Effectiveness of tight glycaemic control on mortality and morbidity in patients undergoing cardiac surgery in hospital: a systematic review

Submitted by
Ali Azam Mohammad Morshed, MBBS

Thesis submitted in fulfilment of the requirements for the degree of
Masters in Clinical Science
The Joanna Briggs Institute, Faculty of Health Sciences,
The University of Adelaide
February 2016
# Table of Contents

Table of contents

List of figures and tabulated data

Thesis declaration

Acknowledgements

Abstract

Chapter 1  Introduction

1.1  Context of the review

1.1.1  Pathophysiology of hyperglycaemia

1.1.2  Perioperative effects of hyperglycaemia

1.1.3  Perioperative effects of hypoglycaemia

1.1.4  Definition of glucose abnormalities and glucose monitoring strategies

1.1.5  Why a systematic review is needed

1.2  Methodological basis of review

1.2.1  Evidence-based healthcare and emergence of systematic review

1.2.2  Difference between systematic review and literature review

1.2.3  The systematic review process and steps

1.3  Review questions/objectives

1.4  Inclusion criteria

1.4.1  Types of participants

1.4.2  Types of interventions

1.4.3  Types of comparators
1.4.4 Types of studies

1.4.5 Types of outcomes

Chapter 2 Review methods

2.1 Search strategy

2.2 Assessment of methodological quality

2.3 Data collection

2.4 Data synthesis

2.5 Findings of the review

2.6 Methods of analysis

Chapter 3 Results

3.1 Description of search and selection process

3.2 Description of included studies

3.3 Methodological quality

3.4 Meta-analysis of outcomes

3.4.1 Very tight glycaemic control versus conventional glycaemic control in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

3.4.1.1 All-cause mortality

3.4.1.2 Length of stay in hospital

3.4.1.3 Length of stay in ICU

3.4.1.4 Time on mechanical ventilation

3.4.1.5 Stroke

3.4.1.6 Atrial fibrillation
3.4.1.7 Renal failure

3.4.1.8 Deep sternal infection

3.4.1.9 Need for cardiac pacing

3.4.1.10 Re-infarction

3.4.2 Tight glycaemic control versus conventional glycaemic control in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

3.4.2.1 All-cause mortality

3.4.2.2 Length of stay in hospital

3.4.2.3 Length of stay in ICU

3.4.2.4 Time on mechanical ventilation

3.4.2.5 Stroke

3.4.2.6 Atrial fibrillation

3.4.2.7 Renal failure

3.4.2.8 Deep sternal infection

3.4.2.9 Need for cardiac pacing

3.4.2.10 Re-infarction

3.4.3 Very tight glycaemic control versus conventional glycaemic control in diabetic patients undergoing cardiac surgery

3.4.3.1 All-cause mortality

3.4.3.2 Length of stay in hospital

3.4.3.3 Length of stay in ICU
3.4.3.4 Time on mechanical ventilation..........................................................45
3.4.3.5 Stroke..................................................................................................45
3.4.3.6 Atrial fibrillation..................................................................................46
3.4.3.7 Renal failure........................................................................................47
3.4.3.8 Deep sternal infection.......................................................................47
3.4.3.9 Need for cardiac pacing......................................................................48
3.4.3.10 Re-infarction......................................................................................48

3.4.4 Tight glycaemic control versus conventional glycaemic control in diabetic patients
undergoing cardiac surgery.............................................................................49

3.4.4.1 All-cause mortality...............................................................................49
3.4.4.2 Length of stay in hospital....................................................................49
3.4.4.3 Length of stay in ICU..........................................................................50
3.4.4.4 Time on mechanical ventilation.......................................................50
3.4.4.5 Stroke..................................................................................................51
3.4.4.6 Atrial fibrillation..................................................................................51
3.4.4.7 Renal failure........................................................................................51
3.4.4.8 Deep sternal infection.......................................................................52
3.4.4.9 Need for cardiac pacing......................................................................52
3.4.4.10 Re-infarction......................................................................................52

Chapter 4 Discussion.......................................................................................53

4.1 Outcomes.....................................................................................................54

4.1.1 All-cause mortality................................................................................54
4.1.2 Length of stay in hospital.................................................................55
4.1.3 Length of stay in ICU.................................................................56
4.1.4 Time on mechanical ventilation.................................................56
4.1.5 Stroke.................................................................57
4.1.6 Atrial fibrillation.................................................................57
4.1.7 Renal failure.................................................................58
4.1.8 Deep sternal infection.................................................................59
4.1.9 Need for cardiac pacing.................................................................59
4.1.10 Re-infarction.................................................................60
4.2 Summary of findings table.................................................................61
4.3 Current recommendation in clinical guidelines...........................................61
4.4 Discussion on related reviews and studies...........................................62
4.5 Limitations of the review.................................................................64

Chapter 5 Conclusion........................................................................65
5.1 Implications for practice.................................................................65
5.2 Implications for research.................................................................66

References.......................................................................................67

Appendix I Search strategy..................................................................76

Appendix II JBI critical appraisal checklist for randomised controlled/pseudo randomised controlled trials...........................................83

Appendix III JBI data extraction form for experimental/observational studies...........................................84

Appendix IV Included studies................................................................85

Appendix V Excluded studies and reasons for exclusion..........................102
List of figures and tabulated data

Table 1 Summary of findings........................................................................................................2

Table 2 Critical appraisal scores of included randomised controlled trials/pseudo-randomised
controlled trials..........................................................................................................................25

Figure 1 Flow diagram of study selection process....................................................................19

Figure 2 Meta-analysis of all-cause mortality in very tight glycaemic control group compared
to conventional glycaemic control group in all (both diabetic and/or nondiabetic)
patients undergoing cardiac surgery (fixed effect).................................................................27

Figure 3 Meta-analysis of all-cause mortality in very tight glycaemic control group compared
to conventional glycaemic control group in all (both diabetic and/or nondiabetic)
patients undergoing cardiac surgery (random effect)............................................................27

Figure 4 Meta-analysis of length of stay in hospital in very tight glycaemic control group compared
to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients
undergoing cardiac surgery........................................................................................................28

Figure 5 Meta-analysis of length of stay in ICU in very tight glycaemic control group compared
to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients
undergoing cardiac surgery......................................................................................................29

Figure 6 Meta-analysis of time on mechanical ventilation in very tight glycaemic control group
compared to conventional glycaemic control group in all (both diabetic and/or
nondiabetic) patients undergoing cardiac surgery.................................................................30

Figure 7 Meta-analysis of stroke in very tight glycaemic control group compared to conventional
glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing
cardiac surgery...................................................................................................................................31

Figure 8  Meta-analysis of atrial fibrillation in very tight glycaemic control group compared to
contventional glycaemic control group in all (both diabetic and/or nondiabetic)
patients undergoing cardiac surgery.....................................................................................................32

Figure 9  Meta-analysis of renal failure in very tight glycaemic control group compared to
conventional glycaemic control group in all (both diabetic and/or nondiabetic)
patients undergoing cardiac surgery.....................................................................................................33

Figure 10 Meta-analysis of deep sternal infection in very tight glycaemic control group
compared to conventional glycaemic control group in all (both diabetic and/or
nondiabetic) patients undergoing cardiac surgery....................................................................................33

Figure 11 Meta-analysis of need for cardiac pacing in very tight glycaemic control group
compared to conventional glycaemic control group in all (both diabetic and/or
nondiabetic) patients undergoing cardiac surgery....................................................................................34

Figure 12 Meta-analysis of re-infarction in very tight glycaemic control group compared to
conventional glycaemic control group in all (both diabetic and/or nondiabetic)
patients undergoing cardiac surgery.....................................................................................................35

Figure 13 Meta-analysis of all-cause mortality in tight glycaemic control group compared
to conventional glycaemic control group in all (both diabetic and/or nondiabetic)
patients undergoing cardiac surgery.....................................................................................................36

Figure 14 Meta-analysis of length of stay in hospital in tight glycaemic control group compared
to conventional glycaemic control group in all (both diabetic and/or nondiabetic)
patients undergoing cardiac surgery.....................................................................................................37

Figure 15 Meta-analysis of length of stay in ICU in tight glycaemic control group compared
to conventional glycaemic control group in all (both diabetic and/or nondiabetic)
Figure 16 Meta-analysis of atrial fibrillation in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery..........................37

Figure 17 Meta-analysis of deep sternal infection in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery..........................40

Figure 18 Meta-analysis of re-infarction in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery..........................41

Figure 19 Meta-analysis of length of stay in hospital in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery..........................42

Figure 20 Meta-analysis of stroke in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery..........................43

Figure 21 Meta-analysis of atrial fibrillation in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery..........................44

Figure 22 Meta-analysis of renal failure in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery..........................44

Figure 23 Meta-analysis of re-infarction in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery..........................44
surgery.........................................................................................................................45

Figure 24 Meta-analysis of length of stay in hospital in tight glycaemic control group

cmpared to conventional glycaemic control group in diabetic patients undergoing
cardiac surgery.........................................................................................................47

Figure 25 Meta-analysis of length of stay in ICU in tight glycaemic control group

cmpared to conventional glycaemic control group in diabetic patients undergoing
cardiac surgery.........................................................................................................47

Figure 26 Meta-analysis of atrial fibrillation in tight glycaemic control group compared to

conventional glycaemic control group in diabetic patients undergoing cardiac

surgery.........................................................................................................................48
Declaration

I, Ali Morshed, certify that this work contains no material that has been accepted for the award of any other degree or diploma in any university or any other tertiary institution, and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the university library, to be made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the university's digital research repository, the library catalogue and also through web search engines, unless permission has been granted by the university to restrict access for a period of time.

Ali Azam Mohammad Morshed
5 February 2016
Acknowledgement

I would like to thank the following people who helped and inspired me during my Masters of Philosophy degree study. First and foremost, my utmost gratitude goes to my primary supervisor, Dr. Zachary Munn, who has provided me with relentless support throughout my thesis through his patience, knowledge and excellent positive attitude whilst allowing me room to work in my own way; without his supervision this thesis would not have been written or completed. I would also like to thank my supervisor, Associate Professor Craig Lockwood, for his professional guidance, advice and input at different stages of my study. Last but not least, I would like to acknowledge the invaluable support from the University of Adelaide and Joanna Briggs Institute staff.
Abstract

Background

Hyperglycaemia is a well-documented and common response to critical illness and metabolic stress during the perioperative period of cardiac surgery; however, there remains considerable controversy regarding the role of tight glycaemic control during and/or after cardiac surgery. The objective of this review was to identify the effectiveness of tight glycaemic control compared to conventional glycaemic control on the mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery.

Methods

A three-step search strategy was employed that aimed to locate both published and unpublished studies in the English language between 1990 until March 2014. An initial search in PubMed and CINAHL was followed by a second search using all identified keywords and index terms across multiple databases and grey literature sites. Critical appraisal was undertaken by two independent reviewers using the standard critical appraisal instrument from the Joanna Briggs Institute Meta-Analysis of Statistical Assessment and Review Instrument (JBI-MAStARI). Results from randomized controlled trials were pooled in statistical meta-analysis using RevMan V 5.3 software where appropriate. Effect sizes were calculated using a fixed effects model. Where the findings could not be pooled using meta-analysis, results are presented in a narrative form.

Results

Twelve studies including 2713 participants were identified that met the inclusion criteria and were considered to be of adequate methodological quality. The included randomised controlled trials were generally of good quality with a clear description of study design and statistical analysis methods employed. Meta-analysis was conducted on comparisons between very tight glycaemic control (80-150mg/dl), tight glycaemic control (100-200mg/dl) and conventional glycaemic control (160-250mg/dl).

For all patients (both diabetic and/or nondiabetic) undergoing cardiac surgery, very tight glycaemic control as compared to conventional glycaemic control significantly reduced all-cause mortality (odds ratio [OR] 0.59, 95% confidence interval [CI] of 0.37 to 0.96), length of stay in hospital (mean difference [MD] -0.21,95% CI of -0.28 to -0.14); and tight glycaemic control compared to conventional glycaemic control significantly reduced all-cause mortality (OR 0.25, 95% CI of 0.09 to 0.68), length of stay in intensive care units (MD -0.65, 95% CI of -0.68 to -0.62), length of stay in hospital (MD -2.70, 95% CI of -2.77 to 2.63), atrial fibrillation (OR 0.42, 95% CI 0.26 to 0.66) and renal failure (OR 0.09, 95% CI 0.02 to 0.51). In diabetic patients undergoing cardiac surgery, very tight glycaemic control in comparison with conventional glycaemic control showed significant reduction in length of stay in hospital (MD -0.21, 95% CI -0.28 to -0.14), and tight glycaemic control compared to conventional
glycaemic control showed significant reduction in length of stay in hospital (MD -2.71, 95% CI -2.78 to -2.63), length of stay in ICU (MD -0.65, 95% CI -0.68 to -0.62) and atrial fibrillation (OR 0.36, 95% CI 0.22 to 0.59).

Conclusions

The findings of this review indicate that very tight and/or tight glycaemic control compared to conventional glycaemic control during the perioperative period in patients undergoing cardiac surgery may have some positive effects in reducing mortality and morbidity following surgery.

Keywords

Tight glycaemic control, strict glycaemic control, aggressive glycaemic control, cardiac surgery, cardiovascular surgery, insulin therapy, intensive insulin therapy, mortality, morbidity, deep sternal infection, atrial fibrillation, mechanical ventilation, epicardial pacing.

Table 1: Summary of findings

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional glycaemic control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very tight glycaemic control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>52 per 1000</td>
<td>32 per 1000 (20 to 50)</td>
<td>OR 0.59 (0.37 to 0.96)</td>
<td>⊕⊕⊕⊕ ⊝⊝ ⊝ ⊝ low&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Length of stay in hospital (in days)</td>
<td>The mean length of stay in hospital (in days) in the control groups ranged from 3-17 days</td>
<td>The mean length of stay in hospital (in days) in the intervention groups was 0.21 days lower (0.28 to 0.14 lower)</td>
<td>861 (5 studies)</td>
<td>⊕⊕⊕⊕ ⊝⊝ ⊝ ⊝ low&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio
Tight glycaemic control versus conventional glycaemic control in all patients (diabetic and/or nondiabetic patients) undergoing cardiac surgery

**Patient or population:** All patients (diabetic and/or nondiabetic patients) undergoing cardiac surgery  
**Settings:** Inpatient  
**Intervention:** Tight glycaemic control (100-200mg/dl)  
**Comparison:** Conventional glycaemic control (160-250mg/dl)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk Conventional glycaemic control</th>
<th>Corresponding risk Tight glycaemic control</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>72 per 1000</td>
<td>19 per 1000 (7 to 50)</td>
<td>OR 0.25 (0.09 to 0.68)</td>
<td>529 (3 studies)</td>
<td>⊕⊕⊕ moderate¹</td>
<td></td>
</tr>
<tr>
<td>Length of stay in hospital (in days)</td>
<td>The mean length of stay in hospital (in days) in the control groups ranged from 9-10 days</td>
<td>The mean length of stay in hospital (in days) in the intervention groups was 2.7 days lower (2.77 to 2.63 lower)</td>
<td>553 (3 studies)</td>
<td>⊕⊕⊕ low²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

---

**GRADE Working Group grades of evidence**

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  
**Very low quality:** We are very uncertain about the estimate.

¹ Downgraded as wide confidence intervals and small sample size  
² Downgraded two levels as I² is 87% indicates substantial to considerable heterogeneity
### Very tight glycaemic control versus conventional glycaemic control in diabetic patients undergoing cardiac surgery

**Patient or population:** Diabetic patients undergoing cardiac surgery  
**Settings:** Inpatient  
**Intervention:** Very tight glycaemic control (80-150mg/dl)  
**Comparison:** Conventional glycaemic control (160-250mg/dl)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay in hospital (in days)</td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional glycaemic control</td>
<td>The mean length of stay in hospital (in days) in the control groups ranged from 3-11 days</td>
<td>The mean length of stay in hospital (in days) in the intervention groups was 0.21 days lower (0.28 to 0.14 lower)</td>
<td>182 (2 studies)</td>
<td>⊗⊗⊗ ⊝ ⊝</td>
<td>low</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

**GRADE Working Group grades of evidence**  
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  
**Very low quality:** We are very uncertain about the estimate.

1 Downgraded as small sample size.
**Tight glycaemic control versus conventional glycaemic control in diabetic patients undergoing cardiac surgery**

**Patient or population:** Diabetic patients undergoing cardiac surgery  
**Settings:** Inpatients  
**Intervention:** Tight glycaemic control (100-200mg/dl)  
**Comparison:** Conventional glycaemic control (160-250mg/dl)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional glycaemic control</td>
<td>See comment¹</td>
<td>See comment¹</td>
<td>Not estimable</td>
<td>341 (2 studies)</td>
<td>See comment</td>
</tr>
<tr>
<td>Tight glycaemic control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**All-cause mortality**  
The mean length of stay in hospital (in days) in the control groups ranged from 9-10 days  
The mean length of stay in hospital (in days) in the intervention groups was 2.71 days lower (2.78 to 2.63 lower)

**Length of stay in hospital (in days)**  
The mean length of stay in hospital (in days) in the control groups ranged from 9-10 days  
The mean length of stay in hospital (in days) in the intervention groups was 2.71 days lower (2.78 to 2.63 lower)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

**GRADE Working Group grades of evidence**  
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  
**Very low quality:** We are very uncertain about the estimate.

¹ One study reported no event whereas another study was statistically significant.  
² Small sample size.