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# Management of hyperglycemia in the perioperative patient. 39th Annual Refresher Course on Anesthesiology and Perioperative Medicine, Mexico

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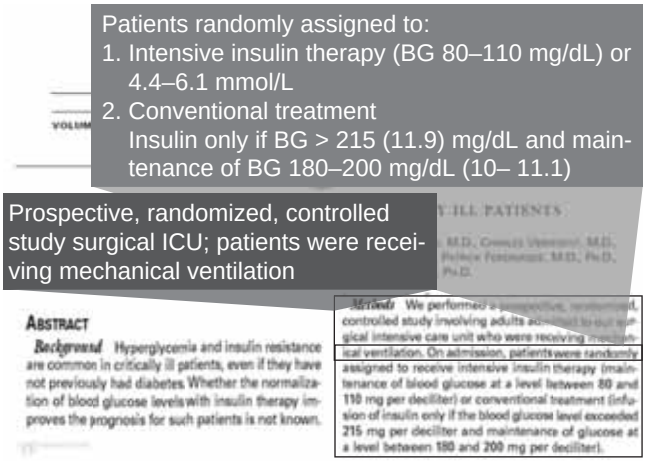
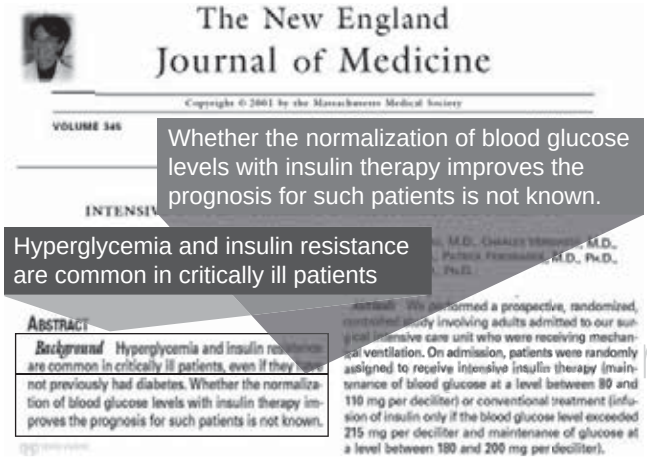
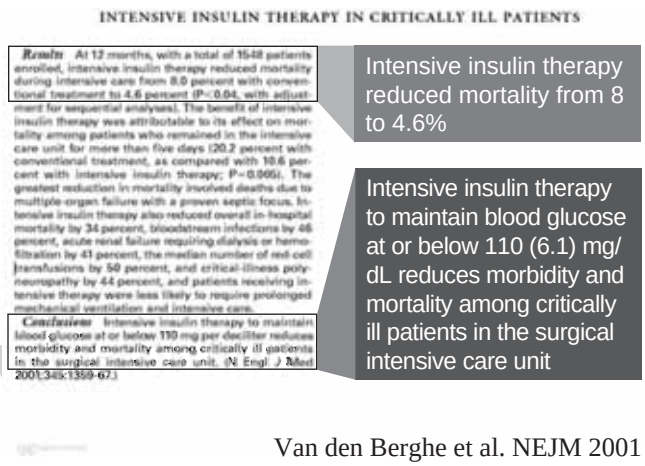
* Mayo Clinic, Rochester, MN. July 2013.

## CASE

- 55 young man in operating room for AVR and CAB
- No known history of diabetes
- Glucose levels 145 mg/dL (8.0 mmol/L)
- HbA1c 5.6%
- Should the hyperglycemia be treated?
- What if blood glucose 167 mg/dL (9.3)?



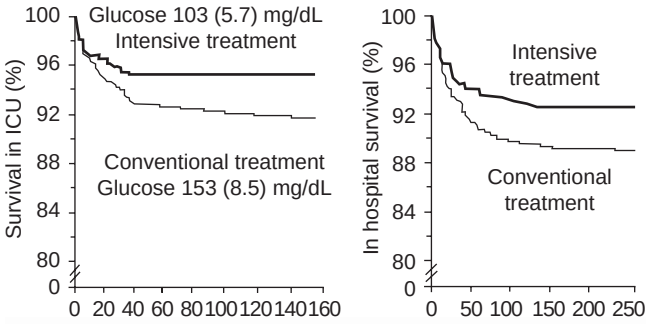




Van den Berghe et al. NEJM 2001

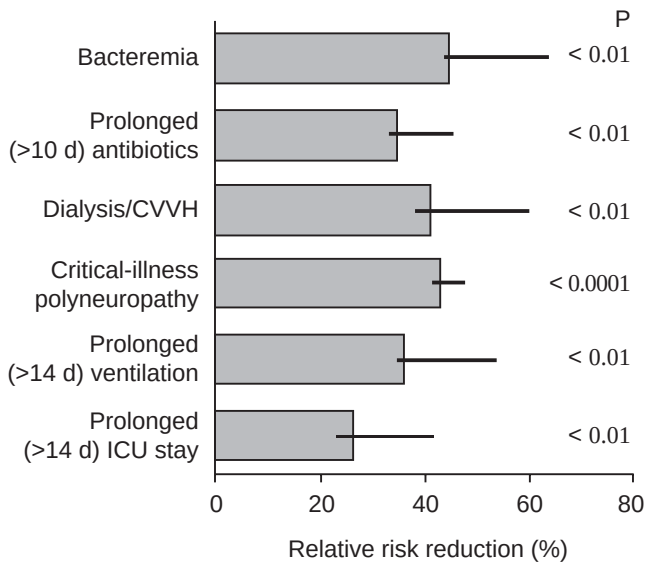
Survival with intensive insulin therapy in ICU

Treatment group had 6-fold increase in hypoglycemia (< 40 (2.2) mg/dL)




Van den Berghe et al. NEJM 2001

Morbidity




Van den Berghe et al. NEJM 2001

## IMPORTANCE OF GLUCOSE CONTROL

- Hyperglycemia during cardiac surgery is frequent and often severe
- Glucose toxicity associated with mitochondrial structural and functional abnormalities
- Improved outcomes with strict glycemic control and/or insulin

Van den Berghe et al. NEJM 2001 Concerns

## CONCERNS

- Single center, not blinded, stopped early
- IV glucose plus nutrition
- High mortality of cardiac surgery
- Implausible reduction in mortality
- Hypoglycemia
- Reproducibility

«However, further study of this approach … is essential to confirm its benefits. Until then, widespread adoption of this treatment would be premature.»

Evans TW. Editorial: NEJM 2001; v 345: 1417

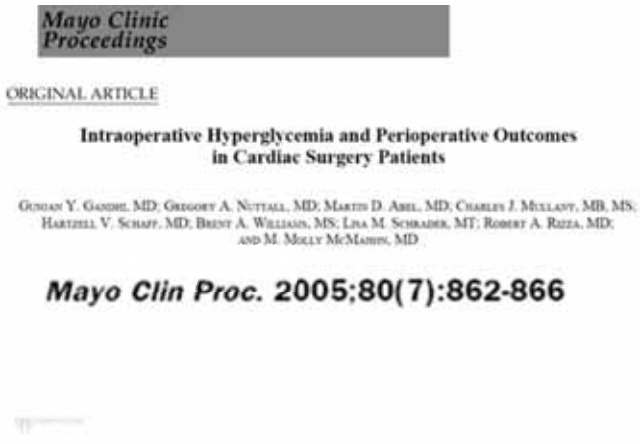
## CONSIDERATIONS

- Studies have focused on post-op control
- Independent contribution of intra-op hyperglycemia on outcomes not known
- Data extrapolated to other clinical settings including the operating room
- Professional organizations recommend tight glycemic control in ICUs

## IMPLEMENT EFFECTIVE GLUCOSE CONTROL

- Intensive insulin therapy halved the prevalence of:
  — Blood stream infections
  — Prolonged inflammation
  — ARF requiring dialysis or hemofiltration critical illness polyneuropathy transfusion requirements

Institute for Healthcare Improvement
http://www.ihi.org


Mayo Clinic Proceedings

ORIGINAL ARTICLE

**Intraoperative Hyperglycemia and Perioperative Outcomes in Cardiac Surgery Patients**

Gunjan Y. Gandhi, MD; Gregory A. Nuttall, MD; Martin D. Abel, MD; Charles J. Mullany, MB, MS; Hartzell V. Schaff, MD; Brent A. Williams, MS; Lisa M. Schrader, MT; Robert A. Rizza, MD; and M. Molly McMahon, MD

*Mayo Clin Proc.* 2005;80(7):862-866

## OBSERVATIONAL STUDY

- Estimate magnitude of association between intraoperative hyperglycemia and perioperative outcomes
- Reviewed 409 consecutive adult patients undergoing cardiac surgery at Mayo Clinic in 2002

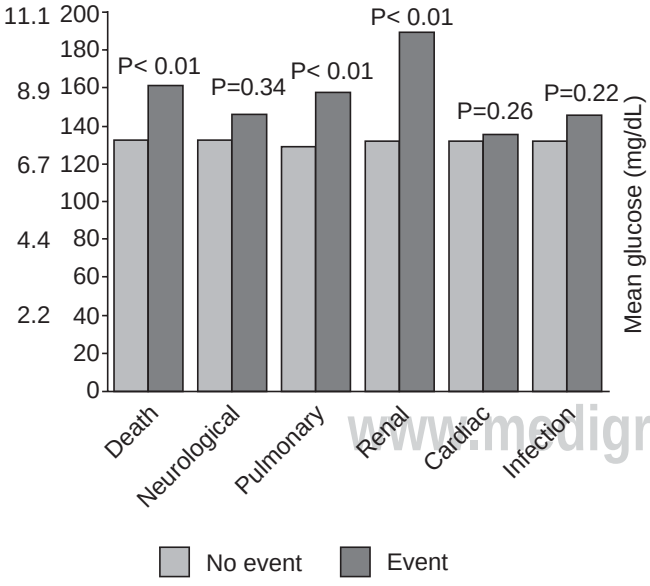
Gandhi et al. Mayo Clin Proc. 2005

## INTRAOPERATIVE GLUCOSE AND OUTCOMES

| | Adverse event (s) | No events | P |
|---|---|---|---|
| | Mean glucose ± SD (mg/dL) | | |
| Initial | 122 ± 33 | 114 ± 26 | < 0.01 |
| | 6.8 | 6.3 | |
| Maximal | 172 ± 53 | 151 ± 44 | < 0.01 |
| | 9.5 | 8.4 | |
| Mean | 141 ± 37 | 127 ± 25 | < 0.01 |
| | 7.8 | 7.0 | |

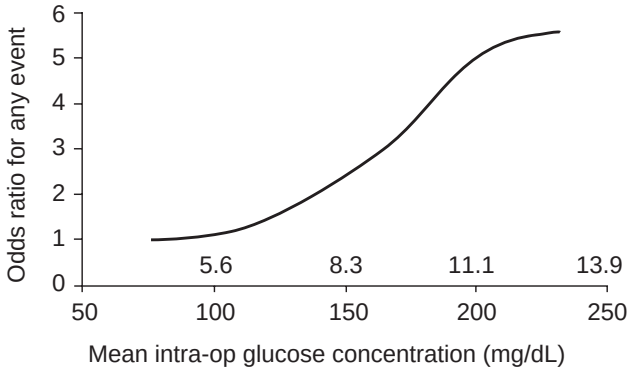
Gandhi et al. Mayo Clin Proc. 2005

## BLOOD GLUCOSE AND OUTCOME




Gandhi et al. Mayo Clin Proc. 2005

## MEAN INTRA-OP GLUCOSE CONCENTRATION AND LIKELIHOOD OF EVENT




Gandhi et al. Mayo Clin Proc. 2005

## OBSERVATIONAL STUDY: CONCLUSIONS

- Intra-op hyperglycemia is independent risk factor for complications
- Maintain glucose levels during surgery close to the normal range
- Causal inference requires randomized, controlled trial to assess risks and benefits

Gandhi et al. Mayo Clin Proc. 2005

Annals of Internal Medicine | ARTICLE

**Intensive Intraoperative Insulin Therapy versus Conventional Glucose Management during Cardiac Surgery**

A Randomized Trial

Gurjan Y. Gandhi, MD, MSc; Gregory A. Nuttall, MD; Martin D. Abel, MD; Charles J. Mullany, MD; Hartzell V. Schaff, MD; Peter C. O'Brien, PhD; Matthew G. Johnson, MPH; Arthur R. Williams, PhD; Susanne M. Cutshall, RN; Lisa M. Mundy, RN; Robert A. Rizza, MD; and M. Molly McMahon, MD

Background: It is not known whether rigorous intraoperative glycemic control reduces death and morbidity in cardiac surgery patients.

Objective: To compare outcomes of intensive insulin therapy during cardiac surgery with those of conventional intraoperative glucose management.

Design: A randomized, open-label, controlled trial with blinded end point assessment.

Setting: Tertiary care center.

Patients: Adults with and without diabetes who were undergoing on-pump cardiac surgery.

Measurements: The primary outcome was a composite of death, dental infections, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure within 30 days after surgery. Secondary outcome measures were length of stay in the intensive care unit and hospital.

Intervention: Patients were randomly assigned to receive continuous insulin infusion to maintain intraoperative glucose levels between 4.4 (80 mg/dL) and 5.6 mmol/L (100 mg/dL) (n = 199) or conventional treatment (n = 201). Patients in the conventional treatment group were not given insulin during surgery unless glucose levels were greater than 11.1 mmol/L (>200 mg/dL). Both groups were treated with insulin infusion to maintain perioperative

Results: Mean glucose concentrations were statistically significantly lower in the intensive treatment group at the end of surgery (6.3 mmol/L [SD, 1.6] [114 mg/dL [SD, 29]] in the intensive treatment group vs. 8.7 mmol/L [SD, 2.3] [157 mg/dL [SD, 42]] in the conventional treatment group; difference, −2.4 mmol/L [95% CI, −2.8 to −1.9 mmol/L] [−43 mg/dL [CI, −50 to −35 mg/dL]]). Eighty-two of 185 patients (44%) in the intensive treatment group and 86 of 196 patients (46%) in the conventional treatment group had an event (risk ratio, 1.0 [CI, 0.8 to 1.2]). More deaths (4 deaths vs. 0 deaths; $P = 0.061$) and strokes (8 strokes vs. 1 stroke; $P = 0.020$) occurred in the intensive treatment group. Length of stay in the intensive care unit (mean, 2 days [SD, 7] vs. 2 days [SD, 3]; difference, 0 days [CI, −1 to 1 day]) and in the hospital (mean, 8 days [SD, 4] vs. 8 days [SD, 5]; difference, 0 days [CI, −1 to 0 days]) was similar for both groups.

Limitations: This single-center study used a composite end point and could not examine whether outcomes differed by diabetes status.

Conclusions: Intensive insulin therapy during cardiac surgery does not reduce perioperative death or morbidity. The increased incidence of death and stroke in the intensive treatment group raises concern about routine implementation of this intervention.



## STUDY AIMS

- Compare outcomes with two strategies of controlling intra-op hyperglycemia in elective on-pump cardiac surgery in adults

— Intensive treatment: IV insulin to maintain glucose 80–100 mg/dL
4.4 – 5.6
— Conventional Treatment: Insulin for glucose ≥ 200 (11.1) mg/dL
- Determine safety and efficacy of insulin infusion protocol

Gandhi et al. Mayo Clin Proc. 2005

## COMPOSITE STUDY ENDPOINT

30 day incidence of
Death
Deep sternal infection
Stroke
Acute renal failure
Cardiac
new AF, heart block, cardiac arrest
Prolonged ventilation

Gandhi et al. Ann Intern Med 2007

## INSULINE INFUSION PROTOCOL CHARACTERISTICS

- Nurse-driven; in-service training
- Easy to use–avoids need for detailed calculations
- Aggressive titration
- Safety maximized by:
— Early tx of low glucose (< 80 mg/dL). Conservative definition of hypo- glycemia (< 60 mg/dL)

Gandhi et al. Ann Intern Med 2007

## BASELINE CHARACTERISTICS

| Variable | Intensive n = 185 | Conventional n = 186 |
|---|---|---|
| Age at surg (yr) | 63 (15) | 63 (16) |
| Male, no.(%) | 134 (72) | 123 (66) |
| BMI (kg/m$^2$) | 30 (6) | 29 (6) |
| Diabetes, no. | (%) 37 (20) | 36 (19) |

## STUDY INSULIN INFUSION ALGORITHM

| Column 1 | | Column 2 | | Column 3 | |
|---|---|---|---|---|---|
| Serum glucose (mg/dL) | Insuline infusion (u/h) | Serum glucose (mg/dL) | Insuline infusion (u/h) | Serum glucose (mg/dL) | Insuline infusion (u/h) |
| > 400 | 18 | > 400 | 25 | > 400 | 30 |
| 351-400 | 16 | 351-400 | 22 | 351-400 | 27 |
| 301-350 | 14 | 301-350 | 20 | 301-350 | 24 |
| 251-300 | 12 | 251-300 | 18 | 251-300 | 21 |
| 201-250 | 10 | 201-250 | 15 | 201-250 | 18 |
| 176-200 | 8 | 176-200 | 12 | 176-200 | 15 |
| 151-175 | 6 | 151-175 | 9 | 151-175 | 12 |
| 121-150 | 4 | 121-150 | 7 | 121-150 | 9 |
| 101-120 | 2 | 101-120 | 4 | 101-120 | 6 |
| 80-100 | 1 | 80-100 | 2 | 80-100 | 3 |
| < 80 | Off | < 80 | Off | < 80 | Off |

Gandhi et al. Ann Intern Med 2007

| | | |
|---|---|---|
| $HbA_1C$ (%) | 7 (2) | 7 (2) |
| ASA class, no. (%) | | |
| ASA 3 | 163 (88) | 161 (88) |
| Type of surgery, no. (%) | | |
| CABG other proc | 86 (46) | 91 (49) |
| No CABG | 99 (54) | 95 (51) |
| Surg time (min) | 221 (77) | 231 (82) |

Gandhi et al. Ann Intern Med 2007

## GLYCEMIC CONTROL

| | Intensive n =185 | Conventional n = 186 | *P* |
|---|---|---|---|
| Glucose mean (SD) | | | |
| Initial OR | 111 (22) | 111 (31) | 0.98 |
| End of surgery | 114 (29) | 157 (42) | < 0.01 |
| 24-h ICU | 103 (17) | 104 (22) | 0.72 |
| Hypoglycemia, no. | 9 | 15 | 0.21 |
| OR | 1 | 1 | |
| ICU | 8 | 14 | |
| Insulin administered | | | |
| Intra-op (total units) | 19 (16) | 2 (5) | < 0.01 |
| ICU (total units) | 72 (41) | 73 (37) | 0.83 |

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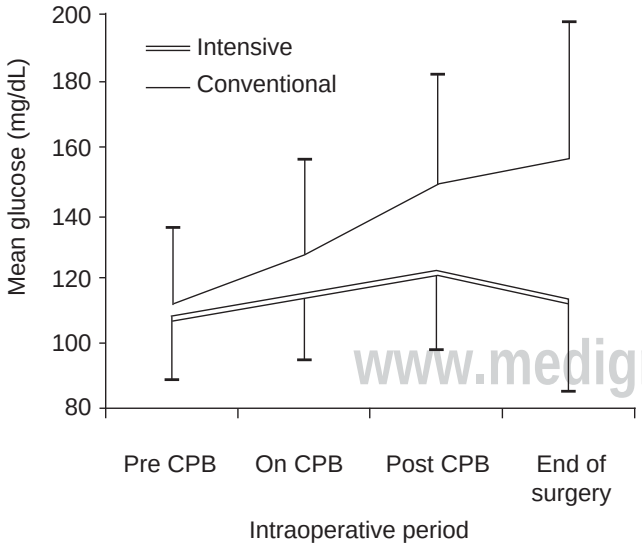
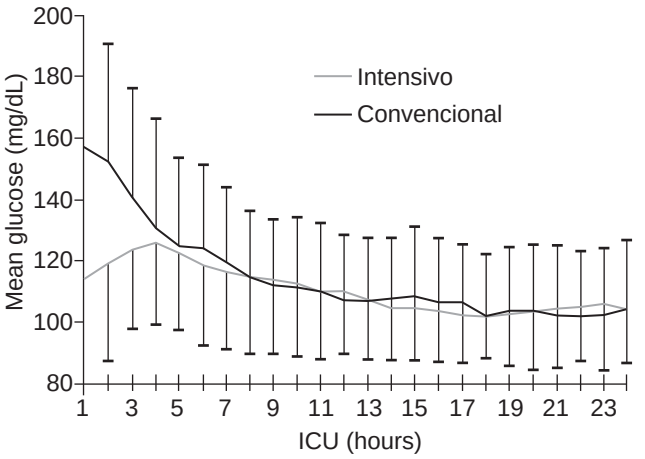
## INTRA-OP GLUCOSE CONTROL




Gandhi et al. Ann Intern Med 2007

## POST-OP GLUCOSE CONTROL




Gandhi et al. Ann Intern Med 2007

## COMPARISON OF PRIMARY AND SECONDARY OUTCOMES

| Outcome | Intensive n = 185 | Conventional n=186 | *P* |
|---|---|---|---|
| Events | | | |
| any event | 82 (44) | 86 (46) | 0.71 |
| In-hosp | 78 (42) | 82 (44) | |
| Post-discharge-30 days | 8 (4) | 9 (5) | |
| Death | 4 (2) | 0 (0) | 0.06 |
| Stroke | 8 (4) | 1 (1) | 0.02 |
| Infection | 6 (3) | 7 (4) | 0.79 |
| Cardiac arrest | 1 (1) | 0 (0) | 0.50 |
| Heart block requiring PPM | 5 (3) | 1 (1) | 0.12 |
| New onset AF | 54 (29) | 59 (32) | 0.60 |
| Acute renal failure | 6 (3) | 4 (2) | 0.54 |
| Prolonged (> 24 h) intubation | 36 (19) | 38 (20) | 0.82 |
| Length of hosp stay (days) | 8 (4) | 8 (5) | 0.66 |
| Leng of ICU stay (days) | 2 (2) | 2 (3) | 0.37 |



## STUDY LIMITATIONS

- Single center study
- Could not be conducted in strictly blinded fashion
- Use of composite outcome as primary endpoint
- 30 day outcomes may not be reliably captured

Gandhi et al. Ann Intern Med 2007

## STUDY CONCLUSIONS

- Insulin infusion protocol maintains intraoperative glucose levels in desired goal range
- Intensive intra-op insulin does not reduce perioperative death or morbidity
- Increased incidence of stroke in intensive treatment group ( ± death)

Gandhi et al. Ann Intern Med 2007

## CLINICAL IMPLICATIONS

- Adding tight glucose control during cardiac surgery
  Does not cause additional benefit to initiating strict glucose control postop
  — May cause harm
- Increased resources needed
- Do not recommend implementing tight glucose control during cardiac surgery

Gandhi et al. Ann Intern Med 2007

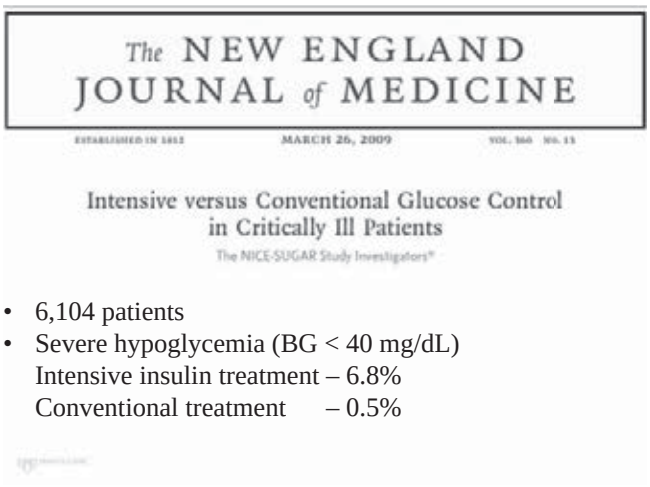
***Continuous Perioperative Insulin Infusion Decreases Major Cardiovascular Events in Patients Undergoing Vascular Surgery***

*A Prospective, Randomized Trial*

Balachundhar Subramaniam, M.B.B.S., M.D.,* Peter J. Panzica, M.D.,† Victor Novack, M.D., Ph.D.,‡ Feroze Mahmood, M.D.,† Robina Matyal, M.B.B.S.,† John D. Mitchell, M.D.,† Eswar Sundar, M.B.B.S.,† Ruma Bose, M.B.B.S.,† Frank Pomposelli, M.D.,§ Judy R. Kersten, M.D.,‖ Daniel S. Talmor, M.D., M.P.H.#

Conclusion: continuous insulin infusion reduces perioperative myocardial infarction after vascular surgery

Subramaniam et al. Anesthesiology 2009; 110: 957–8
Beth Israel, Boston.



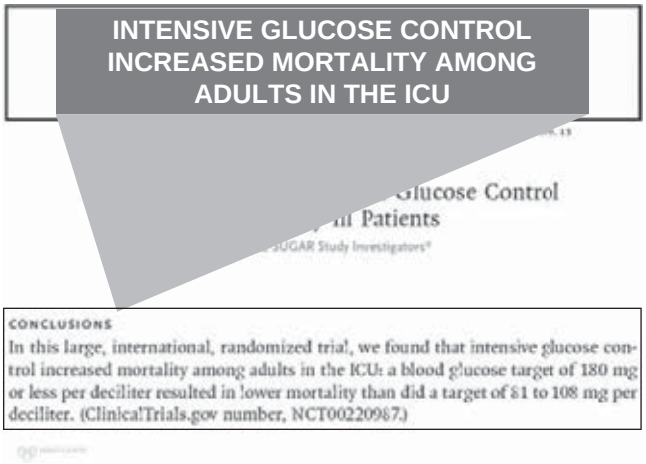
The NEW ENGLAND JOURNAL of MEDICINE

MARCH 26, 2009

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

- 6,104 patients
- Severe hypoglycemia (BG < 40 mg/dL)
  Intensive insulin treatment – 6.8%
  Conventional treatment – 0.5%



**INTENSIVE GLUCOSE CONTROL INCREASED MORTALITY AMONG ADULTS IN THE ICU**

Glucose Control

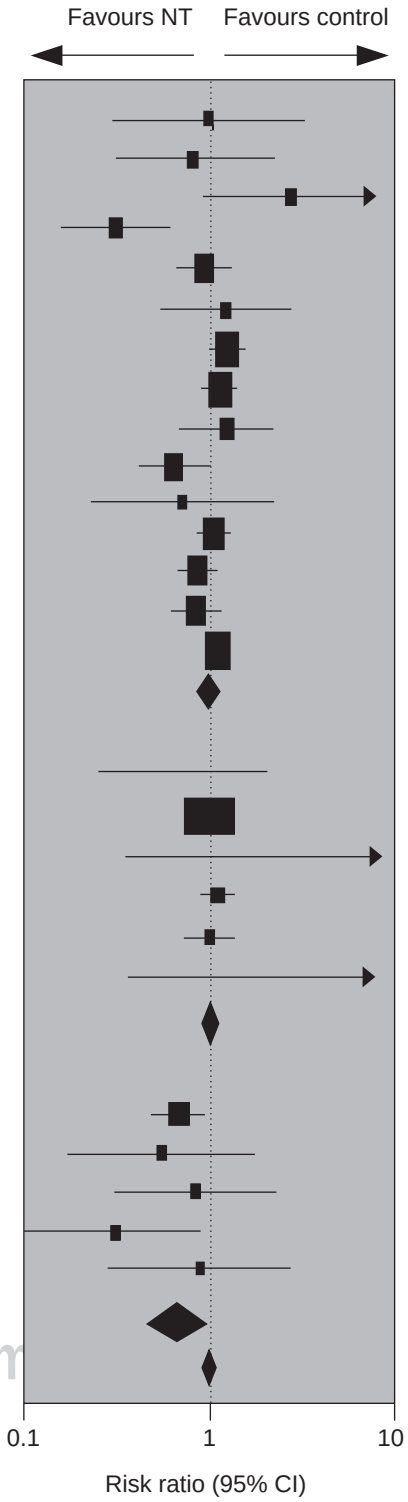
Patients

SUGAR Study Investigators*

CONCLUSIONS

In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter. (ClinicalTrials.gov number, NCT00220987.)

| Study | No. deaths/total No. patients NT | Control | Risk ratio (95% CI) |
|---|---|---|---|
| Mixed ICU. | | | |
| Yu et al. | 4/28 | 4/27 | 0.96 (0.27-3.47) |
| Henderson et al.[31] | 5/32 | 7/35 | 0.78 (0.28-2.22) |
| Mitchell et al. | 9/35 | 3/35 | 3.00 (0.89-10.16) |
| Wang et al. | 7/58 | 26/58 | 0.27 (0.13-0.57) |
| Azevedo et al. | 38/168 | 42/169 | 0.91 (0.62-134) |
| McMullin et al. | 6/11 | 4/9 | 1.23 (0.49-3.04) |
| Devos et al. | 107/550 | 89/551 | 1.20 (0.93-1.55) |
| Brunkhorst et al. | 98/247 | 102/288 | 1.12 (0.90-1.39) |
| Iapichino et al. | 15/45 | 12/45 | 1.25 (0.66-2.36) |
| He et al. | 16/58 | 29/64 | 0.61 (0.37-1.00) |
| Zhang et al. | 4/168 | 6/170 | 0.67 (0.19-2.35) |
| De La Rosa Gael et al. | 102/254 | 96/250 | 1.05 (0.84-1.30) |
| Arabi et al. | 72/266 | 83/257 | 0.84 (0.64-1.09) |
| Mackenzie et al. | 39/121 | 47/119 | 0.82 (0.58-1.15) |
| NICE-SUGAR | 829/3,010 | 751/3,012 | 1.10 (1.01-1.20) |
| All mixed ICU patients | 1,351/5,051 | 1,301/5,089 | 0.99 (0.87-1.12) |
| Medical ICU | | | |
| Bland et al | 1/5 | 2/5 | 0.50 (0.06-3.91) |
| Van den Berghe et al. | 214/595 | 228/605 | 0.95 (0.82-1.11) |
| Walters et al. | 1/13 | 0/12 | 2.79 (0.12-62.48) |
| Farah et al. | 22/41 | 22/48 | 1.17 (0.77-1.78) |
| Oksanen et al. | 13/39 | 18/51 | 0.94 (0.53-1.68) |
| Bruno et al. | 2/31 | 0/15 | 2.50 (0.13-49.05) |
| All medical ICU patients | 253/724 | 270/736 | 1.00 (0.78-1.28) |
| Surgical ICU | | | |
| Van de Berghe et al. | 55/765 | 85/783 | 0.66 (0.48-0.92) |
| Grey et al. | 4/34 | 6/27 | 0.53 (0.17-1.69) |
| Bilotta et al. | 6/40 | 7/38 | 0.81 (0.30-2.20) |
| He et al. | 7/150 | 6/38 | 0.30 (0.11-0.83) |
| Bilotta et al. | 5/48 | 6/49 | 0.85 (0.28-2.60) |
| All surgical ICU patients | 77/1,037 | 110/935 | 0.65 (0.44-0.91) |
| All ICU patients | 1,681/6,812 | 1,681/6,760 | 0.93 (0.83-1.04) |






Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data

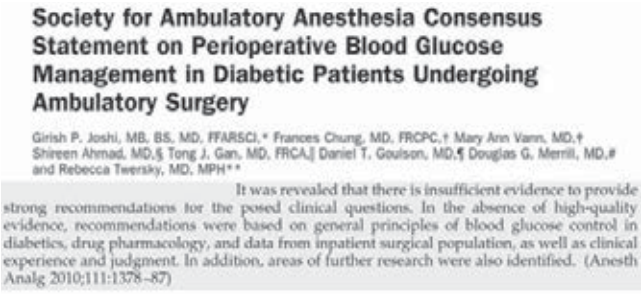
Griesdale et al. CMAJ 2009

## CASE

- 55 yo man in operating room for AVR and CAB
- No known history of diabetes
- Glucose levels 145 mg/dL (8.0)
- A1c 5.6%
- Should the hyperglycemia be treated?
- What if blood glucose 167 mg/dL (9.3)?

## CLINICAL IMPLICATIONS

- Minimize extreme hyper- and hypo- glycemia (goal 140 • 180 mg/dL) in 7.8 – 10.0 critically ill
- Consider tighter goals in elective surgical patients, trauma & those on steroids, epinephrine (adrenalin)
- Research: glycemic variability, hypoglycemia, TPN, goals in non- critically ill
- Uncertainty remains but do not neglect glycemic control



**Society for Ambulatory Anesthesia Consensus Statement on Perioperative Blood Glucose Management in Diabetic Patients Undergoing Ambulatory Surgery**

Girish P. Joshi, MB, BS, MD, FFARSCI,* Frances Chung, MD, FRCPC,† Mary Ann Vann, MD,† Shireen Ahmad, MD,§ Tong J. Gan, MD, FRCA,‖ Daniel T. Goulson, MD,¶ Douglas G. Merrill, MD,# and Rebecca Twersky, MD, MPH**

It was revealed that there is insufficient evidence to provide strong recommendations for the posed clinical questions. In the absence of high-quality evidence, recommendations were based on general principles of blood glucose control in diabetics, drug pharmacology, and data from inpatient surgical population, as well as clinical experience and judgment. In addition, areas of further research were also identified. (Anesth Analg 2010;111:1378–87)

Preoperative Information

- HbA1c reflects average glycemic levels over previous 3–4 months → good indicator of long-term glycemic control
- Medications to control glucose
- Hypoglycemia episodes–occurrence and frequency
- Ability to test blood glucose and manage diabetes

## MEDICATION STRATEGY–ORAL AGENTS

1. Oral agents should not be taken on day of surgery until normal food intake is resumed
2. No evidence metformin increases risk of perioperative lactic acidosis, however
3. Discontinue metformin 24–48 hours before surgery in patients:

   i. Renal dysfunction
   ii. IV contrast agents

Joshi et al. Anesth Analg. 2010

## MEDICATION STRATEGY–INSULIN

| Insulin regimen | Day before surgery | Day of surgery | Comments |
|---|---|---|---|
| Insulin pump | No change | No change | |
| Long-acting insulins | No change | 75%–100% of morning dose | Reduce nighttime dose if history of nocturnal or morning hypoglycemia. On the day of surgery, the morning dose of basal insulin may be administered on arrival to the ambulatory surgery facility. |
| Intermediate-acting insulins | No change in the daytime dose. 75% of dose if taken in the evening | 50%–75% of morning dose | |
| Fixed combination insulins (dispro-protamine only available in combination; therefore use NPH instead, on day of surgery) | No change | 50%–75% of morning dose of intermediate-acting component. | |
| Short- and rapid-acting insulin | No change | Hold the dose | |

Joshi et al. Anesth Analg. 2010

## WHAT IS THE OPTIMAL INTRAOPERATIVE BLOOD GLUCOSE LEVEL?

- Well-controlled diabetics → BG <180 mg/dL
- Poorly-controlled diabetics → maintain BG levels near preoperative baseline values rather than temporarily normalizing them
  — (Chronically elevated BG levels should not be decreased acutely in perioperative period because threshold at which a patient experiences symptoms or organ impairment due to hypoglycemia is dynamic and varies with their long-term glycemic control)

Joshi et al. Anesth Analg. 2010

## HOW DO WE MAINTAIN OPTIMAL BLOOD GLUCOSE LEVEL?

- Type of insulin–rapid-acting preferred over regular
- Route of administration–SC injection preferred over IV (IV bolus has very short duration of action and can cause significant fluctuations in BG level
- Dosing–«rule of 1800»:
  1 u insulin will ↓ BG level by:
  1800÷daily dose insulin, e.g.,
  (1 unit insulin ↓ BG by 1800/60 = 30 mg/dL)

Joshi et al. Anesth Analg. 2010

## WHAT IS THE OPTIMAL PERIOPERATIVE BLOOD GLUCOSE MONITORING?

- BG should be checked on patient's arrival before surgery and before discharge home
- Intraoperative BG should be checked every 1 to 2 hours, or more frequently, if BG is tending to hypoglycemia (< 120 mg/dL)

Joshi et al. Anesth Analg. 2010