INCIDENCE OF HYPOGLYCEMIA AND ASSOCIATED COSTS IN TYPE 1 AND TYPE 2 DIABETES PATIENTS TREATED WITH INSULIN ANALOGS VS. HUMAN INSULIN: A RETROSPECTIVE COHORT STUDY

By

Hiren P. Shah

A dissertation submitted to the faculty of School of Health Related Professions, Rutgers, The State University of New Jersey in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomedical Informatics

Department of Health Informatics

Fall 2013

© 2013 Hiren P. Shah

All Rights Reserved
Final Dissertation Approval Form

INCIDENCE OF HYPOGLYCEMIA AND ASSOCIATED COSTS IN TYPE 1 
AND TYPE 2 DIABETES PATIENTS TREATED WITH INSULIN ANALOGS VS

BY 
Hiren P. Shah

Dissertation Committee:
Dinesh P. Mital, PhD, Committee Chair
Syed Haque PhD, Committee Member
Shankar Srinivasan, PhD, Committee Member

Approved by the Dissertation Committee:

Date Dec 3, 2013

Date Dec 3, 2013

Date Dec 3, 2013

Date

Date

Date
ABSTRACT

Human insulin and insulin analogs are registered for the insulin treatment of Type 1 (T1DM) and Type 2 Diabetes Mellitus (T2DM). However, there is an ongoing debate concerning the hypoglycemic events and associated costs in both treatment options. For this reason, a systematic retrospective study was performed to compare hypoglycemic events and associated costs of both human insulin and insulin analogs treatment options. Relevant articles were identified by a methodical search through the electronic medical databases (MEDLINE, EMBASE, CURRENT CONTENTS, BIOSIS) from 1990 thru 2010. This was a retrospective cohort study of patients’ data in the claims database from 2007 thru 2010. First year of the study period was used as a baseline period to meet inclusion criteria of patients being insulin naive for at least one year prior to the index period. Following three years from the index date 2008 to 2010 was considered as the follow-up period to analyze hypoglycemic events and associated costs. Descriptive analysis of the data suggested that differences in hypoglycemic events existed between the two cohorts of patients treated with insulin analogs and human insulin.

A total of 486 patients treated with Human Insulin (HI) and 6,599 patients treated with Insulin Analogs (IA) fulfilled all the inclusion and exclusion criteria. Medical and prescription claims related records were studied for these patients for hypoglycemic events and associated costs. HI and IA groups were further divided into sub-groups of Human Insulin Regular (HIR, n=106), Human Insulin - Neutral Protamine Hagedorn (NPH) (HIN, n=112), Human Insulin Pre-mixed (HIMIX, n=268); Insulin Analogs Fast Acting (IAFA, n=2,894), Insulin Analogs Long Acting (IALA, n=2,934) and Insulin Analogs Pre-mixed (IAMIX, n=771).
Systematic analysis showed that treatment with IA in T2DM patients compared to HI resulted in significantly better hypoglycemic rates when adjusted for relevant covariates. However in T1DM patients, the treatment with HI resulted in slightly better hypoglycemic rates. Furthermore, comparison of sub-groups (IAFA vs. HIR; IALA vs. HIN; IAMIX vs. HIMIX) showed that treatment with IAFA and IAMIX in T2DM patients resulted in better hypoglycemic rates when adjusted for relevant covariates. However in T1DM patients, the treatment with HIR resulted in slightly better hypoglycemic rates. For T1DM patients treated with HIN and HIMIX, due to extremely small patient population in these sub-groups the algorithm did not converge and the estimate was not established.

Cost analysis showed that treatment with IA in T2DM patients compared to HI resulted in lower cost when adjusted for relevant covariates. However in T1DM patients, treatment with IA resulted in lower cost when adjusted for some covariates. Furthermore, comparison of sub-groups (IAFA vs. HIR; IALA vs. HIN; IAMIX vs. HIMIX) indicated that treatment with IAFA (T1&T2) and IAMIX in T2DM patients compared to HIR and HIMIX resulted in lower cost when adjusted for relevant covariates. IALA in T2DM patients compared to HIN resulted in slightly higher cost. For T1DM patients in IALA vs. HIN and IAMIX vs. HIMIX, the model did not converge.

There is significant evidence to conclude that T2DM patients treated with IA group and sub-group IAFA showed better hypoglycemic rates and associated costs compared to HI and HIR respectively. For other sub-groups, especially in T1DM patients this study cannot provide any statistically significant conclusion due to data limitations. Further research in these sub-groups is warranted using different datasets.
ACKNOWLEDGEMENTS

First and foremost I would like to express my gratitude to my advisor Dr. Dinesh Mital, for essential guidance and insight throughout my graduate career. His influence has contributed to my development as a scientist.

Sincere appreciation is due to Dr. Syed Haque, Dr. Shankar Srinivasan and Dr. Masayuki Shibata who have enlarged my sphere of understanding of Biomedical Informatics with their encyclopedic knowledge and fresh perspectives. I am indebted to Tami Wisniewski in Health Economics and Outcomes Research department at Novo Nordisk Inc. (NNI) for taking the time to serve as my thesis supervisor, helpful advice, original ideas and for countless useful conversations. I also wish to thank Mark Aagren, Jon Bouchard and Dr. Neil Wintfeld for their advice, guidance and research support. I am also very grateful to Tina Young in Biostatistics department at NNI for her technical help.

Needless to say, my family deserves a great deal of credit for my development. I thank my mother Ranjan, my father Pravin, my brother Rupen and his family, and my kids Anya and Bianca for all their love and support. Finally, I offer my most genuine thanks to my wife Miki, whose unwavering compassion, faith, and love carries me through life.
TABLE OF CONTENTS

ABSTRACT ........................................................................................................................................ ii

ACKNOWLEDGEMENTS .................................................................................................................. v

TABLE OF CONTENTS ..................................................................................................................... vi

LIST OF FIGURES ........................................................................................................................... ix

LIST OF TABLES .............................................................................................................................. xi

CHAPTER 1 INTRODUCTION ........................................................................................................ 20

1.1 Background .................................................................................................................................. 24

1.2 Goals and Objectives ................................................................................................................... 25

1.3 Significance of the Problem ......................................................................................................... 25

1.4 Hypothesis ..................................................................................................................................... 26

1.5 Overview of Diabetes .................................................................................................................. 26

1.6 Hypoglycemia – A Serious Side Effect ...................................................................................... 35

CHAPTER 2 LITERATURE REVIEW .............................................................................................. 37

2.1 Literature Sources and Search Strings ......................................................................................... 38

2.2 Type 1 and Type 2 Diabetes Studies .............................................................................................. 38

2.3 Studies of Human Insulin and Insulin Analogs .......................................................................... 39

2.3.1 Regular Human Insulin and Neutral Protamine Hagedorn .................................................. 41

2.3.2 Rapid and Long Acting Insulin Analogs ................................................................................ 43

2.3.3 Comparison of Human Insulin vs. Insulin Analogs ................................................................. 46

2.4 Hypoglycemia Associated Costs ............................................................................................... 47

CHAPTER 3 RESEARCH METHODOLOGY .................................................................................. 50

3.1 Research Overview ...................................................................................................................... 50
3.2 Data Sources and Data Elements ................................................................. 51
3.3 Study Period and Study Group Inclusion/Exclusion Criteria .................... 55
3.4 Exposures and Outcomes of interest........................................................... 61
3.5 Data Analysis Methods................................................................................ 62

CHAPTER 4 RESULTS....................................................................................... 66
4.1 Hypoglycemic Events and Covariate Analysis – Final Results ................. 67
4.2 Descriptive Statistics and Demographic Analysis ....................................... 74
4.2.1 Gender, Age, Insurance Type and Geographic Regions ....................... 74
4.2.2 Medical and Prescription Copay of Patient Cohorts ............................... 79
4.3 Regression Analysis Results – Hypo Events ............................................ 88
4.3.1 Covariate: Drug Class .......................................................................... 90
4.3.2 Covariate: Drug Class and Age ............................................................. 92
4.3.3 Covariates: Drug Class and Gender .................................................... 98
4.3.4 Covariates: Drug Class and Region ..................................................... 102
4.3.5 Covariates: Drug Class and Comorbidities ....................................... 109
4.3.6 Covariates: Drug Class and Comorbidities Relationship .................... 113
4.3.7 Covariates: Drug Class, Age and Gender .......................................... 116
4.3.8 Covariates: Drug Class, Age and Region ......................................... 122
4.3.9 Covariates: Drug Class, Age and Comorbidities ............................... 131
4.3.10 Covariates: Drug Class, Gender and Region .................................... 138
4.3.11 Covariates: Drug Class, Gender and Comorbidities ......................... 145
4.3.12 Covariates: Drug Class, Region and Comorbidities .......................... 150
4.3.13 Covariates: Drug Class, Age, Gender, Region and Comorbidities ...... 157
LIST OF FIGURES

Figure 1: Consort Diagram .................................................................................................................. 37
Figure 2: Insulin Analogs Fast Acting vs. Regular Human Insulin......................................................... 44
Figure 3: Insulin Analogs Long Acting vs. NPH Human Insulin............................................................. 46
Figure 4: Research Overview Diagram................................................................................................. 51
Figure 5: Study Timeline ...................................................................................................................... 56
Figure 6: Patient Selection – Criteria 1 and Criteria 2........................................................................ 63
Figure 7: Patient Selection – Criteria 3.1 and Criteria 4.1................................................................. 64
Figure 8: Patient Selection – Criteria 3.2 and Criteria 4.2................................................................. 65
Figure 9: Hypoglycemic Events (HE) Comparison Follow-up Period – Class ....................... 69
Figure 10: Hypoglycemic Events (HE) Comparison Pre-Index Period – Class ...................... 70
Figure 11: HE Comparison Follow-up Period – Class and Mode of Action...................................... 71
Figure 12: HE Comparison Pre-Index Period – Class and Mode of Action...................................... 72
Figure 13: HE Comparison Follow-up Period – Class, Mode of Action and Type.................... 73
Figure 14: HE Comparison Pre-Index Period – Class, Mode of Action and Type.................... 74
Figure 15: No. of Patients by Gender .................................................................................................. 75
Figure 16: No. of Patients by Drug Class ............................................................................................ 75
Figure 17: No. of Female Patients by Age Group and Drug Class.................................................. 76
Figure 18: No. of Male Patients by Age Group and Drug Class..................................................... 77
Figure 19: No. of Female Patients by Insurance Type................................................................. 78
Figure 20: No. of Male Patients by Insurance Type................................................................. 78
Figure 21: Patients Geographic Region ............................................................................................. 79
Figure 22: Medical Copay Amount Ranges......................................................................................... 80
LIST OF TABLES

Table 1: Diabetes Symptoms ....................................................................................................... 28
Table 2: Current Diabetes Treatment Medications ................................................................. 33
Table 3: Complications ............................................................................................................. 34
Table 4: Data Elements – Database and Columns ................................................................. 51
Table 5: Type 1 and Type 2 Diabetes ICD-9-CM Codes ......................................................... 57
Table 6: Insulin Analogs - NDC Codes .................................................................................. 57
Table 7: Human Insulin - NDC Codes .................................................................................... 59
Table 8: Hypoglycemic Event ICD-9-CM Codes .................................................................. 66
Table 9: Hypoglycemic Events Summary ............................................................................. 68
Table 10: Hypoglycemic Events (HE) - HI vs. IA by Type ...................................................... 90
Table 11: HE - HIR vs. IAFA by Type .................................................................................... 90
Table 12: HE - HIN vs. IALA by Type ................................................................................... 91
Table 13: HE - HIMIX vs. IAMIX by Type ........................................................................... 92
Table 14: HE - HI vs. IA by Type adjusted for Age Range (AR) ........................................... 93
Table 15: HE - HI vs. IA by AR adjusted for Drug Class (DC) ............................................. 93
Table 16: HE - HIR vs. IAFA by Type adjusted for AR ......................................................... 94
Table 17: HE - HIR vs. IAFA by AR adjusted for DC ............................................................. 95
Table 18: HE - HIN vs. IALA by Type adjusted for AR ......................................................... 95
Table 19: HE - HIN vs. IALA by AR adjusted for DC ............................................................ 96
Table 20: HE - HIMIX vs. IAMIX by Type adjusted for AR ................................................ 97
Table 21: HE - HIMIX vs. IAMIX by AR adjusted for DC ..................................................... 97
Table 22: HE - HI vs. IA by Type adjusted for Gender (GC) .................................................. 98
Table 23: HE - HI vs. IA by GC adjusted for DC ............................................................. 99
Table 24: HE - HIR vs. IAFA by Type adjusted for GC .................................................. 99
Table 25: HE - HIR vs. IAFA by GC adjusted for DC ................................................... 100
Table 26: HE - HIN vs. IALA by Type adjusted for GC ................................................ 100
Table 27: HE - HIN vs. IALA by GC adjusted for DC .................................................. 100
Table 28: HE - HIMIX vs. IAMIX by Type adjusted for GC ........................................ 101
Table 29: HE - HIMIX vs. IAMIX by GC adjusted for DC ........................................... 101
Table 30: HE - HI vs. IA by Type adjusted for Region (RE) ......................................... 102
Table 31: HE - HI vs. IA by RE adjusted for DC ........................................................... 103
Table 32: HE - HIR vs. IAFA by Type adjusted for RE ................................................. 104
Table 33: HE - HIR vs. IAFA by RE adjusted for DC ................................................... 105
Table 34: HE - HIN vs. IALA by Type adjusted for RE ................................................ 106
Table 35: HE - HIN vs. IALA by RE adjusted for DC ................................................... 106
Table 36: HE - HIMIX vs. IAMIX by Type adjusted for RE ......................................... 107
Table 37: HE - HIMIX vs. IAMIX by RE adjusted for DC ........................................... 108
Table 38: HE - HI vs. IA by Type adjusted for Comorbidities (CoMo) ......................... 109
Table 39: HE - HI vs. IA by CoMo adjusted for DC ...................................................... 109
Table 40: HE - HIR vs. IAFA by Type adjusted for CoMo ........................................... 110
Table 41: HE - HIR vs. IAFA by CoMo adjusted for DC .............................................. 111
Table 42: HE - HIN vs. IALA by Type adjusted for CoMo ........................................... 111
Table 43: HE - HIN vs. IALA by CoMo adjusted for DC .............................................. 112
Table 44: HE - HIMIX vs. IAMIX by Type adjusted for CoMo .................................... 112
Table 45: HE - HIMIX vs. IAMIX by CoMo adjusted for DC ...................................... 112
Table 46: HE - HI vs. IA by Type and CoMo Relationship ........................................... 113
Table 47: HE - HIR vs. IAFA by Type and CoMo Relationship ........................................ 114
Table 48: HE - HIN vs. IALA by Type and CoMo Relationship ......................................... 114
Table 49: HE - HIMIX vs. IAMIX by Type and CoMo Relationship ................................... 115
Table 50: HE - HI vs. IA by Type adjusted for AR and GC ........................................... 116
Table 51: HE - HI vs. IA by AR and GC adjusted for DC ............................................. 116
Table 52: HE - HIR vs. IAFA by Type adjusted for AR and GC ....................................... 117
Table 53: HE - HIR vs. IAFA by AR and GC adjusted for DC ......................................... 118
Table 54: HE - HIN vs. IALA by Type adjusted for AR and GC ....................................... 119
Table 55: HE - HIN vs. IALA by AR and GC adjusted for DC ......................................... 120
Table 56: HE - HIMIX vs. IAMIX by Type adjusted for AR and GC .................................. 121
Table 57: HE - HIMIX vs. IAMIX by AR and GC adjusted for DC .................................. 121
Table 58: HE - HI vs. IA by Type adjusted for AR and RE ............................................... 122
Table 59: HE - HI vs. IA by AR and RE adjusted for DC ............................................... 123
Table 60: HE - HIR vs. IAFA by Type adjusted for AR and RE ........................................ 125
Table 61: HE - HIR vs. IAFA by AR and RE adjusted for DC .......................................... 125
Table 62: HE - HIN vs. IALA by Type adjusted for AR and RE ........................................ 127
Table 63: HE - HIN vs. IALA by AR and RE adjusted for DC ........................................... 127
Table 64: HE - HIMIX vs. IAMIX by Type adjusted for AR and RE ............................... 129
Table 65: HE - HIMIX vs. IAMIX by AR and RE adjusted for DC ................................. 130
Table 66: HE - HI vs. IA by Type adjusted for AR and CoMo .......................................... 131
Table 67: HE - HI vs. IA by AR and CoMo adjusted for DC ............................................ 132
Table 68: HE - HIR vs. IAFA by Type adjusted for AR and CoMo ................................. 133
Table 69: HE - HIR vs. IAFA by AR and CoMo adjusted for DC ........................................ 134
Table 70: HE - HIN vs. IALA by Type adjusted for AR and CoMo ................................. 135
Table 71: HE - HIN vs. IALA by AR and CoMo adjusted for DC ................................. 135
Table 72: HE - HIMIX vs. IAMIX by Type adjusted for AR and CoMo ......................... 136
Table 73: HE - HIMIX vs. IAMIX by AR and CoMo adjusted for DC ......................... 137
Table 74: HE - HI vs. IA by Type adjusted for GC and RE ........................................... 138
Table 75: HE - HI vs. IA by GC and RE adjusted for DC .............................................. 139
Table 76: HE - HIR vs. IAFA by Type adjusted for GC and RE ....................................... 140
Table 77: HE - HIR vs. IAFA by GC and RE adjusted for DC ....................................... 140
Table 78: HE - HIN vs. IALA by Type adjusted for GC and RE ...................................... 142
Table 79: HE - HIN vs. IALA by GC and RE adjusted for DC ...................................... 142
Table 80: HE - HIMIX vs. IAMIX by Type adjusted for GC and RE ............................ 143
Table 81: HE - HIMIX vs. IAMIX by GC and RE adjusted for DC ............................. 144
Table 82: HE - HI vs. IA by Type adjusted for GC and CoMo ....................................... 145
Table 83: HE - HI vs. IA by GC and CoMo adjusted for DC ....................................... 146
Table 84: HE - HIR vs. IAFA by Type adjusted for GC and CoMo ............................. 146
Table 85: HE - HIR vs. IAFA by GC and CoMo adjusted for DC .................................. 147
Table 86: HE - HIN vs. IALA by Type adjusted for GC and CoMo ............................. 147
Table 87: HE - HIN vs. IALA by GC and CoMo adjusted for DC .................................. 148
Table 88: HE - HIMIX vs. IAMIX by Type adjusted for GC and CoMo ..................... 148
Table 89: HE - HIMIX vs. IAMIX by GC and CoMo adjusted for DC ..................... 149
Table 90: HE - HI vs. IA by Type adjusted for RE and CoMo ...................................... 150
Table 91: HE - HI vs. IA by RE and CoMo adjusted for DC ...................................... 150
Table 92: HE - HIR vs. IAFA by Type adjusted for RE and CoMo ......................... 152
Table 93: HE - HIR vs. IAFA by RE and CoMo adjusted for DC ...................... 152
Table 94: HE - HIN vs. IALA by Type adjusted for RE and CoMo .................. 153
Table 95: HE - HIN vs. IALA by RE and CoMo adjusted for DC ................... 154
Table 96: HE - HIMIX vs. IAMIX by Type adjusted for RE and CoMo .......... 155
Table 97: HE - HIMIX vs. IAMIX by RE and CoMo adjusted for DC .......... 156
Table 98: HE - HI vs. IA by Type adjusted for AR, GC, RE and CoMo .......... 157
Table 99: HE - HI vs. IA by AR, GC, RE and CoMo adjusted for DC ...... 157
Table 100: HE - HIR vs. IAFA by Type adjusted for AR, GC, RE and CoMo ... 160
Table 101: HE - HIR vs. IAFA by AR, GC, RE and CoMo adjusted for DC ... 160
Table 102: HE - HIN vs. IALA by Type adjusted for AR, GC, RE and CoMo ... 162
Table 103: HE - HIN vs. IALA by AR, GC, RE and CoMo adjusted for DC ... 163
Table 104: HE - HIMIX vs. IAMIX by Type adjusted for AR, GC, RE and CoMo 165
Table 105: HE - HIMIX vs. IAMIX by AR, GC, RE and CoMo adjusted for DC 165
Table 106: Hypo Costs (HC) - HI vs. IA by Type .............................................. 168
Table 107: HC - HIR vs. IAFA by Type ................................................................. 169
Table 108: HC - HIN vs. IALA by Type ............................................................... 170
Table 109: HC - HIMIX vs. IAMIX by Type ....................................................... 170
Table 110: HC - HI vs. IA by Type adjusted for AR .......................................... 171
Table 111: HC - HI vs. IA by AR adjusted for DC ........................................... 172
Table 112: HC - HIR vs. IAFA by Type adjusted for AR ..................................... 173
Table 113: HC - HIR vs. IAFA by AR adjusted for DC ...................................... 173
Table 114: HC - HIN vs. IALA by Type adjusted for AR ................................... 174
Table 115: HC - HIN vs. IALA by AR adjusted for DC .......................................................... 175
Table 116: HC - HIMIX vs. IAMIX by Type adjusted for AR ................................................. 176
Table 117: HC - HIMIX vs. IAMIX by AR adjusted for DC .................................................. 176
Table 118: HC - HI vs. IA by Type adjusted for GC .............................................................. 177
Table 119: HC - HI vs. IA by GC adjusted for DC ................................................................. 178
Table 120: HC - HIR vs. IAFA by Type adjusted for GC ...................................................... 178
Table 121: HC - HIR vs. IAFA by GC adjusted for DC ......................................................... 179
Table 122: HC - HIN vs. IALA by Type adjusted for GC ...................................................... 179
Table 123: HC - HIN vs. IALA by GC adjusted for DC ......................................................... 180
Table 124: HC - HIMIX vs. IAMIX by Type adjusted for GC .............................................. 180
Table 125: HC - HIMIX vs. IAMIX by GC adjusted for DC .................................................. 181
Table 126: HC - HI vs. IA by Type adjusted for RE .............................................................. 181
Table 127: HC - HI vs. IA by RE adjusted for DC ................................................................. 182
Table 128: HC - HIR vs. IAFA by Type adjusted for RE ...................................................... 183
Table 129: HC - HIR vs. IAFA by RE adjusted for DC ......................................................... 183
Table 130: HC - HIN vs. IALA by Type adjusted for RE ...................................................... 184
Table 131: HC - HIN vs. IALA by RE adjusted for DC.......................................................... 185
Table 132: HC - HIMIX vs. IAMIX by Type adjusted for RE .............................................. 186
Table 133: HC - HIMIX vs. IAMIX by RE adjusted for DC .................................................. 187
Table 134: HC - HI vs. IA by Type adjusted for CoMo .......................................................... 188
Table 135: HC - HI vs. IA by CoMo adjusted for DC ............................................................ 188
Table 136: HC - HIR vs. IAFA by Type adjusted for CoMo .................................................. 189
Table 137: HC - HIR vs. IAFA by CoMo adjusted for DC..................................................... 189
Table 138: HC - HIN vs. IALA by Type adjusted for CoMo ........................................ 190
Table 139: HC - HIN vs. IALA by CoMo adjusted for DC ........................................ 190
Table 140: HC - HIMIX vs. IAMIX by Type adjusted for CoMo ............................... 191
Table 141: HC - HIMIX vs. IAMIX by CoMo adjusted for DC ............................... 191
Table 142: HC - HI vs. IA by Type and CoMo Relationship ..................................... 192
Table 143: HC - HIR vs. IAFA by Type and CoMo Relationship ............................... 193
Table 144: HC - HIN vs. IALA by Type and CoMo Relationship ............................... 194
Table 145: HC - HIMIX vs. IAMIX by Type and CoMo Relationship ....................... 195
Table 146: HC - HI vs. IA by Type adjusted for AR and GC .................................... 196
Table 147: HC - HI vs. IA by AR and GC adjusted for DC ....................................... 196
Table 148: HC - HIR vs. IAFA by Type adjusted for AR and GC .............................. 197
Table 149: HC - HIR vs. IAFA by AR and GC adjusted for DC ............................... 198
Table 150: HC - HIN vs. IALA by Type adjusted for AR and GC ............................... 199
Table 151: HC - HIN vs. IALA by AR and GC adjusted for DC ............................... 200
Table 152: HC - HIMIX vs. IAMIX by Type adjusted for AR and GC ..................... 201
Table 153: HC - HIMIX vs. IAMIX by AR and GC adjusted for DC ....................... 201
Table 154: HC - HI vs. IA by Type adjusted for AR and RE .................................... 203
Table 155: HC - HI vs. IA by AR and RE adjusted for DC ...................................... 203
Table 156: HC - HIR vs. IAFA by Type adjusted for AR and RE ............................. 205
Table 157: HC - HIR vs. IAFA by AR and RE adjusted for DC ............................... 206
Table 158: HC - HIN vs. IALA by Type adjusted for AR and RE ............................. 207
Table 159: HC - HIN vs. IALA by AR and RE adjusted for DC ............................... 208
Table 160: HC - HIMIX vs. IAMIX by Type adjusted for AR and RE ..................... 210
Table 184: HC - HIMIX vs. IAMIX by Type adjusted for GC and CoMo .................... 230
Table 185: HC - HIMIX vs. IAMIX by GC and CoMo adjusted for DC .................... 230
Table 186: HC - HI vs. IA by Type adjusted for RE and CoMo ............................. 231
Table 187: HC - HI vs. IA by RE and CoMo adjusted for DC ............................. 231
Table 188: HC - HIR vs. IAFA by Type adjusted for RE and CoMo ....................... 233
Table 189: HC - HIR vs. IAFA by RE and CoMo adjusted for DC ....................... 233
Table 190: HC - HIN vs. IALA by Type adjusted for RE and CoMo ........................ 235
Table 191: HC - HIN vs. IALA by RE and CoMo adjusted for DC ........................ 235
Table 192: HC - HIMIX vs. IAMIX by Type adjusted for RE and CoMo .................. 236
Table 193: HC - HIMIX vs. IAMIX by RE and CoMo adjusted for DC ................. 237
Table 194: HC - HI vs. IA by Type adjusted for AR, GC, RE and CoMo ................. 238
Table 195: HC - HI vs. IA by AR, GC, RE and CoMo adjusted for DC .................. 239
Table 196: HC - HIR vs. IAFA by Type adjusted for AR, GC, RE and CoMo ............. 241
Table 197: HC - HIR vs. IAFA by AR, GC, RE and CoMo adjusted for DC ............. 242
Table 198: HC - HIN vs. IALA by Type adjusted for AR, GC, RE and CoMo ............. 244
Table 199: HC - HIN vs. IALA by AR, GC, RE and CoMo adjusted for DC ............. 244
Table 200: HC - HIMIX vs. IAMIX by Type adjusted for AR, GC, RE and CoMo ....... 247
Table 201: HC - HIMIX vs. IAMIX by AR, GC, RE and CoMo adjusted for DC ........ 247
CHAPTER 1 INTRODUCTION

Insulin therapy is an important treatment option for diabetic patients. The initiation of insulin is a vital stage in the management of diabetes. In a prospective diabetes study, 22–40% of patients needed insulin therapy after six years of treatment with Oral Hypoglycemic Agents (OHAs).\(^1\) However, the patients who continues on OHAs would have been better controlled on insulin is not known.\(^2\) The two major form of diabetes Type I and Type 2 Diabetes Mellitus (T1DM and T2DM) have various treatment options. The treatment of T1DM most often includes basal–bolus insulin regimens, and a similar approach is becoming increasingly applied in patients with advanced T2DM in order to achieve the strict glycemic control targets of glycosylated hemoglobin (HbA1c) and Fasting Plasma Glucose (FPG). The benefits of insulin are well recognized, but it does have its limitations, most notably hypoglycemia. This particular side-effect can limit the level of glycemic control achieved in order to attenuate the number of hypoglycemic episodes experienced by patients.\(^3,4\)

Hypoglycemia occurs frequently in diabetic patients treated with insulin therapy. Beyond the milder symptoms, hypoglycemia can result in coma, seizure, injury to the patient and death.\(^5\) The significant fear of hypoglycemic event in patients affects their quality of life and is a hindrance to the effort of lowering blood glucose levels and risks of microvascular complications. Mild hypoglycemic events can be treated by the person experiencing the episode provided that he or she is aware of the symptoms and acts promptly. Severe episode of hypoglycemia requires medical attention like an emergency department visit or hospitalization.
This retrospective research study builds on the previous work of others and publications on the incidence of hypoglycemia in patients treated with insulin therapy. Our primary study objective is to compare the incidence of hypoglycemia in patients treated with Insulin Analogs (IA) vs. Human Insulin (HI), and associated costs. In particular, Insulin Analogs Fast Acting (IAFA) vs. Human Insulin Regular (HIR), Insulin Analogs Long Acting (IALA) vs. Human Insulin - Neutral Protamine Hagedorn (NPH) (HIN), and Insulin Analogs Pre-mixed (IAMIX) vs. Human Insulin Pre-mixed (HIMIX).

Hypoglycemia is a fearful side-effect that is very unpleasant and sometimes embarrassing. In some cases, patients can lose their consciousness that can result in accidents and injuries. Repeated hypoglycemic episodes can give rise to hypoglycemia unawareness, which is characterized by loss of autonomic warning symptoms and it can be further exacerbated by nocturnal hypoglycemia, as people experiencing these episodes may not be aware of symptoms during sleep.\textsuperscript{6,7,8,9,10} Hypoglycemia has been associated epidemiologically with increased risk of all-cause mortality in patients with diabetes and cardiovascular disease. At present, the clinical significance of hypoglycemia as a precipitant of cardiovascular disease and mortality remains uncertain.\textsuperscript{6} However, the risk of hypoglycemia is a barrier to achieve recommended HbA1c targets. Patients and their physicians continuously face the challenge of glycemic control using insulin dose titration and thus delays in the start of appropriate insulin therapy.\textsuperscript{6}

Clinical studies have shown that the initiation and intensification of insulin therapy is pivotal in the treatment of both T1DM and T2DM patients.\textsuperscript{11} The Diabetes Control and Complications Trial (DCCT) and other landmark studies have shown that tight metabolic control can reduce the incidence of, and delay the development of, late complications in