



Systematic Literature Review of the Incidence and Prevalence of Diabetic Ketoacidosis among Adults with Type 1 Diabetes

Search Strategy, v2 (FINAL)

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1.0 INTRODUCTION

Boehringer Ingelheim (BI) GmbH seeks to better understand the available published data describing the incidence and prevalence of diabetic ketoacidosis (DKA) in adults with type 1 diabetes mellitus (T1DM), including any relevant epidemiological data reported for stratified patient subgroups (such as by age, gender, geographic location, ethnicity, or typical method of insulin administration). To achieve this, Xcenda will perform a systematic literature review (SLR) which will follow the processes outlined within this study protocol.

The purpose of this protocol is to prospectively define the specific parameters by which the SLR of the incidence and prevalence of DKA in adults with T1DM will be conducted. Once agreed to by all parties, Xcenda will follow this protocol for all aspects of the review. Any changes made after agreement may impact the final research findings, associated project fees, and timeline. A change log of protocol amendments is located in Appendix A.

2.0 KEY RESEARCH QUESTIONS

This study will seek to answer the following key question and related query:

1. What is the overall incidence and prevalence of DKA in adult patients (≥ 18 years, including elderly patients) with T1DM?
 - a. What is the incidence and prevalence of DKA in adult T1DM patients by subgroups (when reported in the manuscript and if possible to determine), including: age, gender, geographic location, ethnicity, type of insulin administration (insulin pumps versus injections)?

3.0 SEARCH STRATEGY

The overall approach to the search is outlined below. Additional features of the search strategy and search terms are further detailed in Section 5.0.

3.1 Data Sources

- MEDLINE (via PubMed)
- Embase

3.2 Search Filters and Limitations

3.2.1 Timeframe

- Studies published between January 1, 2000 and the date of the search will be included

3.2.2 Language and Countries

- Language: English only¹
- Geography: no geographic limitations will be applied, but areas of greatest interest include North and South America, Europe, Japan, Taiwan, and Australia.

¹ Articles that appear relevant but are not published in English will be noted during screening and citations will be provided to BI for review.

3.2.3 Humans

- Only studies conducted in humans will be identified by the search.

3.2.4 Publication Status

- Published studies will be considered; conference abstracts will not be included in the review.

4.0 STUDY SELECTION CRITERIA

4.1 Population

- Adult (≥ 18 years) patients with T1DM
 - Elderly patients will be included
 - Studies of mixed populations (pediatric and adult, and/or type 1 and type 2 diabetes) will be included if stratified data are reported for adult T1DM patients. These publications will be categorized in a separate table.

4.2 Interventions/Comparators

The SLR will include all T1DM patients, regardless of treatment. Type of insulin and route of administration are of particular interest and will be captured when these data are available in the literature.

4.3 Outcomes

- Study endpoints (for overall patient population and relevant subgroups)
 - Incidence of DKA
 - Prevalence of DKA

4.4 Study Design

Included study designs:

- Population-based observational studies
- SLRs and meta-analyses²

Excluded study designs:

- Randomized controlled trials / clinical trials
- Pharmacokinetic and pharmacodynamic studies
- Non-randomized interventional studies
- Preclinical or animal studies
- Editorials, letters, and commentaries
- Case studies, reports, or case series

² Reference lists of SLRs will be hand-searched for any articles that may have been missed by the database search. If additional studies are identified (published from 2000 onwards), the data from those studies will be extracted separately. Data extraction for SLRs will only include a basic summary of the study design and overall results.

- Theses and dissertations
- Narrative literature reviews
- Small studies (n<50)
- Guidelines

5.0 SEARCH TERMS

Table 5-1 outlines the search terms to be considered as well as specific details on the search strategy.

Table 5-1. Search Strategy (with Sample Searches in MEDLINE and Embase)

Database	MEDLINE (via PubMed)	
Search Limitations or Filters Applied	Publication dates: 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	Query	Number of records found
#1	(((((((diabetes mellitus, type 1[MeSH Terms]) OR type 1 diabetes[Title/Abstract]) OR juvenile onset diabetes[Title/Abstract]) OR brittle diabetes[Title/Abstract]) OR insulin dependent diabetes[Title/Abstract]) OR iddm[Title/Abstract]) OR autoimmune diabetes[Title/Abstract]) OR sudden onset diabetes[Title/Abstract]	85,033
#2	(((diabetic ketoacidosis[MeSH Terms]) OR diabetic ketoacidosis) OR diabetic acidosis) OR diabetic ketosis	8,267
#3	(((adult[MeSH Terms]) OR adult) OR young adult) OR middle age) OR elderly	6,589,216
#4	#1 AND #2 AND #3	1,265
#5	review NOT (systematic OR (meta AND analys*))	2,372,581
#6	#4 NOT #5	1131
#7	Filters applied: Publication date from 2000/01/01 to 2016/12/31; Humans	596

Database	Embase	
Search Limitations or Filters Applied	Publication date from 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	Query	Number of records found
#1	'diabetes mellitus, type 1'/exp OR 'type 1 diabetes mellitus':ab,ti OR 'juvenile onset diabetes':ab,ti OR 'brittle diabetes':ab,ti OR 'insulin dependent diabetes':ab,ti OR iddm:ab,ti OR 'autoimmune diabetes':ab,ti OR 'sudden onset diabetes':ab,ti	106,633

Database	Embase	
Search Limitations or Filters Applied	Publication date from 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	Query	Number of records found
#2	'diabetic ketoacidosis'/exp OR 'diabetic acidosis'/exp OR 'diabetic ketosis'/exp	9,093
#3	'adult'/exp OR 'young adult'/exp OR 'middle age'/exp OR 'elderly'/exp	6,066,920
#4	#1 AND #2 AND #3	1,078
#5	review NOT (systematic OR (meta AND analys*))	3,002,962
#6	#4 NOT #5	950
#7	Filters applied: Publication date from 2000/01/01 to 2016/12/31; Humans	766

6.0 DATA EXTRACTION

Data extraction will be conducted in MS Excel and converted into MS Word tables for the final report. The elements for data extraction are outlined in Table 6-1.

Table 6-1. Example Data Extraction Templates

Author, year	Country	Type of study	Study period	Definition of DKA	Guidelines used for defining DKA	T1DM cases were identified based on?	Study participants				
							Mean, median, and range of age (as available)	Male%	Inclusion/ exclusion criteria	Sample size	Ethnicity

Author, year	Type of insulin	Insulin pump (Y/N)	Follow up years	N of new cases of DKA	Denominator for calculating rates of DKA	INC of DKA per 1000 PY	PREV of DKA per 1000 people	Conclusions	Notes/Comments/study limitations

APPENDIX A: PROTOCOL CHANGE LOG

Date	Protocol Section	Amendment	Status
<i>Date of change</i>	<i>Section X</i>	<i>Description of change</i>	<i>Completed Y/N</i>
8 July 2016	Section 6.0 Data Extraction	Additional DKA-related data (specifically potential risk factors associated with DKA) as reported in the included studies will be captured during data extraction.	Y