Glucose meters in various settings

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Objectives

- **Define uses of glucose meters in home, outpatient, inpatient ICU and NICU settings**

- **Weigh benefits of glycemic control vs. adverse effects of hypoglycemia**

- **List various proposed and established guidelines for glucose meter accuracy**

Introduction

- **How accurate do glucose meters need to be?**

  Monitor glucose level for subq dosing
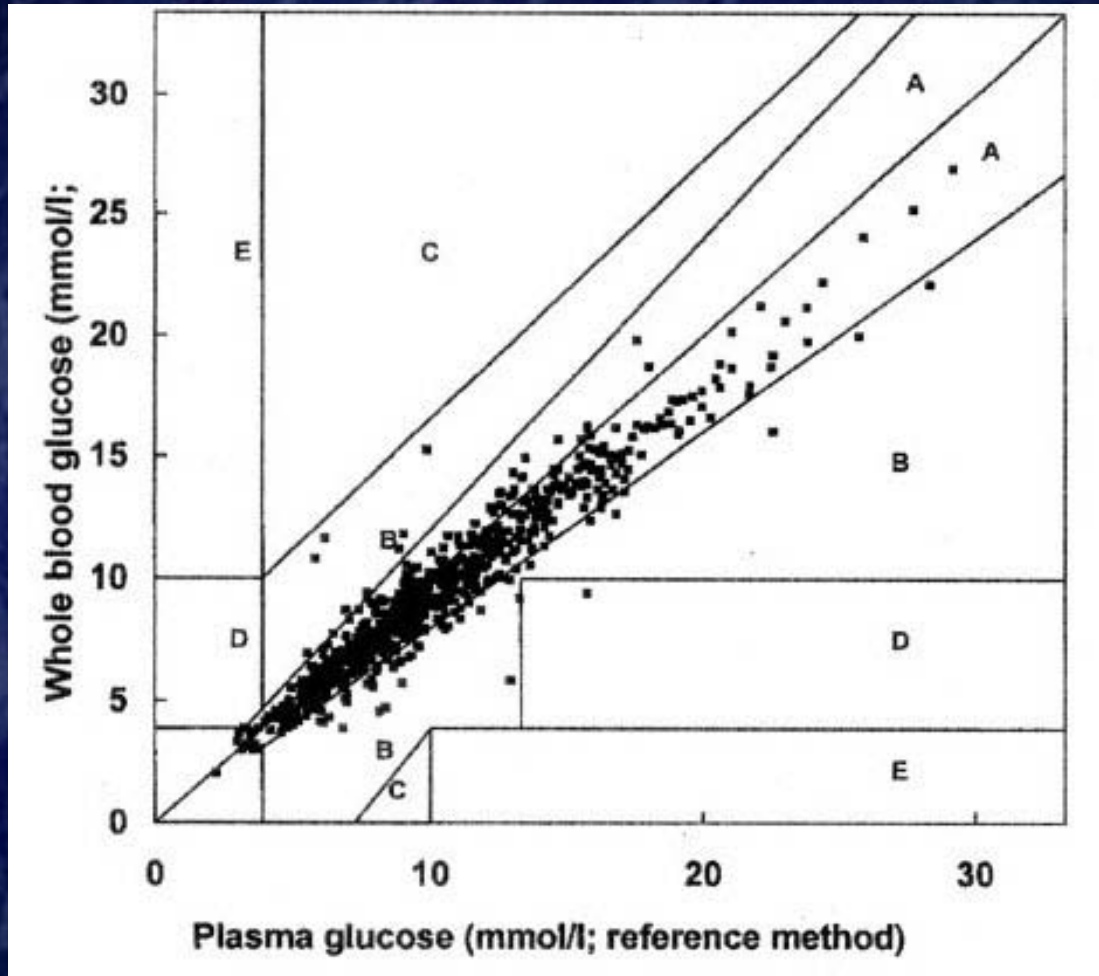 **In home**
  In hospital

  Wide therapeutic ranges

  Wide distribution of glucose values

  Error grid analysis

Introduction

Introduction

- **Error Grid zones**

  A = Clinical accurate
  B = Clinically irrelevant deviation (> 20%)
  C = Unnecessary overcorrection possible
  D = dangerous failure to detect and treat
  E = erroneous treatment

  % A and B most common form of evaluation

Introduction

- **Advantage of error grid analysis**
  Translates error into clinical impact

  Visual display of current guidelines (ISO 15197)
  ± 15 mg/dL at glucose < 75 mg/dL
  ± 20% at glucose ≥ 75 mg/dL

- **Limitations of error grid analysis**
  Only meaningful for subq insulin dosing
  Every meter looks good (% A and B)

Introduction

- **Traditional use of glucose meters in home and hospital**

    Dose subcutaneous insulin in diabetic patients

    Critically ill patients:

    Keep glucose levels < 200 mg/dL

    Dose insulin in diabetic patients

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What are issues with use of glucose meter in hospital?

- **Whole blood vs. plasma glucose**

    Whole blood glucose ~ 15% lower than plasma glucose

    For many years 10-15% differences between lab (plasma) and glucose meter (whole blood) glucose were observed

    Caused confusion to clinicians, labs didn't like it

    US Vendors now calibrate reagents to express "plasma-equivalent" units

    If calibration works, essentially no difference between glucose meter (whole blood) and lab (plasma) glucose
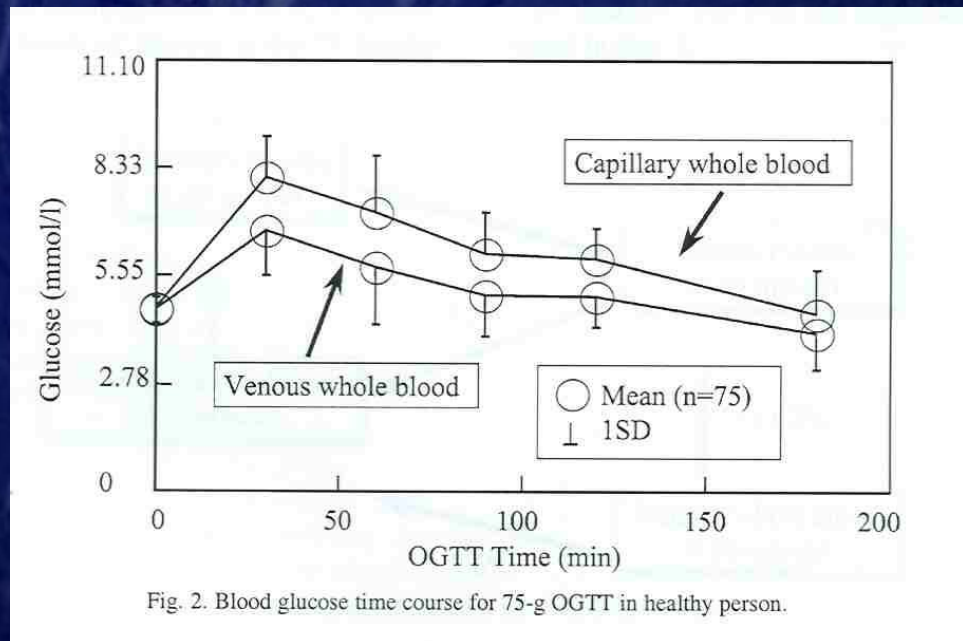
What are issues with use of glucose meter in hospital?

- **Capillary vs. arterial/venous glucose**

In fasting state, capillary and venous glucose equivalent

In response to insulin, capillary glucose increases relative to venous

Kuwa et al., Clin Chim Acta 2001;307:187-192

Fig. 2. Blood glucose time course for 75-g OGTT in healthy person.

Why might meters work better in patients with diabetes?

- Capillary vs. venous glucose
- What about patients with insulin resistance?

Weiss et al., 1998 Am J Ob Gyn 178;830-5

30 patients with gestational diabetes and 30 controls
2 hr glucose challenge test

Controls: Fasting capillary = venous glucose
            1 hr, 2 hr capillary glucose > venous whole

Diabetes: Fasting, 1 hr and 2 hr capillary = venous

What are issues with use of glucose meter in hospital?

- **Other issues**

- **Blood pressure: Shock (systolic BP less than 80 mm Hg) associated with falsely decreased capillary glucose measurement**

- **Critically ill: ED studies showing venous whole blood greater than capillary whole blood, both greater than venous plasma**

What are issues with use of glucose meter in hospital?

- **Glucose meters work to monitor glucose at home and in in diabetic hospitalized patients because:**

   Glucometers calibrated to plasma-equivalent units

   Sliding scale dosing allows moderate error

   Intent to measure in fasting state, where differences between capillary and venous minimal

   Difference between capillary and venous glucose diminished in diabetics

Introduction

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D.,
FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D.,
PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

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Van den Berghe

- **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)

After Van den Berghe

- ## 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

- ## NICE SUGAR (NEJM 3/2009)
  - Multi-center trial of TGC (42 hospitals, Australia, New Zealand, Canada, US)
  - TGC increased mortality in mixed medical and surgical ICU patients
  - 14-fold increase in hypoglycemia (6.8% intensive group)
  - Multiple meters and lab methods used

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Adverse effects of hypoglycemia

- **TGC protocols associated with 5-14 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)**

Adverse effects of 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 TGC

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Adverse effects of hypoglycemia

- **Theoretically increased SH may offset benefits of glycemic control**

- **Realize not all SH caused by insulin in ICU**
  - **Liver failure, sepsis, etc**

- **Rates and percent increase in SH differ dramatically by site and TGC protocol**

What should performance criteria be for glucose monitors?

- **Vendors: ISO 15197**
  - $\pm$ 15 mg/dL at glucose < 75 mg/dL
  - $\pm$ 20% at glucose $\geq$ 75 mg/dL

    Sufficient by Clarke Error grid for subq insulin dosing

- **American Diabetes Association**
  - $\pm$ 10% of true value for all devices for all purposes (home use, hospital use)
  - $\pm$ 5% of true value is ideal

- **"Expert consensus" that error tolerance needs to be decreased for next revision of ISO 15197 and related CLSI guidelines**

    Separate home use and hospital use guidelines?

    Separate hospital use, ICU and NICU guidelines?

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Glucose meters OK in ICU?

• **Ideal study would relate device accuracy to patient outcome**

• **Most studies compare meter result to reference result for small # patients**

• **~ 12 studies specifically looking at glucose meter accuracy in ICU and/or TGC**

> **Small insulin dosing errors common but in general OK**
>
> **Meters not accurate in hypoglycemic range, not OK**
>
> **Meters OK for TGC using Parkes error grid**
>
> **Meters not OK for critically ill using ISO 15197 criteria**

Does glucose meter inaccuracy contribute to poor outcome during TGC?

Perspectives

Tight Glucose Control in the Intensive Care Unit: Are Glucose Meters up to the Task?

Mitchell G. Scott,[1*] David E. Bruns,[2] James C. Boyd,[2] and David B. Sacks[3]

Error simulation modeling

Quality Specifications for Glucose Meters: Assessment by Simulation Modeling of Errors in Insulin Dose

JAMES C. BOYD[*] and DAVID E. BRUNS

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Error simulation modeling

- **Boyd and Bruns, Clin Chem 2001;47:209-14**

- **Randomly generated glucose values between 150-450 mg/dL**

- **Assume target ranges of 30 or 50 mg/dL (subq dosing algorithms)**

- **Result simulation to model effect of various levels of bias and imprecision on dosing category**

- **Acceptable performance if ≥ 2 dose category errors occurred ≤ 0.2% of time**

- **Meter performance acceptable for subq dosing**

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Error simulation modeling

- **Accuracy requirements for TGC?**

Histogram of 29,920 glucose values for patients on intravenous insulin
Median value = 116 mg/dL (IQR 102-135)

Glucose range (insulin dose)
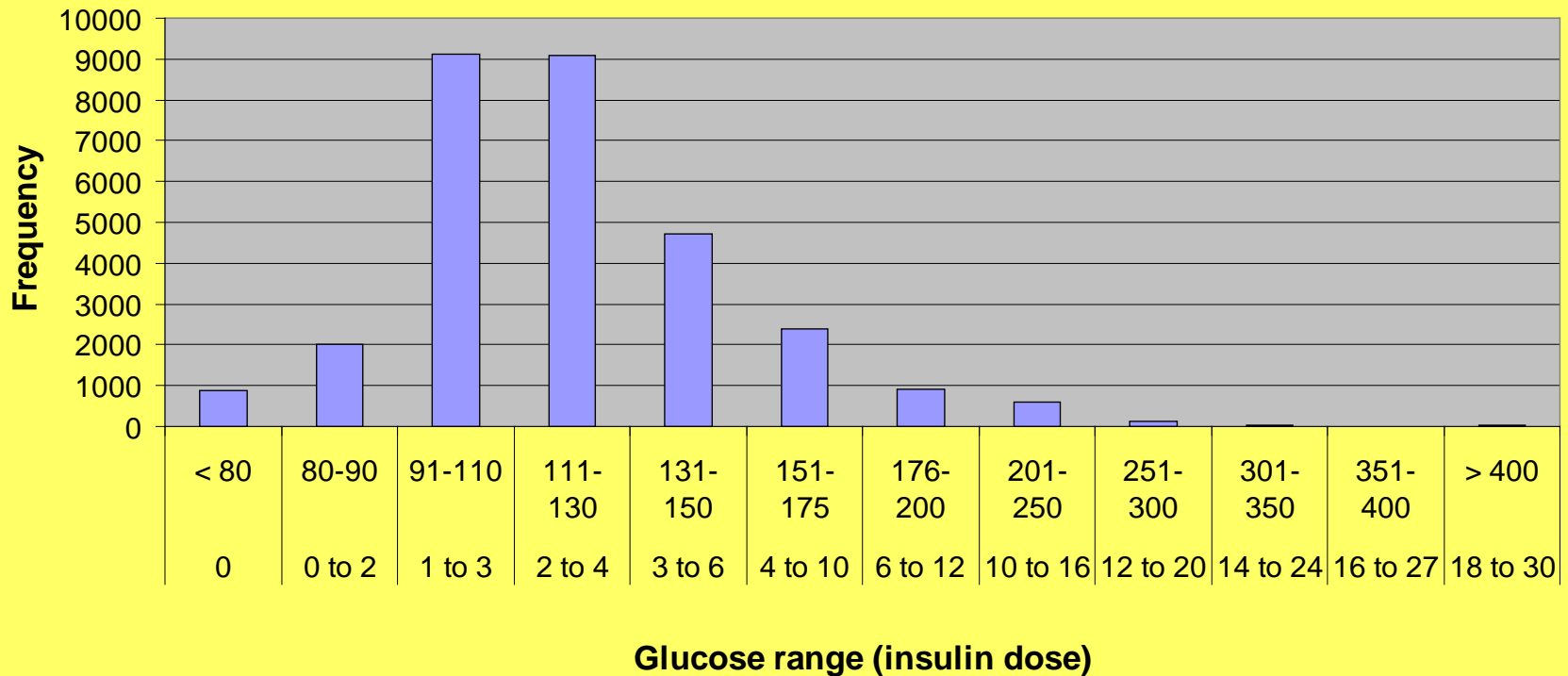
86% values ≤ 150 mg/dL, prevent hypoglycemia

Error simulation modeling for TGC

- **Start with distribution of glucose values in patients on TGC**

- **Sample this distribution, for each initial value sampled simulate 10,000 values with distribution of bias and imprecision:**

  Glucose (simulated) = Glucose initial +

  [n(0,1) x CV x glucose (initial)] + [Bias x glucose (initial)

  n(0,1) random number drawn from gaussian distr centered on zero with SD=1

  CV varies from -20 to +20%

  Bias varies from 0 to 20%

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Error simulation modeling for TGC

- **Calculate % simulated values that fall in same insulin dosing category as initial**

- **Calculate % 1, 2, or ≥ 3 category dosing errors based on Mayo TGC protocol**

- **Express results as contour plots, showing % dosing errors as a function of bias and imprecision**

- **Superimpose boundaries for 10%, 15% and 20% total error (TEa) on contour plots**

Error simulation modeling for TGC

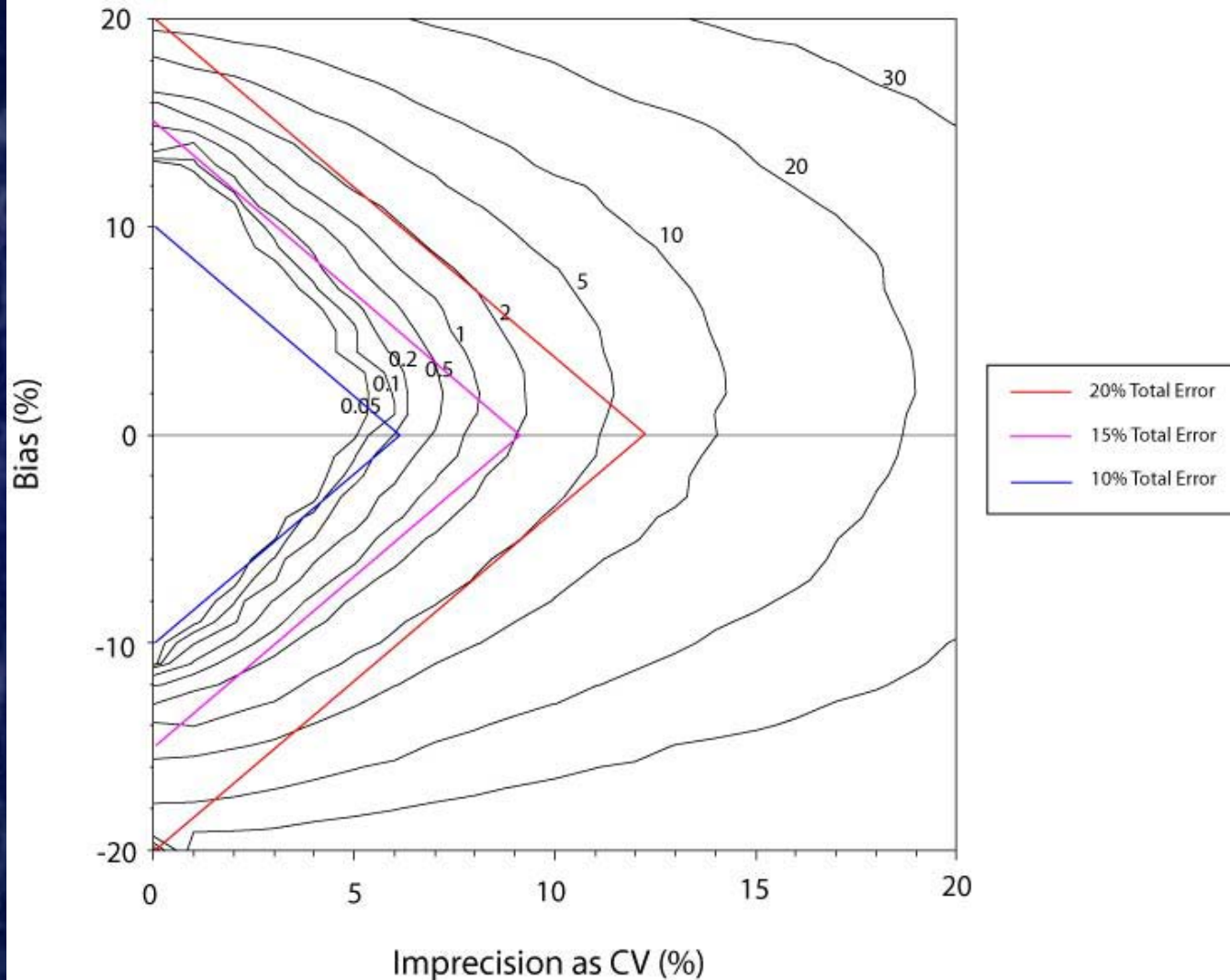Mayo Intensive Insulin 1 Step Dosing Errors (%)
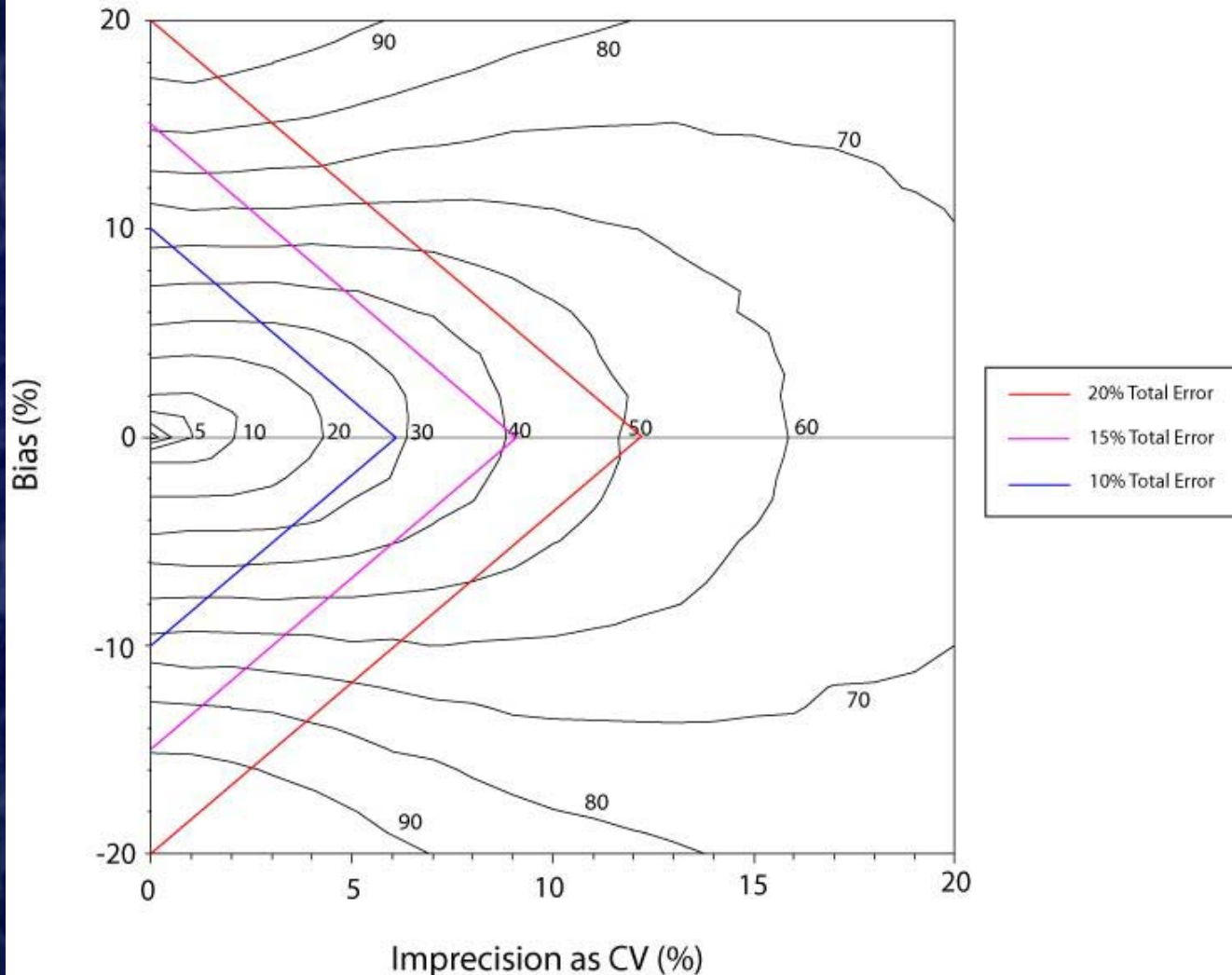
Error simulation modeling for TGC

- **Up to 60% one category dosing errors when 10% TEa is simulated**

- **Up to 80% one category dosing errors when 15% TEa is simulated**

- **Up to 90% one category dosing errors when 20% TEa is simulated**

Error simulation modeling for TGC


Mayo Intensive Insulin 2 Step Dosing Errors (%)

Error simulation modeling for TGC

- **Only 0.2% two category dosing errors when 10% TEa is simulated**

- **Up to 5% two category dosing errors when 15% TEa is simulated**

- **Up to 20% two category dosing errors when 20% TEa is simulated**

- **Negative bias produces more errors than positive bias**
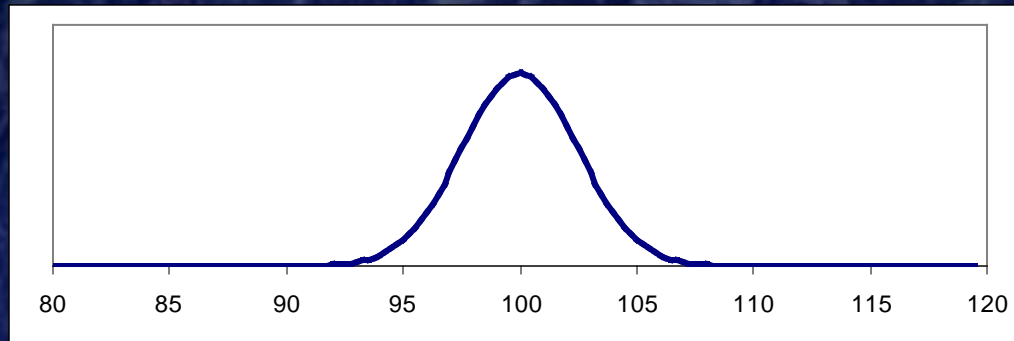
Error simulation modeling for TGC

Mayo Intensive Insulin 3 Step Dosing Errors (%)
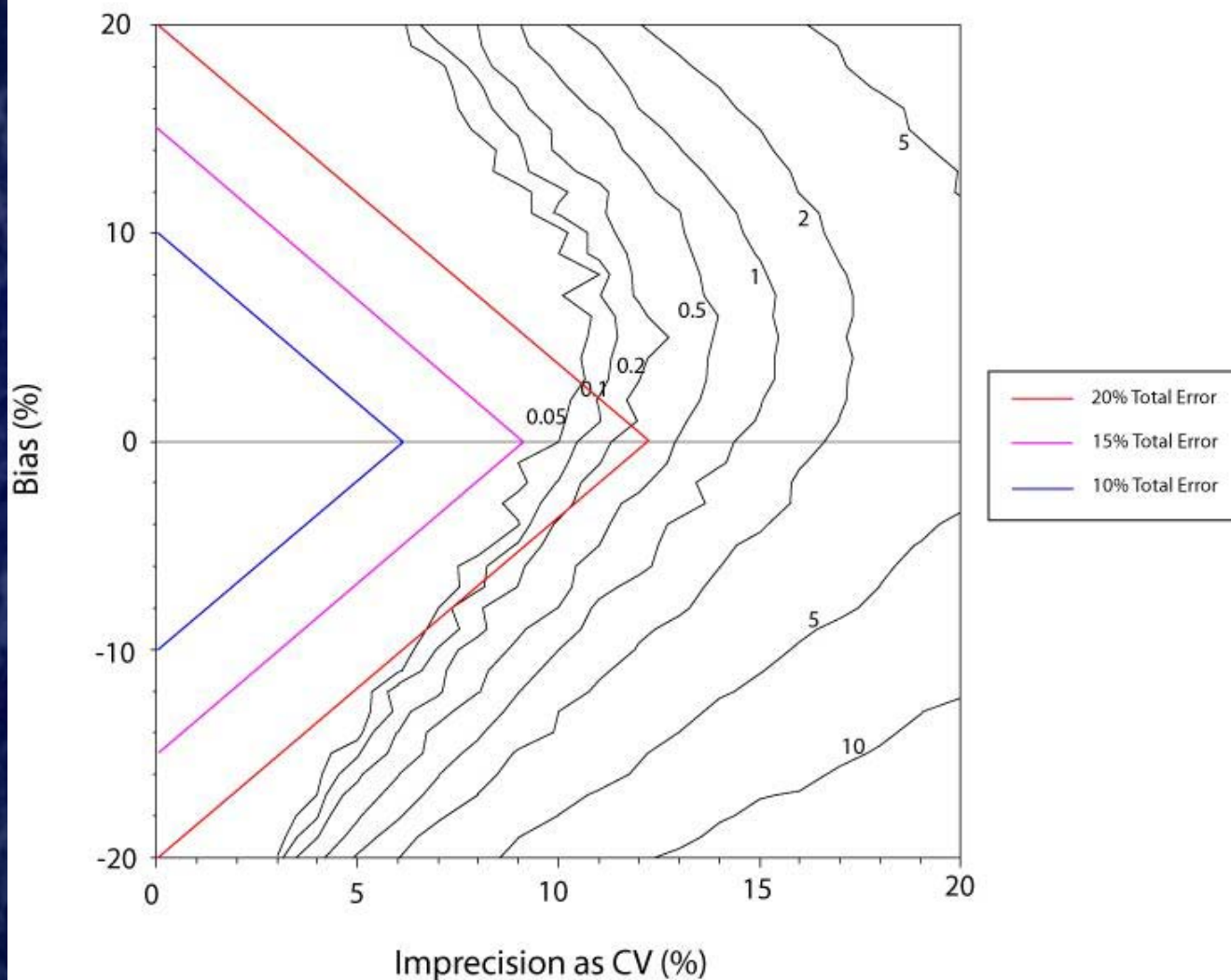
Error simulation modeling for TGC

- **Only the 20% TEa condition was associated with any frequency of 3 or more category insulin dosing errors**

Error simulation model for TGC

- **For each of 29,920 initial values:**

  Generate 1000 simulated values with distribution of X% error using SAS (Carey, NC)

  Determine how many simulated values would change insulin dosing category relative to original value

Error simulation model for TGC

- **3 sets of 29,290,000 simulated values assuming 10%, 15% or 20% total error**

- **For each set calculated % 0, 1, 2, $\geq$ 3 category dosing error based on Mayo TGC protocol**

Error simulation model for TGC

Error condition	10 % error	15 % error	20 % error
No change dose	71.4 %	58.7 %	48.8 %
1 category dose	28.4 %	39.3 %	44.8 %
2 category dose	0.2 %	2.0 %	6.1 %
≥ 3 category dose	0.0 %	0.02 %	0.3 %

Summary of error models

- **Decreasing acceptable error tolerance from 20% to 10% will decrease 2 category errors**
  - Additional studies necessary to understand impact of 2 category dosing errors
  - Both bias and imprecision need to be minimized to reduce 2 category errors

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Summary of error models

- **Only 20% TEa condition allowed 3 category or critical errors in either model**
  - **Imprecision drives 3 category dosing errors**

- **So far models predict that meters that maintain 15% TEa and minimize imprecision may be safe and effective for TGC monitoring**

- **Model assumes single dosing error leads to patient harm, more complex models needed to understand cumulative dosing errors**

Effect of moderate glycemic targets

- **Many institutions moderate glycemic targets after NICE-SUGAR**
    - 140-180 mg/dL
    - 110-150 mg/dL

- **Insulin target range driver of hypoglycemia and glycemic protocol effectiveness**
    - Should affect glucose meter accuracy needs

- **Future simulation studies will compare effects of bias and imprecision during MGC vs. TGC**

Neonatal hypoglycemia

- **Postnatal glucose homeostasis in late-preterm and term infants**
  Pediatrics 2011;127:575-9

- **Common during first 1-12 hrs life**

- **Infants of diabetic mothers, SGA, LGA, septic or sick at risk**

- **No definition of NH**

- **Treatment guidelines**
  Symptomatic: glucose < 40 mg/dL (IV glucose)
  Asymptomatic at-risk infants
    Birth-4 hrs: < 25 and 25-40 mg/dL
    4 – 24 hrs: < 35 and 35-45 mg/dL

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Neonatal hypoglycemia

- **Laboratory information**

  Plasma or blood glucose using enzymatic method (hexokinase, glucose oxidase, dehydrogenase)

- **"There is no point of care method that is sufficiently reliable to be used as the sole method for screening for NH"**

- **Point of care glucose results must be confirmed by laboratory glucose ordered stat**

Conclusion

- **Glycemic control in the ICU will continue to be a hot topic**
  - Moderate glycemic control (140-180) or some variation may be optimal?

- **Avoiding hypoglycemia essential in successful glycemic control protocol**
  - Human factors in addition to technical performance of monitoring devices
  - Role of glycemic variability?

- **Recommendations for glucose meter accuracy likely to be tightened**
  - Separate home vs. hospital use?
  - 10, 12 or 15% TE for all?
  - Separate home, hospital and ICU use?

Questions?

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