Metformin plus insulin combination therapy compared with insulin monotherapy for patients with type 2 diabetes mellitus

Protocol information

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What's new

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Background

Description of the condition

The prevalence of type 2 diabetes mellitus (T2D) is increasing world-wide (King 1998). Insulin resistance in peripheral tissues and inadequate compensatory insulin secretion are essential elements in the pathogenesis of T2D (LeRoith 2002). Reduced insulin secretion is caused by a decrease in the β-cell mass, a dysfunction of existing β-cells, or both (LeRoith 2002). A consequence of this is chronic hyperglycaemia (elevated levels of plasma glucose) with disturbances of carbohydrate, fat, and protein metabolism (LeRoith 2002).

Chronic hyperglycaemia leads to microvascular (i.e., nephropathy, retinopathy, and neuropathy) as well as macrovascular complications (i.e., ischaemic heart disease, stroke, and lower extremity ischaemia). Mortality is increased among patients with T2D compared to the non-diabetic population (Almdal 2004). The main reason for the increased mortality is macrovascular disease (Almdal 2004; de Marco 1999; Stamler 1993).

For a detailed overview of diabetes mellitus, please see under 'additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About', 'Cochrane Review Groups'). For an explanation of methodological terms, see the main glossary in *The Cochrane Library*.

Description of the intervention

As T2D is a progressive disease, the glucose-lowering intervention strategy must be adjusted over time to achieve and maintain good glycaemic control (UKPDS-33 1998). All patients with T2D are initially advised to follow lifestyle interventions including weight loss and increased physical activity. In order to maintain optimal glycaemic control, the large majority of the patients with T2D will with time require additional pharmacological glucose-lowering therapy. The most commonly used first-line glucose-lowering medications are metformin (which increases insulin sensitivity) and insulin secretagogues (sulphonylureas or glinides - which stimulate insulin secretion) (Nathan 2009).

In a substudy of the United Kingdom Prospective Diabetes Study (UKPDS), 753 overweight patients with T2D were randomised to intensive glycaemic control with metformin versus conventional (diet) treatment for an average of 10 years (UKPDS-34 1998). Metformin resulted in lower insulin levels and improved glycaemic control compared with conventional (diet) treatment. Compared with the conventional treated group, patients allocated to metformin treatment had a significant risk reduction for any diabetes-related outcome measures, as well as significant risk reductions of myocardial infarction, diabetes-related death, and all-cause mortality. Secondary analysis compared the 342 overweight patients allocated to metformin with 951 overweight patients allocated to intensive glycaemic control with sulphonylurea or insulin. Metformin significantly reduced the incidence of cardiovascular disease compared with treatment with sulphonylurea or insulin independent of the achieved level of glycosylated haemoglobin (HbA1c) (UKPDS-34 1998). A recent follow-up study of patients who participated in the UKPDS reported continued benefit of metformin therapy 10 years after the end of the intervention period (UKPDS-80 2008).

If lifestyle changes and maximum tolerated doses of an oral glucose-lowering drug given as monotherapy fail to achieve the glycaemic goal other oral glucose-lowering drugs may be added. The most often recommended choice is combination of metformin plus an insulin secretagogue or insulin (Nathan 2009).

In case of sub-optimal glycaemic control by use of oral glucose-lowering drugs, insulin treatment can be initiated (Nathan 2009). In contrast to other glucose-lowering medications, theoretically, there is no upper limit of the dose of insulin above which further glucose-lowering effect will be absent. Hence, insulin therapy can be used at all stages of the disease including the most severe stages. However, there is only limited evidence of the benefit of different insulin regimens on clinical outcomes. A Cochrane review showed that the combination of insulin and glucose-lowering drugs significantly reduced the daily insulin requirements compared with insulin

monotherapy (Goudswaard 2004). The authors did not find any studies assessing diabetes-related morbidity or mortality (Goudswaard 2004). Insulin can be administered as an insulin analogue or as a preparation of human insulin. Recently, a meta-analysis did not find any differences in clinical relevant outcomes for patients with T2D receiving insulin analogues compared with a preparation of human insulin (Horvath 2007). Also, the recent published 'Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME)–trial' randomised 390 patients with T2D to combination therapy of metformin plus insulin versus insulin monotherapy. In this trial there was no significant difference regarding the primary composite outcome (aggregate of micro- and macrovascular complications and mortality). However, the addition of metformin reduced the risk of macrovascular disease after a follow-up period of 4.3 years (Kooy 2009). The longest trial conducted on patients with T2D so far, is the UKPDS, spanning a period of 10 years, did not test if the positive effect of metformin on clinical outcomes was preserved in combination with insulin therapy (UKPDS-33 1998; UKPDS-34 1998). Also, other insulin trials have been of much shorter duration (only rarely up to one year) and the majority of these trials therefore lack data on relevant clinical outcomes.

How the intervention might work

Metformin is a biguanide and improves liver and peripheral sensitivity to insulin and increases insulin-stimulated uptake and utilisation of glucose (UKPDS-34 1998). Metformin may produce a modest favourable effect on serum lipids and some weight stabilisation or weight loss. Metformin lowers both fasting and postprandial blood glucose levels (Bailey 1996). Several trials indicate that metformin may have anti-atherogenic effects (i.e., reduced levels of blood cholesterol, inflammatory markers, vascular adhesion molecules, and coagulation variables as well as reduced endothelial dysfunction) (Davis 2006; De Jager 2005; Mather 2001; UKPDS-34 1998). Metformin also reduces insulin requirements compared with insulin monotherapy (Kooy 2009). It has been proposed that metformin may possess anti-oncogenic effects (Pearce 2009).

Adverse effects of the intervention

There are specific adverse reactions to metformin, mainly gastro-intestinal (Saenz 2005). A recent Cochrane review on metformin monotherapy did not find any increased risk for lactate acidoses, if the contraindications to initiating and continuing metformin therapy are taken into account (Salpeter 2003). The most common adverse reactions to insulin therapy are hypoglycaemia, injection site reactions, and weight gain (UKPDS-33 1998).

Experimental and observational studies have shown that exogenous insulin stimulates the atherosclerotic pathways (Muis 2005; Ruige 1998; Stout 1990). When metformin and insulin are used in combination adverse effects from both interventions may occur (Kooy 2009). Insulin is a growth hormone with mitogenic effects (van der Burg 1988). Cohort studies have found an increased incidence of cancer in patients with T2D on insulin therapy compared to other antidiabetic interventions (Bowker 2006).

Why it is important to do this review

It is common clinical practice to combine insulin with oral hypoglycaemic drugs, mainly metformin (Nathan 2009). A previous Cochrane review compared insulin monotherapy with the combination of insulin and any peroral anti-diabetic drugs in insulin naive patients with T2D. The review did not find any studies assessing morbidity and mortality (Goudswaard 2004). A Cochrane protocol is published that is going to investigate the effect of addition of oral hypoglycaemic drugs to insulin therapy compared with insulin monotherapy in patients with T2D on insulin therapy at baseline (Van Avendonk 2008). The review by Van Avendonk et al. does only look into the effect of adding any oral hypoglycaemic agents in patients with T2D, which already are treated with insulin. There is no up-to date review focusing on clinical relevant outcomes when insulin therapy is combined with metformin compared with insulin monotherapy (or in combination with placebo) including both insulin naive and insulin treated patients with T2D.

Objectives

To assess the effects of metformin plus insulin in combination therapy versus insulin monotherapy in patients with T2D.

Methods

Criteria for considering studies for this review

Types of studies

All randomised clinical trials comparing metformin plus insulin in combination therapy versus insulin monotherapy in patients with T2D irrespective of intervention at baseline. Published and unpublished trials in all languages will be included.

Types of participants

Adults at or more than 18 years with T2D. The diagnosis of T2D should have been established using standard criteria at randomisation in the trial (e.g., ADA 1997; ADA 1999; ADA 2003; ADA 2008; NDDG 1979; WHO 1980; WHO 1985; WHO 1998). Ideally diagnostic criteria should have been described. If necessary, authors definition of T2D will be used.

The anti-diabetic intervention, prior to randomisation to a combination of metformin plus insulin in combination therapy versus insulin monotherapy, may be one of the following:

- Lifestyle interventions.
- Any oral hypoglycaemic agents.
- Insulin monotherapy.
- Combination of insulin and oral hypoglycaemic agent.

Types of interventions

Combination of metformin plus insulin in combination therapy versus insulin monotherapy or insulin in combination with placebo.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Cardiovascular mortality (death from myocardial infarction, stroke, abdominal aorta aneurism, and peripheral vascular disease).

Secondary outcomes

- Composite macrovascular complications (non-fatal myocardial infarction, non-fatalstroke, abdominal aorta aneurism, amputation of lower extremity, or cardial or peripheral revascularization).
- Components of the composite macrovascular complications assessed seperately (non-fatal myocardial infarction, non-fatal stroke, abdominal aorta aneurism, amputation of lower extremity, or cardial or peripheral revascularization).
- Composite microvascular complications (manifestation and progression of nephropathy, end-stage renal disease, manifestation and progression of retinopathy, or retinal photocoagulation).

- Microvascular complications (manifestation and progression of nephropathy, end-stage renal disease, manifestation and progression of retinopathy, or retinal photocoagulation).
- Glycaemic control (measured by the level of fasting plasma glucose or HbA1c).
- Adverse events.
- Serious adverse events.
- Drop-outs due to adverse events related to treatment.
- Hypoglycaemia, definitions may be heterogenous between trials. Hypoglycaemia will be reported as mild or severe.
- Cancer.
- Blood pressure (diastolic and systolic).
- Quality of life measured with validated instruments.
- Costs of treatment.
- Required amount of insulin for glycaemic control.
- Body mass index (BMI).

Covariates, effect modifiers and confounders

- Disease duration.
- Prior use of insulin or oral hypoglycaemic agents.

Timing of outcome measurement

We included trials with a minimum follow-up period of 12 weeks. The trials will be divided according to their intervention period into short (equal to or greater than 12 weeks to less than two years) and long (equal to or greater than two years) duration.

Search methods for identification of studies

Electronic searches

The following sources will be included in the literature search to identify relevant trials:

- *The Cochrane Library* (latest issue);
- MEDLINE (until recent);
- EMBASE (until recent);
- Science Citation Index Expanded (until recent);
- Latin American Caribbean Health Sciences Literature (LILACS) (until recent);
- Cumulative Index to Nursing & Allied Health Literature (CINAHL) (until recent).

The search strategies are listed in full in Appendix 1.

Searching other resources

In addition, we will hand search abstracts of major diabetes conferences (American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD)) and the references from included trials.

We will also contact relevant pharmaceutical companies and the U.S. Food and Drug Administration and the

European Medicines Agency for unpublished clinical trial data relevant to the review. We will try to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses, and health technology assessment reports noticed.

We will obtain evaluations of all relevant non-English articles.

Additional key words of relevance may be identified during any of the electronic or other searches. If this is the case, electronic search strategies will be modified to incorporate these terms.

Data collection and analysis

Selection of studies

Publications will be included if two of the authors (BH and TA or LC) from the initial search can determine with certainty from the title and the abstract that the trial has been done in patients with T2D, is a randomised clinical trial, and is comparing the combination of metformin and insulin therapy with insulin monotherapy or insulin in combination with placebo. If we are not able to include with certainty a publication on the basis of title, and abstract or both, the full text of the article will be obtained.

Full text articles will be retrieved for further assessment if the information given suggest that the trial; (i) compares combination of insulin and metformin with insulin monotherapy; (ii) includes patients with T2D; (iii) is a randomised clinical trial.

Inter-rater agreement for study selection will be measured using the kappa statistic (Cohen 1960).

A flow diagram of the number of studies identified and rejected at each stage will be prepared in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Liberati 2009)

Data extraction and management

Two authors (BH and TA or LLC) will independently extract information on each trial using standard data extraction forms. The forms include data concerning trial design, participants, interventions, and outcomes as detailed in the selection criteria described above. Any relevant missing information will be sought from the original author(s) of the article if required.

Differences between authors will be resolved by discussion and involvement of a third author.

Assessment of risk of bias in included studies

Methodological quality is defined as the confidence that the design and the report of the randomised clinical trial will restrict bias in the comparison of the intervention (Moher 1998). According to empirical evidence, the methodological quality of the trials is based on sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias (Gluud 2006; Higgins 2008; Kjaergard 2001; Moher 1998; Schulz 1995; Wood 2008).

Two authors (BH and TA or LLC) will independently assess the risk of bias in each trial. Any differences of opinion will be resolved through discussion with third author.

Dealing with missing data

We will attempt to find out missing data by contacting the trial authors and the impact of any missing data will be discussed. Best-worst case and worst-best case scenarios will be performed for the primary outcomes. The ‘best-worst case’ scenario is that all participants with missing outcomes in the experimental intervention group

have good outcomes (i.e., alive), and all those with missing outcomes in the control intervention group had poor outcomes; the 'worst-best case' scenario is the converse (Higgins 2008).

Assessment of heterogeneity

A priori the authors will evaluate clinical diversity of the included trials. Heterogeneity will be identified by using a standard χ2-test with a significance level of α = 0.1. Heterogeneity will be specifically examined with diversity (D^2) (Wetterslev 2009) and inconsistency factor (I^2), where I^2 values of 50% and more represent substantial heterogeneity (Higgins 2008). When heterogeneity is found, we will attempt to determine potential reasons for it by examining individual trial characteristics and those of subgroups of the main body of evidence.

Clinical heterogeneity will be assessed by comparing the trials with regard to different clinical variables: patient characteristics, duration of disease, previous T2D therapy, glycaemic target, target other metabolic variables, and outcome. When significant clinical, methodological, or statistical heterogeneity is found, we will survey the individual trials in trying to determine potential reasons for it.

We plan to use both a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). In case of discrepancy between the two models we will report and discuss both results. Otherwise, we will report only the results from the random-effects model.

Between-trial heterogeneity will be explored by meta-regression depending on the data available.

Assessment of reporting biases

Funnel plots will be used for the primary outcomes to provide visual assessment whether effects are associated with trial size. There are a number of reasons for the asymmetry of a funnel plot (for example methodological design of trials and publication bias) (Higgins 2008).

Data synthesis

Data will be summarised statistically if they are available and of sufficient quality. Statistical analysis will be performed according to the statistical guidelines in the newest version of *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Trial sequential analysis

Trial sequential analysis (TSA) is a methodology that combines an information size calculation (cumulated sample sizes of included trials) for meta-analysis with the threshold of statistical significance. TSA is a tool for quantifying the statistical reliability of data in a cumulative meta-analysis adjusting P values for repetitive testing on accumulating data. TSA will be conducted on the primary outcomes and on the secondary outcomes if possible (Brok 2009; Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2008).

Meta-analysis may result in type I errors due to sparse data or due to repeated significance testing when updating meta-analysis with new trials (Brok 2009; Higgins 2010; Wetterslev 2008). In a single trial, interim analysis increases the risk of type I errors. To avoid type I errors, group sequential monitoring boundaries are applied to decide whether a trial could be terminated early because of a sufficiently small P value that is the cumulative Z-curve crosses the monitoring boundaries (Lan 1983). Sequential monitoring boundaries can be applied to meta-analysis as well, called trial sequential monitoring boundaries (Wetterslev 2008). In TSA, the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to clarify whether additional trials are needed.

The idea in TSA is that if the cumulative Z-curve crosses the boundary, a sufficient level of evidence is reached and no further trials may be needed. If the Z-curve does not cross the boundary then there is insufficient evidence to reach a conclusion. To construct the trial sequential monitoring boundaries the required

information size is needed and is calculated as the least number of participants needed in a well-powered single trial (Brok 2009; Pogue 1997; Pogue 1998; Wetterslev 2008). We will apply TSA since it prevents an increase of the risk of type I error (< 5%) due to potential multiple updating in a cumulative meta-analysis and provides us with important information in order to estimate the level of evidence of the experimental intervention. Additionally, TSA provides us with important information regarding the need for additional trials and the required sample size of such trials.

We will apply trial sequential monitoring boundaries according to a heterogeneity-adjusted required information size based on an apriori 10% relative risk reduction (RRR) (APHIS) employing α = 0.05 and ß = 0.20.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be performed mainly if one of the primary outcome measures demonstrates statistically significant differences between intervention groups. In any other case subgroup analysis will be clearly marked as a hypothesis generating exercise. The following subgroup analyses are planned:

- Trials classified as low-risk of bias compared to trials with high-risk of bias (assessed through sequence generation, allocation concealment, and blinding).
- Published trials compared to unpublished trials.
- Trials designed to design participants and investigators compared to trials with open-label design.
- Insulin type used (analogue insulin preparations compared to human insulin preparations).
- Trials of short duration of the intervention (equal to or greater than 12 weeks to less than two years) compared to trials of long duration (equal to or greater than two years).
- Mean age < 65 years compared to $\geq$ 65 years.
- Mean BMI < 30 compared to BMI $\geq$ 30.
- Trials including participants with insulin therapy at baseline compared to trials including insulin naive participants

Tests of interaction will be applied to determine the effect of subgroup on the intervention effect (Altman 2003).

Heterogenity examined by meta-regression

Meta-regression will be conducted for the following covariates:
- Average duration of the intervention.
- Average duration of diabetes at baseline.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of different patient and trials characterics on effect size.

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Contributions of authors

BIANCA HEMMINGSEN: development of protocol, undertaking of searches, selection of trials, data extraction, quality assessment of trials, contact person, development of protocol.
LOUISE L. CHRISTENSEN: development of protocol, selection of trials, data extraction, quality assessment of trials, development of protocol.
JØRN WETTERSLEV: development of protocol, advised on statistical methods to be used, data analysis.
ALLAN VAAG: development of protocol.
CHRISTIAN GLUUD: development of protocol.

SØREN S. LUND: development of protocol.
THOMAS ALMDAL: development of protocol, selection of trials, data extraction, quality assessment of trials.

Declarations of interest

Søren Søgaard Lund, Louise Lundby Christensen, Thomas Almdal, and Allan Vaag have reported equity in Novo Nordisk A/S. Søren Søgaard Lund and Allan Vaag have received fees from Novo Nordisk A/S for speaking. Louise Lundby Christensen and Thomas Almdal are employed at Steno Diabetes Center, Gentofte, Denmark. Steno Diabetes Center is an academic institution owned by Novo Nordisk A/S and The Novo Nordisk Foundation.

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Other published versions of this review

Figures

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Feedback

Appendices

1 Search strategy

Search terms
Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent. **MEDLINE:** 1. exp Diabetes Mellitus, Type 2/ 2. (MODY or NIDDM or T2DM).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 4. ((typ* 2 or typ* II) adj3 diabet*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 5. ((keto?resist* or non?keto*) adj6 diabet*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 6. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 7. 1 or 2 or 3 or 4 or 5 or 6 8. exp Diabetes Insipidus/ 9. diabet* insipidus.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 10. 8 or 9 11. 7 not 10 12. exp Biguanides/ 13. (metformin* or glucophag* or biguanid*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 14. 12 or 13 15. exp Insulin/ 16. insulin*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 17. 15 or 16 18. 11 and 14 and 17 19. (random* or blind* or placebo* or meta-analysis).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 20. 18 and 19 **EMBASE** 1. exp diabetes mellitus/ 2. (MODY or NIDDM or T2DM).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

3. (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
4. ((typ* 2 or typ* II) adj3 diabet*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
5. ((keto?resist* or non?keto*) adj6 diabet*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
6. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp diabetes insipidus/
9. diabet* insipidus.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
10. 8 or 9
11. 7 not 10
12. exp biguanide/
13. (metformin* or glucophag* or biguanid*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
14. 12 or 13
15. exp INSULIN/
16. insulin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
17. 15 or 16
18. 11 and 14 and 17
19. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
20. 18 and 19

The Cochrane Library
1. MeSH descriptor Diabetes Mellitus, Type 2 explode all trees 6549
2. MODY OR NIDDM OR T2DM 1348
3. non insulin* depend* OR noninsulin* depend* OR non insulin?depend* OR noninsulin?depend* 3259
4. (typ* 2 OR typ* II) near/3 diabet* 8930
5. (keto?resist* OR non?keto*) near diabet* 0
6. (late OR adult* OR matur* OR slow OR (stabl*) near/3 onset) AND diabet* 12046
7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6) 17474
8. MeSH descriptor Diabetes Insipidus explode all trees 41
9. diabet* insipidus 117
10. (#8 OR #9) 117
11. (#7AND NOT #10) 17375
12. MeSH descriptor Biguanidesexplode all trees 2419
13. metformin* OR glucophag* OR biguanid* 1865
14. (#12 OR #13) 3088
15. MeSH descriptor Insulinexplode all trees 7405
16. insulin* 16568
17. (#15 OR #16) 16568
18. (#11 AND #14 AND #17) 851

LILACS
metformin [Words] and insulin [Words]

CINAHL
1 MW Diabetes Mellitus
2. TX MODY OR NIDDM OR T2DM
3. TX non insulin* depend* OR noninsulin* depend* OR non insulin?depend* OR noninsulin?depend*
4. TX (typ* 2 OR typ* II) AND diabet*
5. TX (keto?resist* OR non?keto*) AND diabet
6. TX (late OR adult* OR matur* OR slow OR stabl*) AND onset AND diabet*
7. S1 or S2 or S3 or S4 or S5 or S6
8. MW Diabetes insipidus
9. TX diabet* insipidus
10. S8 or S9
11. S7 NOT S10
12. MW metformin
13. TX metformin* OR glucophag* OR biguanid*
14. S12 or S13
15. MW insulin
16. TX insulin*
17. S15 or S16
18. S11 and S14 and S17
19. TX random* or blind* or placebo* or meta-analysis
20. S18 and S19

Science Citation Index Expanded
1. 14,877 TS=(MODY or NIDDM or T2DM)
2 15,360 TS=(non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*)
3. 79,124 TS=((typ* 2 or typ* II) SAME diabet*)
4. 0 TS=((keto?resist* or non?keto*) SAME diabet*)
5. 2,932 TS=(((late or adult* or matur* or slow or stabl*) SAME onset) AND diabet*)
6. 97,504 #5 OR #4 OR #3 OR #2 OR #1
7. 6,161 TS=diabet* insipidus
8. 97,316 #6 NOT #7
9. 10,099 TS=(metformin* or glucophag* or biguanid*)
10. >100,000 TS=(insulin*)
11. 2,880 #10 AND #9 AND #8
12. >100,000 TS=(random* or blind* or placebo* or meta-analysis)
13. 1,215 #12 AND #11