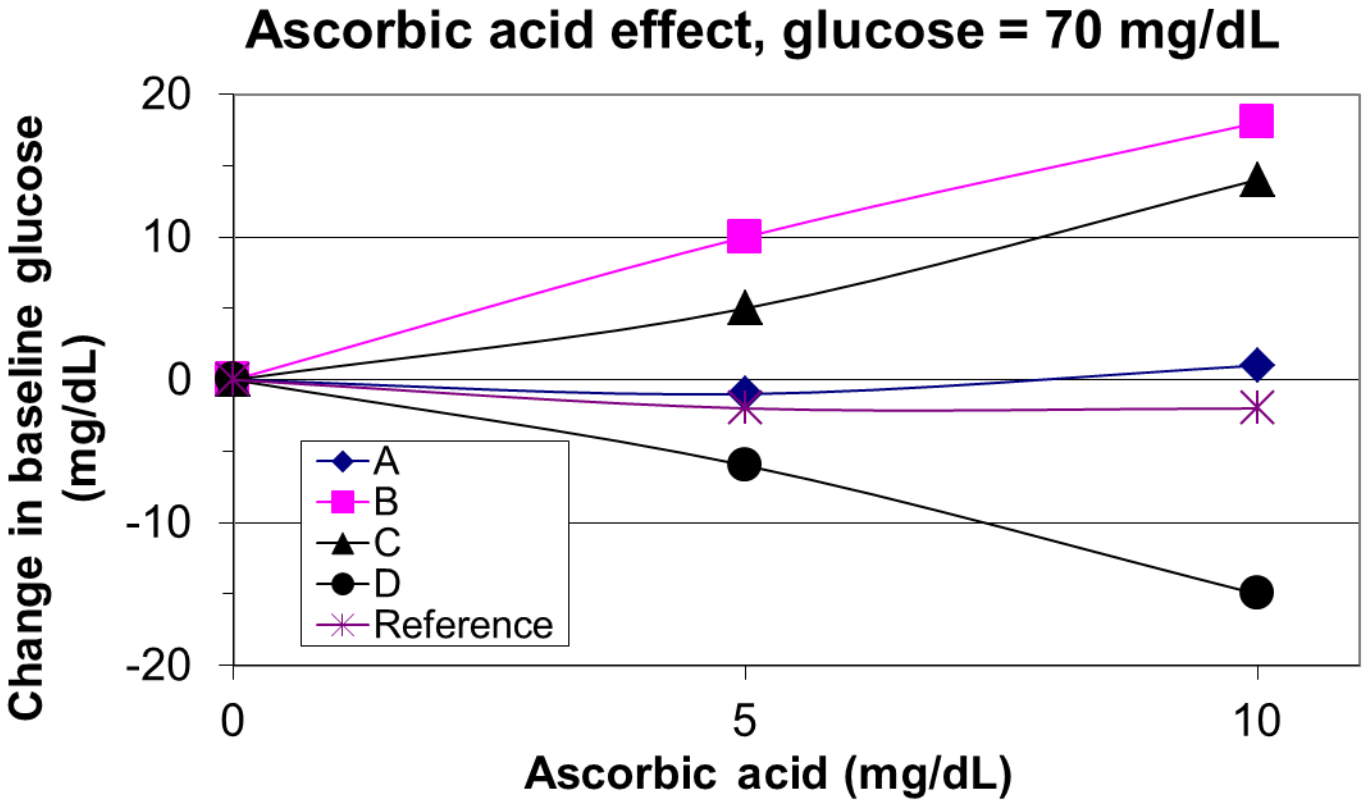
- Capillary vs. arterial/venous glucose
- Impact of BP, edema and shock, tissue perfusion
  - Blood pressure: Shock (systolic BP less than 80 mm Hg) associated with falsely decreased or increased capillary glucose measurement
- Accuracy of capillary WB at low and high glucose
  - Khan et al Arch Pathol Lab Med 2006;130:1527-32
  - Kanji et al Crit Care Med 2005;33:2778-85
- Technologic vs. physiologic limitations of capillary sampling largely unknown

Technologic limitations of glucose meters

- Venous catheter WB glucose in critically ill
- Overestimates venous plasma glucose
  - Cook et al Am J Crit Care 2009;18:65-75
  - Shearer et al Am J Crit Care 2009;18:224-30
  - Karon et al Am J Clin Pathol 2007;127:919-26
- Bias with venous catheter samples differs by meter technology
  - Karon et al, Diabetes Technol Ther 2009:11:819-25
- Arterial catheter whole blood best available sample for glucose meter monitoring
- Assess meter technology with venous catheter whole blood if that will be primary sample type

Technologic limitations of glucose meters

- **Interference studies, ascorbic acid**



Karon et al Diabetes Tech Ther 2008;10:111-20.

Glucose meters in hospital

- **Error and outliers with WB glucose**

Condition	Sample type
Shock, hypotension, dehydration, edema	Capillary
Hematocrit effect	All
Failure to let alcohol dry	Capillary
Underdosing strips	Capillary, All
PW or RW effect	All, CVC > art line?
Medication interference	All
pH, O2 or CO2 tension	All
Use of expired or incorrectly stored strips	All
Temperature extremes	All
Incorrect calibration info	All
Improper/incorrect disinfection	All
Operator error/untrained operators	All

Glucose meter regulatory issues timeline

- March 2010
  - FDA public forum on glucose meter accuracy
  - Consensus that 2003 ISO 15197 not appropriate for ICU glucose meter use (95% results within ± 15 mg/dL for glucose < 75 mg/dL, ± 20% for glucose ≥ 75 mg/dL)
  - Debate about whether separate home and hospital, or home/hospital/ICU criteria needed
  - FDA announced new criteria forthcoming

Glucose meter regulatory issues timeline

- **2011 NACB guidelines on glucose meter accuracy**
  - **95% of glucose meter results within…**
    - *± 15 mg/dL at glucose < 100 mg/dL*
    - *± 15% at glucose ≥ 100 mg/dL*
- **November 2012, AccuChek Inform II FDA approval**
  - **No draft guidance on required accuracy**
  - **Limitation statement: "the performance of this meter has not been evaluated on critically ill patients"**
  - **FDA notes limitation statement to be added to all approved hospital use glucose meters**
  - **FDA opinion is that critical care use constitutes "off label" use of device**

Glucose meter regulatory issues timeline

- **January 2013 CLSI POCT12-A3 guidelines on glucose meter accuracy**
  - **95% of glucose meter results within…**
    - *± 12 mg/dL at glucose < 100 mg/dL*
    - *± 12.5% at glucose ≥ 100 mg/dL*
    - *98% within 2003 ISO 15197 guidelines*
- **2013 ISO 15197 revision**
  - **95% of glucose meter results within…**
    - *± 15 mg/dL at glucose < 100 mg/dL*
    - *± 15% at glucose ≥ 100 mg/dL*
    - *use of Parkes Error grid (99% zones A and B)*

Glucose meter regulatory issues timeline

- **Sept 2014**
  - **StatStrip receives FDA approval for all hospitalized patients**
    - *Venous and arterial whole blood only (neonates)*
- **Nov 2014**
  - **CMS memo to state surveyors, use meters according to intended use and limitation statement, other use "off-label"**
    - *Makes critical care use for most meters high complexity*
    - *Validation requirements in specific patient population*
    - *Personnel requirements (4 yr degree, transcripts)*
- **Oct 2016**
  - **FDA final guidance for glucose meter manufacturers**
    - *Home use: slightly more stringent but similar to ISO 15197*
    - *Hospital use: similar to CLSI POCT12A-3*

Glucose meters in the hospital

- **Will improving glucose meter accuracy and reducing interferences and outliers lead to better patient outcomes during glycemic control in the ICU?**

Variables impacting glycemic control outcome

- **Elements of glycemic control protocol that may impact patient outcome**
  - **Glucose target range**
  - **Sophistication of dosing algorithm (point to point vs trending)**
  - **System to prompt glucose measurement (manual vs. IT system)**
  - **System to relate gluc conc to insulin dose (paper vs. electronic)**
  - **Accuracy of glucose monitoring device**
    - *Hematocrit, bias and precision, medication interference*
  - **Competency of staff performing measurement**

Variables impacting glycemic control outcome

- TGC protocols associated with 5 X increase incidence of hypoglycemia
- Absolute rates of hypoglycemia vary widely between TGC studies depending on target and protocol
  - 0.34% (Stamford Hospital)
  - 18.7 % (Leuven II)
- Does the glucose meter accuracy have anything to do with glycemic control outcomes or rate hypoglycemia?

Mayo glucose meter accuracy study

- **Can "newer" glucose meter technologies achieve 12-15% total error when fresh whole blood samples are tested on critically ill patients after cardiovascular surgery?**
  - *If so, because bias or imprecision is reduced?*
  - *Where are we at today, how did we get there (reducing bias or reducing imprecision)*
- **Does reducing glucose meter error improve efficacy of glycemic control in the cardiovascular ICU?**
  - *Does it matter?*

Mayo glucose meter accuracy study

- **At Mayo Rochester StatStrip replaced AccuChek Inform 10/2012**
- **Assess impact on accuracy and precision of glucose measurements in ICU**
  - **Accuracy when routine clinical samples tested at bedside**
    - *Retrospective study with Inform and StatStrip*
  - **Precision with fresh arterial whole blood from critically ill patients**

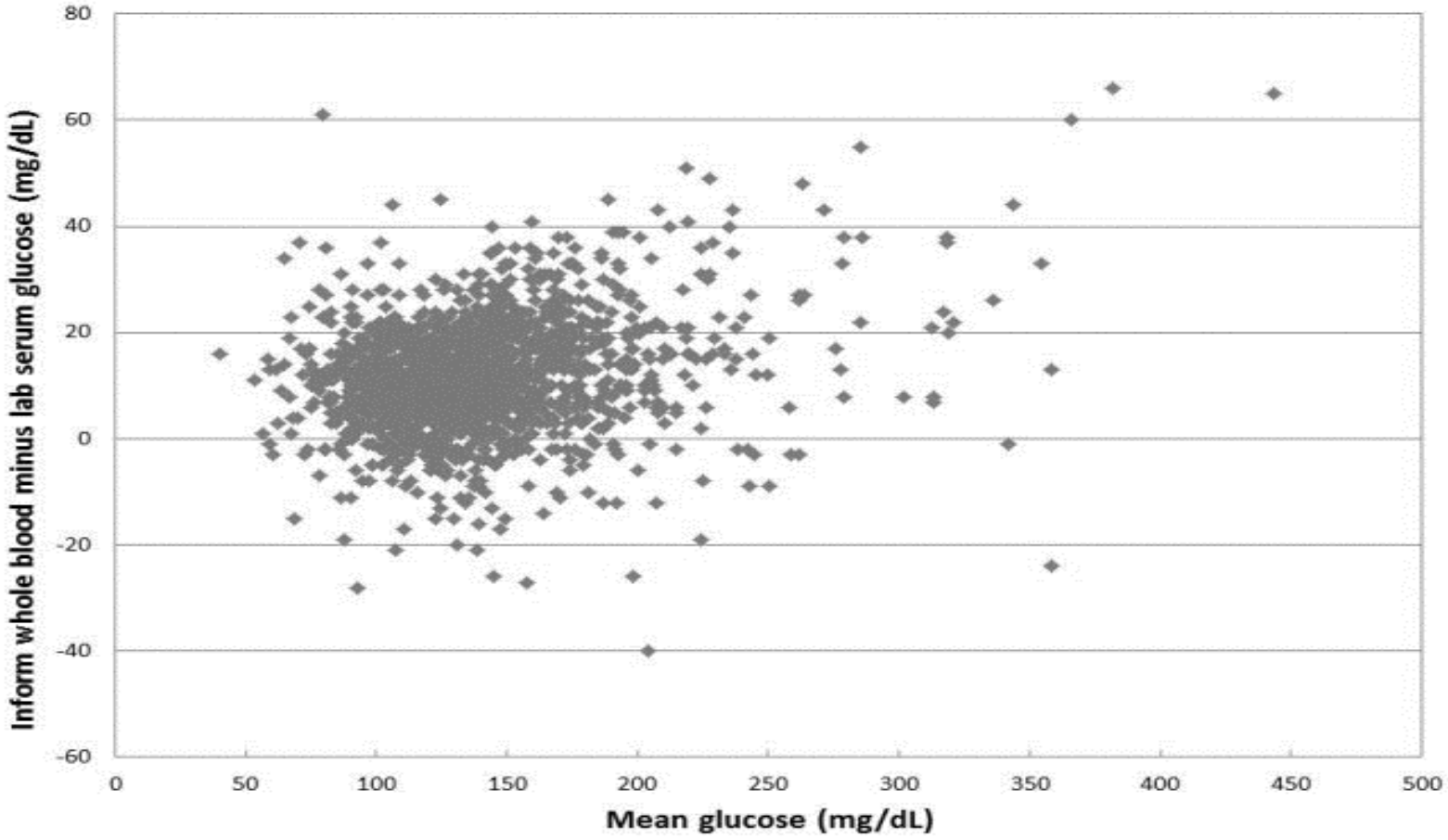
Mayo glucose meter accuracy study

- Precision (prospective study)
- AccuChek Inform I (20 ICU patients with 5x measurement at the bedside)
  - CV of 2.0% at an average glucose value of 142 mg/dL (7.89 mM)
- StatStrip (20 ICU patients with 5x measurement at the bedside)
  - CV of 2.7% at an average glucose value of 140 mg/dL (7.78 mM)
- Both meters precise when fresh whole blood tested at bedside

Mayo glucose meter accuracy study

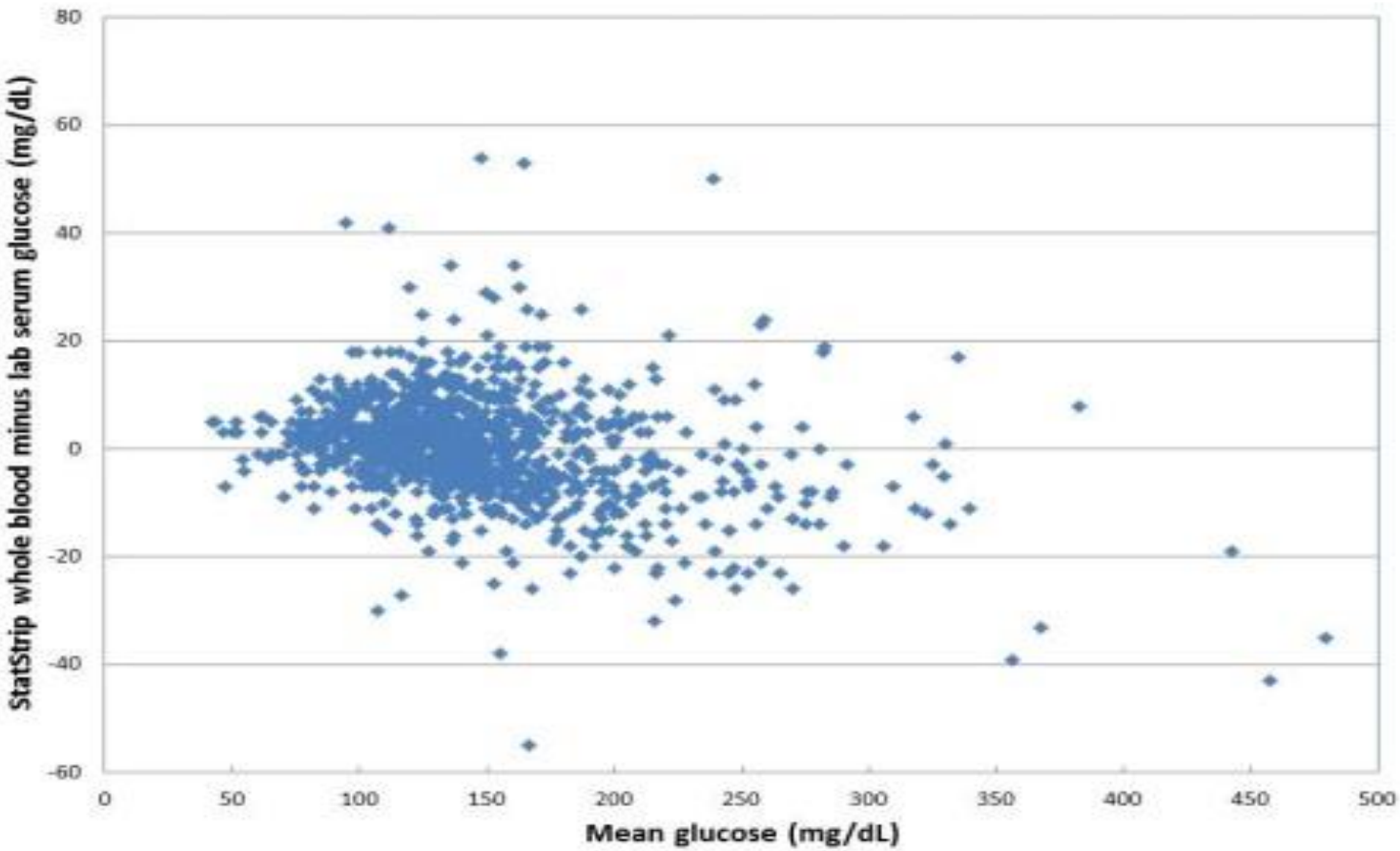
- **Accuracy (retrospective study)**
  - **Over 3 month period, 1602 Inform whole blood glucose measurements performed within 5 minutes of drawing serum glucose (Roche Hexokinase)**
  - **Over separate 3 month period, 1093 StatStrip whole blood glucose performed within 5 minutes of serum glucose**

Mayo glucose meter accuracy study



- Median bias 11 mg/dL (0.61 mM)
- Median (IQR) % bias 9 (4 to 14) %

Mayo glucose meter accuracy study



- Median bias 1 mg/dL (0.06 mM)
- Median (IQR) % bias 1 (-3 to 5) %

Mayo glucose meter accuracy study

	Inform (n=1602)	StatStrip (n=1093)
Percent within 10% lab	55%	89%
Percent with 20% lab	92%	98%
% within 12.5%/12.5 mg/dL (CLSI POCT12-A3) serum	69%	95%

- **By reducing bias, reduced TEa from ~20% ⟹ 12.5%**

Is StatStrip accurate in different ICU settings?

- **Prospective accuracy study across 5 ICUs**
  - **2 Netherlands, 1 Belgium, 2 US sites**
  - **Surgical, medical, burn patients**
  - **1815 paired measurements from 1698 patients**
  - **96.1% met CLSI POCT12-A3 criteria**
  - **99% zone A Parkes Error Grid, 100% zones A/B**
  - **99.1% (223/225) concordance in characterizing hypoglycemia (glucose < 70 mg/dL)**

  - ***DuBois et al, Crit Care Med 2017;45:567-71.***

Impact of insulin dosing errors on glycemic control in ICU

- **Impact on patient outcome**
  - ICU/hospital mortality
  - Hospital morbidity (infections, transfusions, renal failure)
  - Requires randomized trial > 1000 patients
- **Impact on glycemic control efficacy**
  - Glycemic variability
  - Time within target range
  - Incidence hypo and hyperglycemia
  - Requires 50-150 patients per study arm

Impact of insulin dosing errors on glycemic control in ICU

- **Why measure glycemic control efficacy?**
  - **Hypoglycemia important outcome**
  - **Hyperglycemia is what is being avoided**
  - **Glycemic variability**
    - *More variability = more hypo and hyperglycemia*
    - *Increased variability (extreme highs and lows) may alone decrease survival in ICU*
  - **↑ time in target range, ↓ hypo and hyperglycemia, ↓ variability = better protocol**
  - **Can reducing meter error alone lead to a better protocol?**

Study design

- Given improved accuracy of meter in ICU
  - ~20% ⟹ 12.5% TEa
- Can we measure impact on glycemic control efficacy?
- Retrospective review patients post cardiovascular surgery placed on glycemic control in CVS ICU
  - 12-24 consecutive (30-120 min) glucose values on insulin drip
  - Period 1 (70 patients monitored with AccuChek Inform)
  - Period 2 (70 patients monitored with StatStrip)
  - No change infusion protocol, testing personnel, etc

Study design

- **Measures glycemic variability**
  - **Standard deviation (SD)**
  - **Continuous overall net glycemic action (CONGA)**
  - **Percent values in target range (110-150 mg/dL)**
  - **Incidences of hypoglycemia and hyperglycemia**

Patient demographics	Period 1 (6-11/2012)	Period 2 (8/13-2/14)	P value
Mean ± SD age (range)	68 ± 12 (28-92)	65 ± 12 (29-86)	0.22
Gender	39 M/ 31 F	42 M/ 28 F	0.61
Diabetes	35 ND/ 35 T2DM	35 ND/ 35 T2DM	
Median (range) number glucose values	22 (12-24)	21 (12-24)	0.16

Results—Glycemic variability and time within target range

- **Overall results (non-diabetic and T2DM)**

	Period 1 (n=70)	Period 2 (n=70)	P value
Median (IQR) glucose (mg/dL)	**141** (126, 156) mg/dL	**136** (125, 148) mg/dL	0.005
Median (IQR) standard deviation (SD)	**21.6** (16.9, 26.3) mg/dL	**13.7** (12.4, 19.1) mg/dL	< 0.0001
Median (IQR) CONGA	**19.4** (16.0, 24.2) mg/dL	**13.5** (10.9, 17.3) mg/dL	< 0.0001
Median (IQR) percent values in target range (%)	**66.7** (50, 74.2) %	**74.5** (58.5, 86.7) %	0.002

Glycemic variability decreased and time in target range increased with improved meter accuracy

Results—Glycemic variability and time within target range

- **Non-diabetic patients only**

	Period 1 (n=35)	Period 2 (n=35)	P value
Median (IQR) standard deviation (SD)	**18.7** (16.3, 25.6) mg/dL	**15.4** (12.4, 19.9) mg/dL	0.004
Median (IQR) CONGA	**18.3** (13.3, 21.6) mg/dL	**13.5** (10.2, 19.0) mg/dL	0.04
Median (IQR) time in target range (%)	68.8 (61.9, 79.2) %	73.7 (62.5, 87.5) %	0.10

- Glycemic variability (SD and CONGA) decreased ~ 20%
- No significant change in time in target range

Results—Glycemic variability and time within target range

- **Type 2 diabetes only**

	Period 1 (n=35)	Period 2 (n=35)	P value
Median (IQR) standard deviation (SD)	**22.4** (17.7, 28.0) mg/dL	**13.6** (12.3, 18.3) mg/dL	<0.0001
Median (IQR) CONGA	**21.4** (18.3, 27.5) mg/dL	**13.5** (11.7, 15.2) mg/dL	<0.0001
Median (IQR) time in target range (%)	**61.9** (46.7, 72.7) %	**78.3** (54.2, 85.7) %	0.006

- ~ 40% decrease in glycemic variability (SD and CONGA)
- ~25% increase in time in target range

Bigger impact on patients with Type 2 diabetes

Results—Incidence of hypo and hyperglycemia

- **Hypoglycemia (< 70 mg/dL, 3.89 mM)**
  - **1 patient, 1 value Period 1**
  - **0 patients, 0 values Period 2**
- **Hyperglycemia (> 200 mg/dL, 11.11 mM)**
  - **26 patients (7 non-diabetic and 19 T2DM), Period 1**
  - **6 patients (1 non-diabetic and 5 T2DM), Period 2**

Pediatric burn patients

- **Similar before and after retrospective study design**
  - **63 patients monitored with Inform 1**
  - **59 patients monitored with StatStrip**
  - **Glycemic target 80-130 mg/dL (lower)**
- **Mean bias 7.4 ± 13.5 (Inform 1) vs. -1.7 ± 6.9 mg/dL (StatStrip)**
- **Glycemic control improved with StatStrip (CONGA, CV, MAGE, MODD)**
- **Time to therapeutic range 13.1 ⟶ 5.7 hours**
- **Time in range 57.9 ⟶ 85.2%**
- *Tran et al, Pediatr Crit Care Med 2016;17:e406-12*

Conclusions

- **Glucose meter use in the hospital**
  - **Capillary sampling and hematocrit effects major issues**
  - **Technology can address hematocrit effects**
  - **Capillary sampling limitations remain largely undefined**

Conclusions

- **Glucose meter use in the hospital**
  - **Often done on non-diabetic patients**
  - **Tighter glucose ranges, more opportunities to "translate" glucose measure error into insulin dosing error**
  - **Sources of error (hematocrit, medication interferences, sample type differences) more pronounced effects**
- **Newer glucose meter technologies reduce error of glucose measurement when used at the bedside on critically ill patients**
- **Evidence emerging that improving glucose meter performance (reducing error) will improve efficacy of glycemic control**

Questions?