Effect of new anti-diabetic medications in combination with metformin compared to sulfonylurea in combination with metformin in patients with type 2 diabetes

kunnskapssenteret
Norwegian Knowledge Centre for the Health Services

Background: Type 2 diabetes is a serious, chronic disease that can increase the risk of death, heart attack, stroke and kidney disease. This overview of reviews updates evidence comparing the effects of the currently recommended treatment (sulfonylurea + metformin) to treatment with newer anti-diabetic medications (DPP-4 inhibitors or GLP-1 analogs) added to metformin when neither life-style changes nor metformin alone are effective in reducing blood sugar levels. • No conclusions can be drawn about the effect on mortality of adding DPP-4 inhibitor versus sulfonylurea to metformin because of few events and low quality evidence. There was no documentation for the effect on mortality of adding GLP-1 analogs versus sulfonylurea to metformin. • We found no evidence on the effects on micro and macrovascular complications for either comparison. • Results for intermediate outcomes (HbA1c change, weight, hypoglycemic incidents) are mixed. Reduction in HbA1c is larger with sulfonylurea, but DPP-4 inhibitors and GLP-1 analogs result in more weight loss and a lower risk of a hypoglycemic episode. • All differences are small in magnitude and may

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(continued from page one)   be clinically unimportant. • Sulfonylurea + metformin is substantially less costly than either DPP-4 inhibitors or GLP-1 analogs + metformin.

Key messages

Type 2 diabetes is a serious, chronic disease that can increase the risk of death, heart attack, stroke and kidney disease. This overview of reviews updates evidence comparing the effects of the currently recommended treatment (sulfonylurea + metformin) to treatment with newer anti-diabetic mediations (DPP-4 inhibitors or GLP-1 analogs) added to metformin when neither life-style changes nor metformin alone are effective in reducing blood sugar levels.

- No conclusions can be drawn about the effect on mortality of adding DPP-4 inhibitor versus sulfonylurea to metformin because of few events and low quality evidence. There was no documentation for the effect on mortality of adding GLP-1 analogs versus sulfonylurea to metformin.
- We found no evidence on the effects on micro and macrovascular complications for either comparison.
- Results for intermediate outcomes (HbA1c change, weight, hypoglycemic incidents) are mixed. Reduction in HbA1c is larger with sulfonylurea, but DPP-4 inhibitors and GLP-1 analogs result in more weight loss and a lower risk of a hypoglycemic episode.
- All differences are small in magnitude and may be clinically unimportant.
- Sulfonylurea + metformin is substantially less costly than either DPP-4 inhibitors or GLP-1 analogs + metformin.

Executive summary

Background

Diabetes is a serious chronic disease, characterized by higher than normal levels of sugar (glucose) in the blood resulting from inadequate insulin production and/or ineffective use of insulin by the body (insulin resistance). Insulin is the hormone that regulates blood sugar. It enables cells in the body to absorb glucose from the blood and it reduces endogenous glucose production. Over time, an above normal blood glucose level (hyperglycemia) can lead to increased risk of mortality and micro and macrovascular complications, including damage to the heart, blood vessels, kidneys, eyes and nerves. The costs to the individual and society of uncontrolled diabetes are substantial.

Type 2 diabetes, which is associated with excessive weight, poor diet and limited physical activity, accounts for approximately 80-90% of all diabetes and is a growing problem in Norway. Recent estimates suggest that from 300 000 – 350 000 individuals suffer from type 2 diabetes, approximately half of them undiagnosed.

Norwegian national diabetes treatment guidelines from 2009 recommend life-style changes, followed by the addition of metformin (an oral anti-diabetic medication). If metformin therapy is ineffective, the guidelines further recommend adding sulfonylurea, another anti-diabetic drug, or insulin to metformin. Two newer types of drugs, DPP-4 inhibitors and GPL-1 analogs, are only recommended if treatment with metformin + sulfonylurea is not tolerated, because at the time the guidelines were issued there was little clinical evidence about their effects. Recently, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued recommendations that suggested equal preference be given to sulfonylurea, pioglitazone, insulin, DPP-4 inhibitors and GLP-1 analogs in second-line treatment decisions.

Objective

To upgrade the evidence about the effect of DPP-4 inhibitors or GLP-1 analogs in combination with metformin compared to sulfonylurea in combination with

metformin, among adults with type 2 diabetes inadequately controlled with metformin monotherapy.

Method

We have conducted this overview of reviews in accordance with the Handbook for the Norwegian Knowledge Center for the Health Services.

A systematic literature search of several databases was conducted in April 2013 and updated in February 2014. Two review authors reviewed all citations to identify relevant systematic reviews according to pre-specified criteria. Full text publications of potentially eligible references were retrieved, and we assessed the quality of the included systematic reviews. We extracted data from the included references using a pre-designed data recording form. Article selection was completed independently by two review authors and then compared. Data extraction and quality assessment was conducted by one of the review authors and then checked by one of the others.

We used the effect estimates reported in the included reviews. For assessment of individual trials included in the systematic reviews, we relied on assessments performed by the review authors. When such assessments were conducted using tools other than those recommended in the Handbook, we performed our own risk of bias assessments.

Results

Results are based on two recent, high quality systematic reviews. No conclusions can be drawn about differences in mortality for the comparison DPP-4 inhibitors + metformin versus sulfonylurea + metformin because of few events and low quality evidence. No mortality evidence was available for the comparison GLP-1 analogs + metformin versus sulfonylurea + metformin. There was no evidence on micro or macrovascular complications for either comparison.

Sulfonylurea + metformin results in greater reductions in HBA1c than DPP-4 inhibitors + metformin and similar reductions compared to GLP-1 analogs + metformin, but also leads to an increased risk of experiencing at least one hypoglycemic incident and results in weight gain rather than weight loss when compared to metformin combined with either DPP-4 inhibitors or GLP-1 analogs. The evidence was generally of moderate to low quality.

Direct treatment costs differ substantially among the three treatment options. Medication costs are lowest for treatment with sulfonylurea + metformin (NOK 1217). DPP-4 inhibitors + metformin are approximately three to four times more and

GLP-1 analogs + metformin approximately ten to fourteen times more expensive than sulfonylurea + metformin.

Discussion

We conducted a systematic search of the literature to find the most current systematic reviews comparing the effects of adding DPP-4 inhibitors or GPL-4 analogs versus sulfonylurea to metformin for treating type 2 diabetes inadequately controlled by metformin alone.

The results are limited by the lack of long-term data on important clinical outcomes (mortality, micro and macrovascular complications). To the extent that evidence exists, it is of low quality. Effect data for changes in HbA1c and weight is of moderate quality, but the quality of evidence on hypoglycemic episodes is low because relatively few episodes occur and studies often fail to distinguish between serious and minor events. Although differences in outcomes exist among the comparisons, they do not uniformly support one treatment. In addition, the differences are relatively small in size and may not be clinically relevant.

Our estimates of economic costs only include the costs of medications since we assume that other direct costs, such as doctor visits and blood sugar testing materials, would be equivalent across treatment groups. To the extent that sulfonylurea + metformin results in a higher risk of hypoglycemic incidents than DPP-4 inhibitors or GLP-1 analogs + metformin, the associated direct costs may increase. We did not have enough information to estimate the size of this potential effect, but it is not likely to reverse the substantial cost advantage of sulfonylurea.

Conclusion

The most recent systematic reviews still provide either no evidence or evidence of low quality about differences in important outcomes (mortality, micro and macrovascular complications) between DPP-4 inhibitors or GLP-1 analogs + metformin and sulfonylurea + metformin. Differences in intermediate outcomes (HbA1c change, weight, hypoglycemic incidents) exist but do not uniformly support one treatment. The direct cost of sulfonylurea is substantially lower than either DPP-4 inhibitors or GPL-1 analogs when added to metformin.

Continuing research is needed on important long-term outcomes and safety.

Hovedfunn (norsk)

Type 2 diabetes er en alvorlig, kronisk sykdom som kan øke risiko for død, hjerteinfarkt, slag og nyresvikt. Målet for behandlingen er å redusere blodsukkernivå for å hindre senskader, men mange pasienter når ikke behandlingsmålet ved å endre levevaner eller med legemiddelet metformin alene. Denne oversikten over systematiske oversikter sammenligner effekten av nåværende behandlingsanbefaling, dvs. metformin i kombinasjon med et sulfonylurea legemiddel, med metformin i kombinasjon med et av de nyere blodsukkersenkende medikamentene (DPP-4-hemmere eller GLP-1-analoger).

- Vi kan ikke konkludere vedrørende effekt på dødelighet for metformin og DPP-4-hemmere sammenlignet med metformin og sulfonylurea, da det var få hendelser og lav kvalitet på dokumentasjonen.
- Vi fant ingen dokumentasjon for dødelighet for metformin og GLP-1-analoger sammenlignet med metformin og sulfonylurea.
- Vi fant ingen dokumentasjon for noen av sammenligningene for effekt på mikro- og makrovaskulære komplikasjoner, dvs. hjerteinfarkt, slag, nyresvikt eller blindhet.
- Resultater for intermedeære utfall (HbA1c endring, vektendring og hypoglykemiske hendelser) varierte. Nedgang i HbA1c er størst med sulfonylurea, men DPP-4-hemmere og GLP-1-analoger fører til større vekttap og en lavere risiko for minst en føling (hypoglykemiskhendelse).
- Alle forskjellene er små og kan ha liten klinisk betydning.
- Kostnaden ved å bruke sulfonylurea er vesentlig lavere enn kostnaden ved DPP-4-hemmere eller GLP-1-analoger. Kostnaden av metformin vil være den samme uavhengig av hvilket legemiddel man legger til.

Sammendrag (norsk)

Bakgrunn

Diabetes er en alvorlig kronisk sykdom hvor sukkerinnholdet i blodet er høyere enn normalt på grunn av manglende insulinsekresjon og/eller redusert insulinvirkning (insulinresistens). Insulin er et hormon som regulerer kroppens blodsukkernivå. Det gjør at sukker i blodet flyttes inn i cellene hvor det kan brukes som energi eller lagres, og hemmer kroppens egen glukoseproduksjon. Over tid kan forhøyet blodsukker føre til mikro- og makrovaskulære komplikasjoner som igjen innebærer økt risiko for nyresvikt, blindhet, skader på nerver, hjerte- og karsykdommer og hjerneslag. Kostnaden av ukontrollert diabetes er svært høy, både for individet og samfunnet.

Type 2 diabetes står for 80-90 % av diabetes tilfellene og skyldes overvekt, feil kosthold og lite fysisk aktivitet. Nyere anslag tyder på at 300 000 – 350 000 personer i Norge lider av type 2 diabetes, hvorav omtrent halvparten er udiagnostisert.

Nasjonale faglige retningslinjer for diabetes fra 2009 anbefaler at man først skal forsøke endring av levevaner, eventuelt med bruk av det blodsukkersenkende legemiddelet metformin. Hvis behandlingsmålet ikke nås ved bruk av metformin alene, er det anbefalt å legge til sulfonylurea. På grunn av manglende eller svak klinisk evidens da retningslinjen ble utviklet, er de nyere legemiddelklassene DPP-4-hemmere og GLP-1-analoger kun anbefalt hvis pasienter ikke tåler metformin og sulfonylurea. American Diabetes Association (ADA) og European Association for the Study of Diabetes (EASD) har imidlertid nylig foreslått å likestille sulfonylurea, DPP-4-hemmere og GLP-1-analoger som annenlinjebehandling.

Problemstilling

Å oppdatere evidensgrunnlaget for vurdering av effekt av DPP-4-hemmere eller GLP-1-analoger i kombinasjon med metformin sammenlignet med sulfonylurea i kombinasjon med metformin hos voksne med type 2-diabetes når behandlingsmål ikke nås ved metformin monoterapi.

Metode

Vi har laget en systematisk oversikt over systematiske oversikter i henhold til Nasjonalt kunnskapssenteret for helsetjenestens metodehåndbok.

Vi gjennomførte et systematisk litteratursøk av flere databaser i april 2013 og oppdaterte søket i februar 2014. To personer vurderte titler og sammendrag på publikasjoner identifisert via et systematisk litteratursøk og identifiserte de mulig relevante systematiske oversiktene i henhold til forhåndsdefinerte kriterier. De ble så innhentet i fulltekst for endelig vurdering av relevans for vår problemstilling og kvalitetsvurdert. Vi ekstraherte data fra inkluderte referanser ved bruk av et forhåndsdesignet skjema. Artikkelutvelgelse var gjennomført av to uavhengige personer og sammenlignet. Data ble ekstrahert av en person og så kontrollert av en annen person.

Vi rapporterer effektestimatene slik de er rapportert i de inkluderte oversiktene. I de tilfeller hvor forfatterne av de inkluderte systematiske oversiktene hadde utført kvalitetsvurdering av sine inkluderte enkeltstudier, benyttet vi disse. Hvis vurderinger ikke ble gjennomført i henhold til vår metodehåndbok, gjennomførte vi vår egen "risk of bias" vurdering.

Resultat

Vi inkluderte to systematiske oversikter av høy kvalitet. Vi kan ikke konkludere vedrørende effekt på dødelighet for metformin og DPP-4-hemmer sammenliknet med metformin og sulfonylurea, da det var få hendelser og lav kvalitet på dokumentasjonen. Vi fant ingen dokumentasjon for dødelighet for metformin og GLP-1-analoger sammenlignet med metformin og sulfonylurea. Det var heller ingen data for effekter på mikro- eller makrovaskulære komplikasjoner for noen av sammenligningene.

Sulfonylurea + metformin fører til større nedgang i HbA1c enn DPP-4-hemmere og metformin, og omtrent lik nedgang sammenlignet med GLP-1-analoger og metformin. Sulfonylurea og metformin fører til både en økt sannsynlighet for en hypoglykemisk hendelse og økning i vekt i stedet for en nedgang i vekt, sammenlignet med DPP-4-hemmere eller GLP-1-analoger i kombinasjon med metformin. Dokumentasjonen for var av moderat til lav kvalitet for de fleste kombinasjonene.

Direkte behandlingskostnader varierer betydelig mellom de forskjellige behandlingsmulighetene. Legemiddelkostnadene er lavest for sulfonylurea i kombinasjon med metformin (NOK 1217). DPP-4-hemmere og metformin er tre –

fire ganger dyrere, og GLP-1-analoger og metformin er ti – fjorten ganger dyrere enn sulfonylurea og metformin.

Diskusjon

Vi gjennomførte et systematisk søk for å finne de mest aktuelle systematiske oversiktene som sammenligner effektene av å kombinere metformin med DPP-4-hemmere eller GLP-1-analoger versus sulfonylurea i behandling av type 2 diabetes som ikke behandles med metformin alene.

Resultatene viser manglende eller mangelfulle langsiktige data for viktige kliniske utfall som dødelighet og mikro- og makrovaskulære komplikasjoner (hjerteinfarkt, slag, nyresvikt, blindhet). Effektdata for endringer i HbA1c og vekt er av moderat kvalitet, men kvaliteten av evidensen for hypoglykemiske hendelser er lav fordi det er få hendelser og fordi studiene ikke skiller mellom alvorlige og mindre alvorlige hypoglykemiske hendelser. Selv om det eksisterer forskjeller mellom de enkelte sammenligningene, kan vi ikke konkludere med at en av legemiddelkombinasjonene er best for alle utfallene. Forskjellene er i tillegg relativt små og kan ha liten klinisk relevans.

Estimatene av økonomiske kostnader inkluderer bare legemidlerpriser fordi vi antok at andre direkte kostnader, som for eksempel legetimer og blodsukkermåling, var "like på tvers av behandlingsgruppene. I den grad kombinasjonen med sulfonylurea innebærer en høyere risiko for hypoglykemiske hendelser enn DPP-4-hemmere eller GLP-1-analoger kan assosierte direkte kostnader øke. Vi hadde ikke nok informasjon for å estimere størrelsen på denne potensielle forskjellen, men det er usannsynlig at det vil kunne reversere den betydelige kostnadsfordelen av å benytte sulfonylurea.

Konklusjon

Fortsatt finnes det ingen dokumentasjon eller bare dokumentasjon av lav kvalitet på forskjeller mellom DPP-4-hemmere eller GLP-1-analoger i kombinasjon med metformin versus sulfonylurea i kombinasjon med metformin for viktige utfall som dødelighet og mikro- og makrovaskulære komplikasjoner. Det er forskjeller i intermediære utfall som HbA1c endring, vektendring og hypoglykemiske hendelser men ulike legemidler kommer best ut for ulike utfall. Den direkte kostnaden av sulfonylurea i kombinasjon med metformin er betydelige lavere enn for både DPP-4-hemmere og GLP-1-analoger i kombinasjon med metformin.

Videre forskning trengs for å undersøke kliniske endepunkt som dødelighet, hjerteinfarkt, slag, nyresvikt og sikkerhet.

Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester. Kunnskapssenteret er formelt et forvaltningsorgan under Helse-direktoratet, men har ikke myndighetsfunksjoner og kan ikke instrueres i faglige spørsmål.

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Glossary

CI   **Confidence interval**. A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.

DPP-4 inhibitors   A class of oral hypoglycemic drugs that block the enzyme dipeptidyl peptidase-4 (DPP-4) in order to reduce blood glucose levels

GLP-1 analogs   A class of injectable hypoglycemic drugs that mimic the action of glucagon-like peptide-1 (GLP-1), a hormone that increases the release of insulin in response to increases in blood glucose level.

HbA1c   **Glycated hemoglobin**. A form of hemoglobin that is measured to determine average blood glucose concentration over prolonged periods of time. HbA1c ≥ 6.5% is considered a sign of diabetes.

Heterogeneity   In a meta-analysis, heterogeneity refers to lack of uniformity in the results of the primary studies. Standard tests of heterogeneity are the I-squared (I^2) and Chi-squared (χ^2) tests. Heterogeneity is considered low if $I^2 \leq 20\%$, high if $I^2 > 50\%$ and indeterminate for values between 20% and 50%. A Chi-squared test with a low p-value (generally under 0.05) is considered evidence of heterogeneity.

Hypoglycemia   A condition that results from below normal blood glucose levels. Mild hypoglycemia can lead to feelings of nausea or nervousness. Moderate hypoglycemia can result in confusion, blurred vision or unsteadiness. Severe hypoglycemia can cause seizures, unconsciousness, coma or death.

Mean difference   The difference in mean effects between two treatment groups.

MA   **Meta-analysis**. The use of statistical techniques to combine the results of similar, individual studies of the same direct comparison into a single effect estimate. See Appendix 2.

NMA   **Network meta-analysis**. The use of statistical techniques to

	examine comparisons of multiple treatment options by combining evidence from both direct and indirect comparisons. See Appendix 2.
Odds ratio	**Odds ratio.** The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group. When risk is small the odds ratio is very similar to the risk ratio.
RR	**Risk Ratio / Relative Risk.** The risk ratio is the absolute risk (AR) in the intervention group divided by the AR in the control group. It should be distinguished from the odds ratio (OR), which is the ratio of events to non-events in the intervention group divided by the ratio of events to non-events in the control group.
Statistically significant	A result that is unlikely to have occurred by chance. The customary limit for statistical significance is 5% (p-value = 0.05). See Appendix 2 for a discussion of statistical significance.
T2D	Type 2 diabetes

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Preface

The Norwegian Directorate of Health requested that The Norwegian Knowledge Centre for the Health Services perform a summary of systematic reviews of the effects of newer hypoglycemic (blood sugar lowering) medications taken in combination with metformin among adults with type 2 diabetes that is inadequately controlled with metformin monotherapy. This evidence review will contribute to background documentation for national guidelines for treatment of type 2 diabetes.

The project group consisted of:
- Project coordinator: Researcher, Arna Desser, The Norwegian Knowledge Centre for the Health Services
- Other participants: Tove Ringerike, and Marianne Klemp, The Norwegian Knowledge Centre for the Health Services

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Gro Jamtvedt   Marianne Klemp   Arna Desser
Department director   *Research director*   *Project coordinator*

Objective

To upgrade the evidence about the effect of DPP-4 inhibitors or GLP-1 analogs in combination with metformin compared to sulfonylurea in combination with metformin among adults with type 2 diabetes inadequately controlled with metformin monotherapy.

Background

Diabetes as a disease

Diabetes is a serious chronic disease, characterized by higher than normal levels of sugar (glucose) in the blood resulting from inadequate insulin production, ineffective use of insulin by the body (insulin resistance) or a combination of the two. Insulin is the hormone that regulates blood sugar. It enables cells in the body to absorb glucose from the blood and suppresses endogenous glucose production. Cells then convert glucose to energy or store it for future use. If the pancreas produces inadequate amounts of insulin or if cells don't respond properly to insulin that is produced because of insulin resistance, the body's blood glucose level rises. Over time, an above normal blood glucose level (hyperglycemia) can lead to damage of the heart, blood vessels, kidneys, eyes and nerves. As a result, individuals with diabetes face increased risks of mortality, heart disease, stroke, kidney failure, blindness, impotence and amputations (1, 2).

There are two main types of diabetes that differ in terms of underlying causes. Type 1 diabetes, formerly called insulin-dependent or juvenile diabetes, is an auto-immune disease in which the body's immune system destroys pancreatic beta cells necessary for producing insulin. Secretion of insulin by the pancreas is either eliminated or severely reduced and patients require insulin replacement through regular injections to control their blood sugar levels. Type 1 diabetes is typically diagnosed in children, teenagers or young adults. Approximately 10-15% of diabetic patients have type 1 diabetes.

Type 2 diabetes (T2D), formerly called adult-onset diabetes, is the most common type of diabetes, affecting approximately 80-90% of patients with diabetes. T2D is associated with a relative lack of insulin caused by a combination of insulin resistance and the inability of the pancreas to produce enough insulin to meet the body's needs. The relative lack of insulin develops gradually and T2D is diagnosed when the body can no longer maintain a normal blood glucose level as defined by standard blood glucose tests. Diagnostic threshold levels are: HbA1c ≥ 6.5%, fasting blood glucose ≥ 7.0 mmol/L, or a random blood glucose or blood glucose two hours glucose intake ≥ 11.1 mmol/L (3).

Excessive weight, poor diet and physical inactivity are considered important risk factors for type 2 diabetes and the incidence of T2D tends to increase with age. Type 2 diabetes usually develops gradually and is most often found in adults over age 30, but growing numbers of younger people are diagnosed with type 2 diabetes. Treatment usually focuses on lifestyle changes to reduce weight, improve diet and increase physical activity. If these prove ineffective, oral antidiabetic (blood sugar-reducing) medications can be added, and eventually supplemented or replaced by insulin injections.

Prevalence and Burden

Diabetes is a large and growing problem worldwide. Determining the exact number of individuals with diabetes is difficult because standards for defining diabetes vary and because experts suspect that many people with T2D are undiagnosed. A recent study indicated that in 2008 there were between 314 and 382 million individuals with diabetes globally (4).

According to the World Health Organization (WHO), in 2004 diabetes was the twelfth leading cause of death globally, directly accounting for 2% of total deaths (1.1 million of approximately 58.8 million total deaths) (5). For high income countries diabetes was the eighth leading cause of death, with 3% of total deaths (0.2 million deaths). High blood glucose was a risk factor for 6% of total deaths globally (3.4 million deaths) in 2004, reflecting the fact that diabetes is often a contributing factor to other diseases (6). Mortality predictions for 2030 suggest that diabetes will be the seventh leading cause of death worldwide, accounting for 3.0% of total deaths, and the fourth most important cause of death in high income countries, 5 % of total deaths (7). One of the major reasons for this expected increase is the growing numbers of overweight or obese individuals.

Disease burden can also be described using DALYs (disability adjusted life-years), a measure that captures both early mortality and the difficulty of living with disease or disability (6). Diabetes is also among the leading causes of global disease burden as defined using DALYS.

Diabetes in Norway

Diabetes is also a growing problem in Norway. As in other countries, estimating national prevalence of the disease is complicated by the lack of a unique method for diabetes testing and diagnostic criteria, as well as study samples that are not representative of the national population and have high drop-out rates (8). However, recent estimates suggest that the prevalence of diagnosed diabetes was 4.3% in 2011 (9). The actual prevalence of diabetes is likely to be much higher. Evidence (8) indicates that as much as 50% of type 2 diabetes is undiagnosed,

suggesting that the current total number with T2D in Norway is 300,000—350,000 (10).

Rising prevalence of obesity and reduced levels of physical activity in Norway point to the potential for continued increases in the prevalence of type 2 diabetes. From 1985 to 2006 the prevalence of obesity among adult men in North-Trøndelag increased from 7 to 20%, with slightly lower increases among women (11). One in five Norwegian adults may be obese. Approximately 20—30% of adult men are physically inactive during leisure time. The problem is more pronounced among certain immigrant groups. For example, obesity effects 40% of Pakistani and 55% of Turkish women and up to 50% of adult immigrants are physically inactive during leisure time.

The economic cost of diabetes in Norway is high. In 2005, total expenditures associated with diabetes (expressed in 2005 NOK) were estimated at NOK 3.3 billion (1.4% of total health care expenditures) when hospitalizations with diabetes as a secondary diagnosis were excluded. The largest cost components were medications, including cholesterol lowering and anti-hypertensive drugs, NOK 717 million (31% of total), disability pensions, NOK 410 million (15%) and hospital admissions with diabetes as primary cause, 178 million (8%). When hospitalizations with diabetes as a secondary diagnosis were included total costs were NOK 4.35 billion (2.6% of total health care expenditures), with T2D accounting for 65% of costs (12).

Treatment guidelines

Current Norwegian treatment guidelines (11) for T2D stress the importance of lifestyle changes as the primary treatment. Doctors and patients develop treatment goals that specify smoking cessation and targets for regular exercise and weight loss through healthier diets in order to reduce blood glucose, measured by HbA1c levels. If after three months, a patient has not achieved the desired goals, metformin, an oral antidiabetic (blood glucose lowering) medication that suppresses glucose production by the liver, is introduced as the first-line medical treatment. Metformin dosage is adjusted upwards if sufficient reduction in blood glucose doesn't occur. For patients who don't meet treatment goals with metformin monotherapy, sulfonylurea (SU), an oral medication that increases insulin secretion by the pancreas, or an injectable, daily-dose insulin (NPH-insulin) can be introduced in addition to metformin as a second-line medical treatment. Ultimately, a patient can be placed on intensive insulin treatment.

Some individuals don't tolerate one or more of the recommended medications because of side effects that develop or because the recommended medications are not compatible with other drugs the patient may be taking. In this case other medications, developed more recently, can be substituted. The most important of

these are glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors. When the current diabetes guidelines were written, evidence about the long-term effectiveness and safety of these medications was limited so they were not considered appropriate for general use.

Recently, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued recommendations that maintained metformin as the preferred first-line treatment for T2D, but suggested that in decisions about which drug to add to metformin as a second-line treatment equal preference be given to sulfonylurea, NPH-insulin, GPL-1 analogs, and DPP-4 inhibitors (13).

Objective

The Norwegian Directorate of Health requested that the Norwegian Knowledge Centre update the evidence of the effect of newer hypoglycemic (blood glucose lowering) medications, DPP-4 inhibitors or GLP-1 analogs, taken in combination with metformin compared to sulfonylurea in combination with metformin for treatment of adults with diabetes type 2 that is inadequately controlled with metformin monotherapy.

Method

Literature search

Research librarian Ingrid Harboe planned and executed all systematic searches in collaboration with the project group. The strategy included both subject headings (MeSH, Emtree) and text words. Searches were limited to systematic reviews (SR) in the time period from 2009 to the date of the search. The choice of starting date was meant to capture results published after the most recent National Diabetes Guidelines were published in 2009. The complete search strategy is provided in Appendix 1. The search was conducted in April 2013 and updated in February 2014.

We searched the following databases:
* The Cochrane Library; CDSR, DARE, Central, HTA, NHS EED
* Centre for Reviews and Dissemination (CRD); DARE, HTA, NHS EED
* Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present
* EMBASE (Ovid) 1980 to present

Inclusion criteria

Population: Adults aged 18 or over with type 2 diabetes (T2D) inadequately controlled with metformin monotherapy

Intervention: DPP-4 inhibitors (linagliptin, saksagliptin, sitagliptin og vildagliptin) added to metformin
GLP-1 analogs (exenatid, liraglutid) added to metformin

Comparison: Sulfonylurea (glibenklamid, glipizid, glimepirid) added to metformin

Outcome: Mortality
HbA1c
Weight
Hypoglycemic incidents
Microvascular complications (kidney failure, blindness, amputation)
Macrovascular complications (heart failure, MI, stroke)
Direct Norwegian costs

Study design:	Systematic reviews of high quality
Language:	No limitations on language during the search, but we only
	included articles in English, articles with English abstracts or
	articles in a Scandinavian language.

Article selection

Two reviewers independently inspected all citations generated by the search in order to identify potentially relevant articles based on title and/or abstract. Full text publications were obtained for articles appearing to meet the inclusion criteria or in cases where sufficient information was not available to make a decision. Two individuals independently assessed whether the article was relevant or not according to our list of inclusion criteria. Disagreements were resolved by discussion or by consulting a third reviewer.

If more than one systematic review covered our specified outcomes, we chose the most extensive and/or the one with the most recent search.

Quality assessments, data extraction and data analyses

The quality of the included systematic reviews was assessed using a checklist for systematic reviews (3). Assessments were agreed upon by two reviewers. For assessment of individual trials included in the systematic reviews, we relied on the assessment performed by the review authors. When such assessments were conducted using tools other than those recommended in the Handbook (3), we performed our own risk of bias assessments.

One reviewer extracted data from the systematic reviews according to our predefined scope. A second reviewer assessed the extracted data for accuracy.

We did not perform new analyses. Data is presented as it appears in the included systematic reviews.

Grading the quality of evidence (GRADE)

Two persons assessed the overall documentation for each outcome by using GRADE (Grading of Recommendations, Assessment, Development and Evaluation, www.gradeworkinggroup.org). The method used involves an evaluation of factors influencing our confidence in the reported estimates. It includes an evaluation of study type, study quality/risk of bias, consistency of results between trials,

directness (how similar the population, intervention, and outcomes are among the trials and the objectives of this report), precision of the estimates and publication bias. GRADE may also take into account whether there are strong associations between the intervention and the outcome/very large effect, dose-response associations or if all confounding variables would have reduced the effect. Finally the overall quality, or confidence in the estimate for one outcome across all studies, was categorized as high, moderate, low or very low.

Currently there is no standard protocol for assessing evidence based on network meta-analysis (NMA), a statistical technique that combines both direct and indirect evidence (see Appendix 2). In grading evidence from systematic reviews that use NMA, we chose to start from an assumption of high quality and then reduce our assessment based on the indirect nature of the evidence (and other relevant factors).

GRADE gives the following definition of the different levels of evidence.

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Cost information

We relied on the Norwegian diabetes guidelines (11) and expert advice to determine daily dose requirements for each of the treatments. We gathered 2014 price information from the Norwegian Medicines Agency (14).

Results

Result of literature search

The literature searches were performed in April 2013 and updated in February 2014 (see Appendix 1 for details). We identified 227 systematic reviews, of which 14 were found to be potentially relevant based on title and abstract. After examining full text versions of the 14 potentially relevant reviews, we included two in our review (Figure 1). Appendix 3 provides a full list of excluded studies and the reasons for exclusion.

227 identified references from literature search

213 references excluded
on the basis of title and

14 systematic reviews evaluated in full text

12 studies excluded
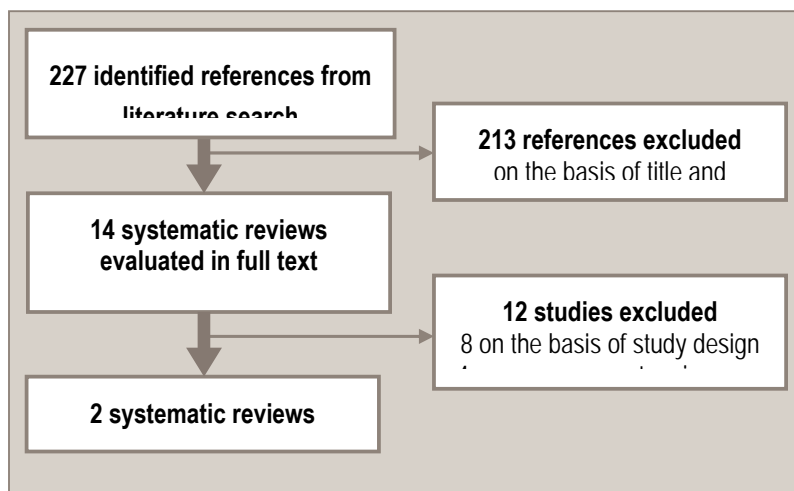8 on the basis of study design

2 systematic reviews

Figure 1 *Flowchart of identification of documentation*

Description of the included systematic reviews

We included two systematic reviews of high quality (see Appendix 4) in our analysis (Table 1). Liu et al. (15) reviewed evidence about the effects of either DPP-4 inhibitors or GLP-1 analogs, each added to metformin, relative to the active comparator, sulfonylurea added to metformin and reported results for changes in HbA1c, weight and the risk of hypoglycemic episodes. Karagiannis et al. (16) reviewed evidence about the effects of DPP-4 inhibitors in comparison to sulfonylurea, each added to metformin. Although the Karagiannis review examined only one of the comparisons of interest, it included some extension studies not reported in Liu, reported additional outcomes (mortality and % subjects achieving HbA1c < 7%) and relied on conventional meta-analysis to determine effect estimates while Liu relied on network meta-analysis results for most outcomes. See Appendix 2 for a discussion of different statistical methods.

Table 1 *– List of included systematic reviews*

Publication	Search performed	Interventions (added to metformin)	Comparator (added to metformin)	Relevant outcomes reported (no. relevant primary studies in analyses)	Type of analysis	Quality of systematic review
Liu 2012 (15)	December 2011 (PubMed, Cochrane)	DPP-4 inhibitors GPL-1 analogs	Sulfonylurea	HbA1c change (DPP-4:5 in MA, GLP-1: 3 in MA, 39 in NMA); Weight (37 in NMA) hypoglycemic incidents (38 in NMA)	Meta-analysis (HbA1c); Network meta-analysis (all)	High
Karagiannis 2012 (16)	March 2011 (PubMed, Cochrane, Embase)	DPP-4 inhibitors	Sulfonylurea	Mortality (7); HbA1c change (6); % achieving HbA1c < 7 (5); Weight (4); hypoglycemic incidents (7)	Meta-analysis (HbA1c: change, HbA1c: % achieving < 7, weight); Individual study results (hypoglycemi)	High

MA – Meta-analysis, **NMA** – Network meta-analysis

Liu et al. reported direct meta-analysis results of the mean change in HbA1c for the comparisons of DPP-4 inhibitors or GPL-1 analogs versus sulfonylurea, all in combination with metformin. For DPP-4 inhibitors they relied on five primary studies, which included a total of 858 to 2789 subjects, 50% to 57% male, with mean age of 56.2 to 59.2 years. For GLP-1 analogs they relied on three studies with a total of 111 to 484 subjects, 49% to 59% male with mean age of 53.1 to 57.0 years. Table 2 provides additional information about subject characteristics in relevant primary studies reviewed by Liu et al. Liu et al. also conducted Bayesian network meta-analyses (NMA) to estimate pair-wise effects of all included treatment options for the outcomes change in HbA1c, change in weight and risk of hypoglycemic events. These analyses included results from 39, 37 and 38 studies, respectively, and involved various combinations of comparisons between DPP4-inhibitors, GLP-1

analogs, sulfonylurea, thiazolidinedione, α-glucosidase inhibitors, basal insulin, biphasic insulin or placebo added to metformin.

Karagiannis et al. conducted random effects meta-analyses for mortality, HbA1c change, percent of patients achieving HbA1c < 7%, and change in weight. They relied on seven, six, five and four primary studies, respectively. Risk of hypoglycemic incidents was reported separately for each of seven primary studies because different definitions of hypoglycemic incidents did not permit a meta-analysis. Among the seven included studies, total number of subjects ranged from 125 to 3099; percent male, from 50% to 57% and mean age, from 56.2 to 59.2. Table 2 provides additional information about subject characteristics in relevant primary studies reviewed by Karagiannis et al.

Both Karagiannis and Liu conducted risk of bias assessments of included studies, with Karagiannis relying on the Cochrane Collaboration's risk of bias tool and Liu using the JADAD scale. Because the risk of bias assessments provided in Karagiannis covered all of the studies used in Liu related to the DPP-4 inhibitor versus sulfonylurea comparison, we relied on the Karagiannis assessments to ensure consistency in methods. We used the Cochrane tool to conduct our own risk of bias assessments (see Appendix 5) of studies comparing GPL-1 analogs versus sulfonylurea that were only rated with the JADAD scale in Liu's review.

Table 2 *– Characteristics of studies and participants contributing to systematic reviews*

Study	Included in	Follow-up (weeks)	Treatments	No. Randomized	Age (yrs.)	Mean disease duration (yrs.)	Baseline HbA1c (%)	Outcomes contributed
DPP-4 inhibitors + metformin vs. Sulfonylurea + metformin								
Nauck (2007) (17)	Liu	52	Sitagliptin 100 mg Glipizide 5-20 mg	588 584	56.8 56.6	6.5 6.2	7.7 7.7	Change HbA1c, weight, hypoglycemia
Seck (2010) (18)	Karagiannis	104	52-week extension study of Nauck (2007)					Change HbA1c, weight, hypoglycemia mortality
Ferrannini (2009) (19)	Liu	52	Vildagliptin 100 mg Gimepiride 2-6 mg	1396 1393	57.5 57.5	5.7 5.7	7.3 7.3	Change HbA1c, weight, hypoglycemia
Matthews (2010) (20)	Karagiannis	104	52-week extension study of Ferrannini (2009) [No. randomized reported as 1562 & 1556]					Change HbA1c, weight, hypoglycemia mortality, HbA1c<7
Filozof (2010) (21)	Liu, Karagiannis	52	Vildagliptin 100 mg Glicalazide 80-120 mg	513 494	59.2 59.7	6.4 6.8	8.5 8.5	Mortality, change HbA1c, HbA1c<7, hypoglycemia
Goke (2010) (22)	Liu, Karagiannis	52	Saxagliptin 5 mg Glipizide 5-20 mg	428 430	57.5 57.6	5.5 5.4	7.7 7.7	Mortality, change HbA1c, HbA1c<7, weight, hypoglycemia
Forst (2010) (23)	Karagiannis	12	Linagliptin 5 mg Glimeperide 1-3 mg	66 65	N/A	7.3 6.7	8.5 8.5	Mortality, hypoglycemia
Arechavaleta (2011) (24)	Liu, Karagiannis	30	Sitagliptin 100 mg Glimepiride 1-6 mg	516 519	56.3 56.2	6.8 6.7	7.5 7.5	Mortality, change HbA1c, HbA1c<7, weight, hypoglycemia
Study 020 B (2009) (25)	Karagiannis	80*	Sitagliptin 100 mg Glipizide 5-15 mg	464 237	N/A	6.0 6.6	8.0 8.0	Mortality, change HbA1c, hypoglycemia

GPL-1 analogs + metformin vs. Sulfonylurea + metformin								
Nauck (2009) (26)	Liu	26	Liraglutide 0.6-1.8 mg	242	57	8	8.4	Change HbA1c, weight, hypoglycemia
			Glimepiride 4 mg	242	57	8	8.4	
Yang (2011) (27)	Liu	16	Liraglutide 0.6-1.8 mg	233	52.7	7.2	8.6	Change HbA1c, weight, hypoglycemia
			Glimepiride 4 mg	231	53.6	7.8	8.5	
Derosa (2011) (28)	Liu	48	Exanetide 20 µg	57	56	N/A	8.7	Change HbA1c, weight, hypoglycemia
			Glimepiride 6 mg	54	56		8.8	

* Study 020 Phase B is an 80-week extension of a 24-week primary study in which the control group received only metformin.

Comparison of DPP-4 inhibitors + metformin versus sulfonylurea + metformin

This section examines the results from both Karagiannis and Liu for the comparison DPP-4 inhibitors + metformin versus sulfonylurea + metformin. Table 3 provides a summary of these findings.

Mortality

Karagiannis reported results of a meta-analysis of seven primary studies (18, 20-25) of DPP-4 inhibitors in combination with metformin versus sulfonylurea in combination with metformin for the outcome all-cause mortality. The relative risk was 0.79 (0.38, 1.62) in favor of the DPP-4 inhibitor combined with metformin. Because of the low number of events, there is a large amount of uncertainty around the estimate, as indicated by the wide confidence interval, and the result is not statistically significant. The reported I^2 was equal to 0%, indicating consistent results across studies. Other heterogeneity measures were not reported.

Microvascular complications

No results were reported for this outcome for the comparison DPP-4 inhibitors + metformin versus sulfonylurea + metformin.

Macrovascular complications

No results were reported for this outcome for the comparison DPP-4 inhibitors + metformin versus sulfonylurea + metformin.

Change in HbA1c

We found two types of outcome measures for the change in HbA1c. Both Liu and Karagiannis reported the weighted mean difference in the change in HbA1c (%) from baseline. Karagiannis also reported the risk ratio for achieving the goal of HbA1c less than 7%.

Weighted mean difference in change in HbA1c (%) from baseline
Karagiannis and colleagues conducted a random effects meta-analysis based on six primary studies (18, 20-22, 24, 25) of DPP-4 inhibitors used in combination with

metformin versus sulfonylurea in combination with metformin and found a mean difference in change from baseline of 0.07 (0.03, 0.11) in favor of sulfonylurea + metformin. Results from heterogeneity tests were I^2=0%; χ^2=3.15, p=0.68.

Liu and colleagues conducted a meta-analysis based on five primary studies (17, 19, 21, 22, 24) of the same comparison. The mean difference in change in HbA1c from baseline was 0.09 (0.04, 0.14). In a network meta-analysis that included both direct and indirect comparisons from 39 studies the same pair-wise comparison yielded a mean difference in change from baseline of 0.12 (0.03, 0.23). Both results indicate a greater decline in HbA1c for sulfonylurea + metformin. No heterogeneity results were reported for either analysis.

Risk ratio for achieving goal of HbA1c < 7%

Karagiannis compared DPP-4 inhibitors + metformin to sulfonylurea + metformin using a random effects meta-analysis of results from five primary studies (18, 20-22, 24). The risk ratio for achieving the goal of HbA1c < 7% was 1.06 (0.98, 1.14) in favor of sulfonylurea + metformin, but not statistically significant. Results from heterogeneity tests were I^2=26%; χ^2=5.40, p=0.25.

Weight mean difference in change in weight (kg) from baseline

Karagiannis compared DPP-4 inhibitors + metformin to sulfonylurea + metformin using a random effects meta-analysis of results from four primary studies (18, 20, 22, 24). The weighted mean difference in change weight (kg) from baseline was -1.92 (-2.34, -1.49) in favor of DPP-4 inhibitors + metformin, with patients in the intervention group experiencing small weight losses and those in the control group experiencing small weight gains. Results from heterogeneity tests were I^2=69%; χ^2=9.80, p=0.02, indicating inconsistent results across studies.

Liu and colleagues made the same pairwise comparison using a Bayesian network meta-analysis that included a total of 37 direct and indirect comparisons. The weighted difference in change in weight (kg) from baseline was -1.93 (-2.35, -1.53) in favor of DPP-4 inhibitors + metformin, with patients in the intervention group experiencing small weight losses and those in the control group experiencing small weight gains. No heterogeneity results were reported for this analysis.

Hypoglycemic incidents – risk of at least one hypoglycemic event

Liu and colleagues compared DPP-4 inhibitors + metformin to sulfonylurea + metformin using a Bayesian network meta-analysis that included 38 direct and indirect comparisons. The odds ratio for experiencing at least one hypoglycemic event was 0.13 (0.08, 0.21) in favor of DPP-4 inhibitors + metformin. No heterogeneity results were reported for this analysis.

Karagiannis and colleagues did not conduct a meta-analysis for this comparison because of differences in definitions of hypoglycemic events across studies. Instead they reported risk ratios for each of seven studies. In all cases, the results favored DPP-4 inhibitors + metformin with risk ratios ranging from 0.01 to 0.53. Results were statistically significant in five of the studies.

Table 3. *Summary of findings for comparison DPP-4 inhibitors + metformin versus sulfonylurea + metformin*

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Metformin + SU	Corresponding risk Metformin + DPP-4				
Mortality follow up: 12 to 104 weeks (Karagiannis)	5 per 1000	4 per 1000 (2 to 8)	RR 0.79 (0.38 to 1.62)	8002 7 RCTs	⊕⊕⊖⊖ LOW [1,2,3,4]	Meta-analysis
Microvascular complications	No studies found					
Macrovascular complications	No studies found					
Change in HbA1c (% points) from baseline follow up: 30 to 104 weeks (Karagiannis)	Range of mean reduction from baseline 0.13 to 0.83	Reduction in HbA1c from baseline in the intervention group was 0.07 lower (0.03 lower to 0.11 lower) than in the control group		7291 6 RCTs	⊕⊕⊕⊖ MODERATE [5]	Meta-analysis Range of mean HbA1c at baseline 7.3% to 8.5%
Change in HbA1c (% points) from baseline follow up: 30 to 52 weeks (Liu)	Range of mean reduction from baseline 0.52 to 0.85	Reduction in HbA1c from baseline in the intervention group was 0.09 lower (0.04 lower to 0.14 lower) than in the control group		5 RCTs	⊕⊕⊕⊖ MODERATE [6]	Meta-analysis Range of mean HbA1c at baseline 7.3% to 8.5%
Change in HbA1c (% points) from baseline follow up: 12 to 52 weeks (Liu)		Reduction in HbA1c from baseline in the intervention group was 0.12 lower (0.23 lower to 0.03 lower) than in the control group		39 RCTs [7]	⊕⊕⊖⊖ **LOW** [6, 8]	Network meta-analysis
Risk ratio for achieving HbA1c < 7% follow up: 30 to 52 weeks (Karagiannis)	420 per 1000	445 per 1000 (412 to 479)	RR 1.06 (0.98 to 1.14)	5507 5 RCTs	⊕⊕⊕⊖ **MODERATE** [5]	Meta-analysis
Change in Weight (kg) follow up: 30 to 52 week (Karagiannis)	Range of mean increase from baseline 0.7 to 1.19	Weight gain in the intervention group was 1.92 lower (2.34 lower to 1.49 lower) than in the control group		5349 4 RCTs	⊕⊕⊕⊖ **MODERATE** [5]	Meta-analysis No baseline information available
Change in Weight (kg) follow up: 12 to 52 weeks (Liu)		Weight gain in the intervention group was 1.93 lower (2.35 lower to 1.53 lower) than in the control group		39 RCTs [7]	⊕⊕⊖⊖ **LOW** [6, 8]	Network meta-analysis

Risk for at least one hypoglycemic episode (Karagiannis)	Meta-analysis not performed because of varying definitions of hypoglycemic episodes				
Risk for at least one hypoglycemic episode follow up: 12 to 52 weeks (Liu)			OR 0.13 (0.08 to 0.21)	38 RCTs [7]	⊕⊕◯◯ LOW [5, 8]	Network meta-analysis

*The basis for the **assumed risk** is the calculated risk in the control group of the included studies. 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. Risk of bias was assessed by authors of the systematic review. They reported high and unclear for several of the studies based on incomplete data and selective reporting on change in HbA1c. This could also have importance for other outcomes.
2. There was not enough information to assess inconsistency as only the average result was reported.
3. Total number of events is less than 300 (a threshold rule-of-thumb value based on: Mueller et al. Ann Intern Med. 2007;146:878-881 <http://www.annals.org/cgi/content/abstract/146/12/878>)
4. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.
5. Risk of bias was assessed by authors of the systematic review. They reported high and unclear for several of the studies based on incomplete data and selective reporting on change in HbA1c.
6. Results of risk of bias assessment were not reported in this systematic review. We used risk of bias information reported by Karagiannis et al. (2012) about the same included studies. They reported high and unclear for several of the studies based on incomplete data and selective reporting on change in HbA1c.
7. Five studies with direct comparisons of 39 total studies in the network meta-analysis.
8. Network meta-analysis including both direct and indirect comparisons.

Comparison of GLP-1 analogs + metformin versus sulfonylurea + metformin

This section examines the results for the comparison GLP-1 analogs + metformin versus sulfonylurea + metformin. All results are from the review by Liu and colleagues. Table 4 provides a summary of these findings.

Mortality

No results were reported for this outcome for the comparison GLP-1 analogs + metformin versus sulfonylurea + metformin.

Microvascular complications

No results were reported for this outcome for the comparison GLP-1 analogs + metformin versus sulfonylurea + metformin.

Macrovascular complications

No results were reported for this outcome for the comparison GLP-1 analogs + metformin versus sulfonylurea + metformin.

Change in HbA1c

Weighted mean difference in change in HbA1c (%) from baseline

Liu and colleagues conducted a meta-analysis based on three primary studies of GLP-1 analogs used in combination with metformin versus sulfonylurea in combination with metformin. The mean difference in change in HbA1c from baseline was 0.00 (-0.12, 0.12). In a Bayesian network meta-analysis that included both direct and indirect comparisons, the same pairwise comparison yielded a mean difference in change from baseline of -0.20 (-0.34, -0.04). This means that based on direct evidence, no difference between treatments was apparent, while including indirect evidence suggests a slightly larger reduction in HbA1c with GLP-1 analogs + metformin. No heterogeneity results were reported for either analysis.

Risk ratio for achieving goal of HbA1c < 7%

No results were reported on this outcome for the comparison GLP-1 analogs + metformin versus sulfonylurea + metformin.

Weight mean difference in change in weight (kg) from baseline

Liu and colleagues compared GLP-1 analogs + metformin to sulfonylurea + metformin using a Bayesian network meta-analysis that included 37 direct and indirect comparisons. The weighted mean difference in change in weight (kg) from baseline was -3.81 (-4.44, -3.24) in favor of GLP-1 analogs + metformin. No heterogeneity results were reported for this analysis.

Hypoglycemic incidents – risk of at least one hypoglycemic event

Liu and colleagues compared GLP-1 analogs + metformin to sulfonylurea + metformin using a Bayesian network meta-analysis that included 38 direct and indirect comparisons. The odds ratio for at least experiencing one hypoglycemic event was 0.10 (0.05, 0.21) in favor of GLP-1 analogs + metformin. No heterogeneity results were reported for this analysis.

Table 4. *Summary of findings for comparison GLP-1 analogs + metformin versus sulfonylurea + metformin*

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Metformin + SU	Corresponding risk Metformin + GLP-1				
Mortality	No studies found					
Microvascular complications	No studies found					
Macrovascular complications	No studies found					
Change in HbA1c (% points) from baseline Follow up: 16 to 48 weeks (Liu)	Range of mean reduction from baseline 1.0 to 1.4	Reduction in HbA1c from baseline in the intervention group was 0 higher (0.12 lower to 0.12 higher) than in the control group		1059 3 RCTs	⊕⊕⊕⊕ **HIGH** [1, 2]	Meta-analysis Range of mean HbA1c at baseline 8.4% to 8.8%
Change in HbA1c (% points) from baseline Follow up: 12 to 48 weeks analysis (Liu)		Reduction in HbA1c (%) from baseline in the intervention group was 0.2 higher (0.04 higher to 0.34 higher) than in the control group		39 RCTs	⊕⊕⊕⊝ **MODERATE** [3, 4]	Network meta-analysis
Risk for achieving HbA1c < 7%	No studies found					
Change in Weight (kg) Follow up: 12 to 48 weeks (Liu)		Weight gain in the intervention group was 3.81 lower (4.44 lower to 3.24 lower) than in the control group		37 RCTs	⊕⊕⊕⊝ **MODERATE** [3, 4, 5]	Network meta-analysis
Risk for at least one hypoglycemic episode Follow up: 12 to 48 weeks (Liu)			OR 0.1 (0.05 to 0.21)	38 RCTs	⊕⊕⊕⊝ **MODERATE** [3, 4]	Network meta-analysis

*The basis for the **assumed risk** is the calculated risk in the control group of the included studies. 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. HbA1c reported as baseline and decrease for individual groups but not as cross-group comparisons; no indication of inconsistency
2. Results of risk of bias assessment not reported; we preformed risk of bias assessment for the 3 direct studies
3. Network meta-analysis including both direct and indirect comparisons
4. Consistency not reported as this is a network meta-analysis
5. Weight change reported for groups separately, but no direct meta-analysis results provided

Direct economic cost

Based on 2014 drug prices (14) and daily doses recommended by the Norwegian diabetes treatment guidelines (11), we computed the annual per patient cost for relevant T2D medications (see Table 5). DPP-4 inhibitors are available as a separate tablet, which must be taken with metformin or as a single tablet that includes appropriate doses of both medications. For tablets that must be taken in addition to metformin annual per patient costs range from NOK 4127 to 5692. The annual cost of metformin is NOK 556. For the DPP-4 inhibitor tablets that include metformin the annual per patient cost ranges from NOK 4635 to 5134. For the treatment of a GLP-1 analog taken in addition to metformin, annual drug costs range from NOK 12 025 to 16 942. Sulfonylurea taken in combination with metformin has an annual per patient cost of NOK 1217. However, there may be additional direct costs associated with more frequent self-testing of blood sugar levels necessitated by the increased risk of hypoglycemic episodes for sulfonylurea + metformin compared to DPP4-inhibitors or GLP-1 analogs + metformin.

Table 5 *– Annual per patient cost of medications for type 2 diabetes, 2014 prices*

Medication	Daily Dose	Cost per DD[1]	Annual Cost (NOK)
Metformin	2000 mg	1.52	556
Sulfonylurea (Glimeperide)	4 mg	1.81	661*
DPP-4 inhibitors			
Galvus (Vildagliptin)	100 mg	9.79	3 572*
Januvia (Sitagliptin)	100 mg	14.07	5 136*
Trajenta (Linagliptin)	5 mg	12.80	4 673*
Janumet (Sitagliptin + met)	100 mg + 2000 mg	12.70	4 635
Jentaduerto (Linagliptin + met)	5 mg + 2000 mg	14.07	5 134
Komboglyze (Saxagliptin + met)	5 mg + 2000 mg	13.62	4 971
GLP-1 analogs			
Victoza (Liraglutid)	1.8 mg	44.89	16 386*
Byetta (Exenatide)	20 µg	31.42	11 470*
Bydureon (Exenatide)	2 mg (taken weekly)	35.02	12 782*

[1] Cost per daily dose for each medication is based on the packaging option with the lowest price for the required daily dose.
* Does not include cost of metformin

Discussion

We searched systematically for systematic reviews of the effects of adding either DPP-4 inhibitors or GLP-1 analogs to metformin compared to adding sulfonylurea to metformin as a treatment for T2D that is inadequately controlled by metformin monotherapy. Effect estimates from the two most recent systematic reviews form the basis for the information presented in this report on the outcomes mortality, micro and macrovascular complications, HbA1c, weight and hypoglycemic incidents. We also gathered evidence about direct economic costs from Norwegian sources.

Summary of results

The most current systematic reviews provide little evidence on differences in important clinical endpoints (mortality, micro and macrovascular complications) for either of the comparisons of interest. No conclusions can be drawn about the effect on mortality of DPP-4 inhibitor + metformin versus sulfonylurea + metformin because of few events and low quality evidence. No mortality evidence was available for the comparison GLP-1 analogs + metformin versus sulfonylurea + metformin. Similarly, there was no evidence on micro or macrovascular complications for either comparison.

Differences do exist in comparisons between DPP-4 inhibitors or GLP-1 analogs + metformin and sulfonylurea + metformin for the outcomes change in HbA1c, change in weight and risk of at least one hypoglycemic episode, but the results do not uniformly favor either sulfonylurea + metformin or one of the other interventions. The observed differences in these intermediate outcomes, though statistically significant, tend to be small in magnitude and may not be clinically important.

For the comparison DPP-4 inhibitors + metformin versus sulfonylurea + metformin, there was a larger reduction in HbA1c with sulfonylurea + metformin, but a smaller weight gain and a lower risk for at least one hypoglycemic episode with DPP-4 inhibitors + metformin. There was no statistically significant difference in the risk for achieving the treatment goal of HbA1c < 7. For the outcomes change in HbA1c and weight we examined effect estimates from both direct meta-analyses (Karagiannis, Liu) and network meta-analyses (Liu), which incorporate direct and indirect treatment comparisons. The direct meta-analysis evidence was of moderate

quality, while evidence from network meta-analysis was of low quality. In both cases, however, the resulting effect estimates for a given outcome were statistically significant and of similar size, but the effects were small in absolute terms and potentially not clinically important. The possibility of achieving the treatment goal of HbA1c < 7 was reported in only one meta-analysis (Karagiannis), with moderate quality of evidence. The effect estimate for the risk of experiencing at least one hypoglycemic episode was based on a network meta-analysis (Liu) while Karagiannis did not perform a meta-analysis of the risk for hypoglycemic episode because he and co-workers believed the definitions of hypoglycemic episodes varied substantially among the primary studies. Some caution may be warranted in interpreting the results, but given the similarity of individual effect estimates from the included primary studies to the results of the network meta-analysis it is unlikely that is an important problem. It was difficult to assess based on the information in the systematic reviews how many hypoglycemic episodes were actually severe, but the total number of episodes was generally low.

For the comparison GLP-1 analogs + metformin versus sulfonylurea + metformin the effect estimate for change in HbA1c varied by the type of analysis performed. Meta-analysis results from direct comparisons (high quality of evidence) revealed no significant difference in change in HbA1c between the two treatment groups while the network meta-analysis that included both direct and indirect comparisons (moderate quality of evidence) indicated a greater decline in HbA1c among subjects receiving GLP-1 analogs + metformin. Change in weight and risk of at least one hypoglycemic episode were both smaller with GLP-1 analogs + metformin (moderate quality of evidence). In all cases, the effects were relatively small and may not be clinically important.

Several additional factors could affect our confidence in the effect estimates for the GLP-1 versus sulfonylurea comparisons. There is a potential bias in Liu's meta-analysis effect estimate for change in HbA1c because of the way that missing standard errors in one of the included studies were treated, but it is impossible to know in which direction without additional information about the primary data. Liu's reporting of methods used in conducting the network meta-analysis, which formed the basis for all remaining results, did not meet some of the standards suggested by NICE and EUnetHTA (29, 30) to ensure transparency of evidence and appropriate application of methods for conducting network meta-analyses. However, because network meta-analysis is a relatively new method, a single, widely accepted set of standards is still under development. Two of the included studies were of limited duration. Finally, one of the primary studies was conducted in China, where the population and treatment patterns could differ from those in Norway for diabetes patients.

Costs of medications for T2D are substantially lower for treatment with sulfonylurea + metformin than with the combination of either DPP-4 inhibitors or GLP-1 analogs

+ metformin. DPP-4 inhibitors + metformin are approximately three to four times more expensive than sulfonylurea + metformin, and GLP-1 analogs + metformin approximately ten to fourteen times more expensive.

The drugs come as oral formulations, except for GLP-1 analogs which are given as subcutaneous injections. Potential preference in administration form and dosing interval was not evaluated in this report.

Strengths and limitations of this report

This report, which is based on a systematic literature search, has the advantage of providing evidence from the most recent systematic reviews of the effects of DPP-4 inhibitors or GLP-1 analogs used in combination with metformin compared with sulfonylurea in combination with metformin among patients with type 2 diabetes inadequately controlled by metformin monotherapy. An updated search (February 2014) did not uncover other relevant systematic reviews. Based on the commission we received we did not, however, examine recent primary studies so it is possible that additional data is available that could affect our results.

Also based on our commission, we did not examine differences between different medications within the same treatment class or examine other comparisons that could be of clinical interest, for example those involving pioglitazone and the recently approved SGLT-2 inhibitor, dapagliflozine, nor did we examine the question of whether adding DPP-4 inhibitors or GLP-1 analogs to metformin should be considered before moving patients to treatment with insulin. Because DPP-4 inhibitors and GLP-1 analogs are relatively new classes of drugs, there is still much that is unknown about their long-term effects on final clinical endpoints that this report does not capture.

We assessed the quality of the evidence for this review by using GRADE. For effect estimates of the comparison DPP-4 inhibitors + metformin versus sulfonylurea + metformin taken from the Karagiannis systematic review, we relied on their risk of bias assessment of primary articles included in the review. Liu and colleagues stated that they used the more limited JADAD score so we applied the assessments by Karagiannis to the five overlapping articles of the same comparison in Liu for consistency in evaluation tools. We also performed a risk of bias assessment of the three articles in Liu that compared GLP-1 analogs + metformin to sulfonylurea + metformin. It is therefore possible that the risk of bias assessments for the GLP-1 analog comparisons were evaluated somewhat differently than those for the DPP-4 inhibitor comparisons performed by Karagiannis.

When determining the direct costs for the three treatment options, we only included the cost of the medications. We assumed that costs of doctor visits for regular controls and test strips for home testing of blood glucose levels would be relatively

similar among the three treatment groups. It is possible that some T2D patients taking sulfonylurea + metformin would require extra home glucose testing and extra doctor visits as a result of an increased risk of hypoglycemic episodes. Unfortunately, we did not have enough information to estimate these extra costs. Definitions of a hypoglycemic episode varied across primary studies so it is difficult to know what portion of the increased risk represents serious episodes that require extra treatment rather than more minor episodes. The absolute risk of hypoglycemic episodes is low so it is unlikely that this would have a large impact on treatment costs.

Finally, our results do not account for patient preferences. This maybe an important issue when considering differences between treatments for the intermediate outcomes weight change and hypoglycemic episodes. Our results indicate that sulfonylurea + metformin leads to both more weight gain and an increased risk for at least one hypoglycemic episode compared to either DPP-4 inhibitors or GLP-1 analogs + metformin. While the size of these differences are relatively small, and possibly of little clinical relevance, they nonetheless may be important for patients who experience reduced quality of life because of anxiety about potential hypoglycemic episodes or weight gain. Determining to what extent such concerns should drive treatment decisions is a question for policy makers at the health system level and between doctors and patients at the individual level.

Our results compared to other systematic reviews or HTA

Our overall results are similar to those in both a 2010 CADTH (Canadian Agency for Drugs and Technologies in Health) report on second-line pharmacotherapy for T2D (31) and its newly updated version (32), which includes many of the same primary studies as our review. The reports relied on both meta-analyses of direct comparisons and network meta-analyses to examine a wide range of potential second-line treatments when metformin monotherapy was inadequate. Results indicated a lack of evidence on the effect of newer medications on long-term complications of diabetes. The revised CADTH study (32) found that, compared to sulfonylurea + metformin, DPP-4 inhibitors + metformin resulted in a smaller reduction in HbA1c, a weight loss rather than weight gain, and a smaller risk of experiencing at least one hypoglycemic episode. Results were similar for GLP-1 analogs + metformin, except that there was no significant difference in change in HbA1c. None of the results were considered large enough to be clinically important. The CADTH report (32) also included the results of a cost-effectiveness study for the Canadian setting that showed sulfonylurea + metformin was the most cost-effective treatment and DPP-4 inhibitors or GLP-1 analogs + metformin were among the least cost-effective. The high cost of DPP-4 inhibitors and GLP-1 analogs was the driving factor in this result. Sensitivity analyses of both clinical and cost-effectiveness results indicated that expanded evidence provided by more recently published primary studies had little impact on the results.

Conclusion

The most current systematic reviews still provide either no evidence or low quality evidence comparing the effects of DPP-4 inhibitors or GLP-1 analogs + metformin with sulfonylurea + metformin for the clinically important outcomes mortality and micro and macrovascular complications. The combination of sulfonylurea and metformin resulted in larger reductions in HbA1c than DPP-4 inhibitors and metformin, but no significant difference in change in HbA1c compared to GLP-1 analogs and metformin. Both DPP-4 inhibitors and GPL-1 analogs added to metformin resulted in weight loss, while sulfonylurea and metformin led to weight gain. The risk of experiencing at least one hypoglycemic episode is higher with sulfonylurea and metformin than either DPP-4 inhibitors or GLP-1 analogs and metformin. However, the differences in effect estimates are all quite small and possibly of little clinical importance. The evidence was generally rated as moderate to low. The direct cost of sulfonylurea and metformin is substantially less than either DPP-4 inhibitors or GLP-1 analogs and metformin.

Need for further research

To date there is still little evidence or only low quality evidence about clinically important outcomes such as diabetes-related micro and macrovascular complications, death and severe hypoglycemia for either DPP-4 inhibitors or GLP-1 analogs combined with metformin. There is also little information on the long-term safety effects of these medications. Further research in these areas is necessary. Additional direct comparison studies of longer duration or studies that use patient registries to investigate these issues could be particularly useful.

Implications for practice

Current Norwegian guidelines for treatment of type 2 diabetes inadequately controlled using metformin monotherapy recommend adding sulfonylurea to metformin as the second-line therapy. DPP-4 inhibitors are recommended instead of sulfonylurea only if the combination of metformin and sulfonylurea is not tolerated. GLP-1 analogs, which were still quite new when the most recent guidelines were issued, are only recommended after other additional options fail.

Based on additional evidence provided in this review, particularly for direct comparisons of GLP-1 analogs + metformin and sulfonylurea + metformin, we find that little has changed since the guidelines were written. Very little evidence exists about long-term effects for the important clinical outcomes mortality and micro and macrovascular complications, or for long-term safety issues. Small differences in effect do exist between the examined treatment options. Sulfonylurea + metformin results in reductions in HbA1c that are greater than those with DPP-4 inhibitors + metformin and similar to those with GLP-1 analogs + metformin. DPP-4 inhibitors or GLP-1 analogs + metformin lead to weight loss while sulfonylurea + metformin leads to weight gain. DPP-4 inhibitors or GLP-1 analogs + metformin have a lower risk for experiencing at least one hypoglycemic episode than sulfonylurea + metformin. All of these effects are relatively small in magnitude and may be of limited clinical significance. The difference in price between DPP-4 inhibitors or GLP-1 analogs and sulfonylurea is substantial, particularly for GLP-1 analogs.

For individual patients who are at greater risk for hypoglycemic episodes, DPP-4 inhibitors or GLP-1 analogs could be an appropriate treatment choice, a decision that needs to be made in consultation between doctor and patient. As pointed out by both systematic reviews included in this article, as well as the recent report by the Canadian Agency for Drugs and Technologies in Health, which chose not to change their own guidelines, decisions about societal guidelines regarding the appropriate treatment for type 2 diabetes when metformin monotherapy proves ineffective need to evaluate the clinical evidence in relation to costs and to update decisions as new information on long-term effects becomes available.

References

1. World Health Organization. Diabetes - Fact sheet No. 312. [Updated October 2013; Accessed 15/03/2013]. Available from: www.who.int/mdiacentre/factsheets/fs312/en/.

2. MedlinePlus. Diabetes. U.S. National Library of Medicine. [Updated 27/06/2012; Accessed 15/03/2013]. Available from: www.nim.nih.gov/medicineplus/ency/article/001214.htm.

3. Norwegian Knowledge Centre for the Health Services. Slik oppsumerer vi forskning. http://wwwkunnskapssenteretno/Verkt%C3%B8y/Slik+oppsummerer+vi+f orskning2139cms. 3 ed: Nasjonalt kunnskapssenter for helsetjenesten; 2013.

4. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. The Lancet 2011;378(9785):31-40.

5. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. The Lancet 2010;375(9730):1969-1987.

6. Mathers C, Stevens G, Mascarenhas M. Global health risks: mortality and burden of disease attributable to selected major risks. World Health Organization; 2009.

7. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS medicine 2006;3(11):e442.

8. Stene LC, Midthjell K, Jenum AK, Skeie S, Birkeland KI, Lund E, et al. Hvor mange har diabetes mellitus i Norge? [Prevalence of diabetes mellitus in Norway]. TidsskrNor Laegeforen 2004;124(11):1511-1514.

9. Hanssen KF. Diabetes i Norge - en utfordring for indremedisinere (Diabetes in Norway - a challenge for internists). Indremedisineren 2013;2013(2):20-21.

10. Diabetesforbundet. Diabetes type 2. [Updated 04/06/2013; Accessed 03/03/2013]. Available from.

11. Norwegian Directorate of Health. Nasjonale faglige retningslinjer om Diabetes - forebygging, diagnostikk og behandling (National Guidelines: Diabetes - Prevention, Diagnosis and Treatment). 2009.

12. Solli O. Diabetes in Norway: Costs, Health-related Quality of Life and Cost-Effectiveness of Lifestyle Interventions. Faculty of Medicine, University of Oslo; 2013.

13. Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577-1596.

14. Norwegain Medicines Agency. Legemiddelsøk (Drug Search). [Updated 11.12.2013; Accessed 05.01.2014]. Available from: http://www.legemiddelverket.no/Sider/default.aspx.

15. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes Obes Metab 2012;14(9):810-820.

16. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369.

17. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP, Sitagliptin Study G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2007;9(2):194-205.

18. Seck T, Nauck M, Sheng D, Sunga S, Davies MJ, Stein PP, et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract 2010;64(5):562-576.

19. Ferrannini E, Fonseca V, Zinman B, Matthews D, Ahren B, Byiers S, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab 2009;11(2):157-166.

20. Matthews DR, Dejager S, Ahren B, Fonseca V, Ferrannini E, Couturier A, et al. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes Obes Metab 2010;12(9):780-789.

21. Filozof C, Gautier JF. A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. Diabet Med 2010;27(3):318-326.

22. Goke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I, Investigators DC. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. Int J Clin Pract 2010;64(12):1619-1631.

23. Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and

efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabet Med 2010;27(12):1409-1419.

24. Arechavaleta R, Seck T, Chen Y, Krobot KJ, O'Neill EA, Duran L, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2011;13(2):160-168.

25. Merck & Co. Study 020 Phase B. 2008.

26. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009;32(1):84-90.

27. Yang W, Chen L, Ji Q, Liu X, Ma J, Tandon N, et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial(*). Diabetes Obes Metab 2011;13(1):81-88.

28. Derosa G, Putignano P, Bossi AC, Bonaventura A, Querci F, Franzetti IG, et al. Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients. Eur J Pharmacol 2011;666(1-3):251-256.

29. Ades A, Caldwell DM, Reken S, Welton NJ, Sutton AJ, Dias S. Evidence Synthesis for Decision Making 7 A Reviewer's Checklist. Medical Decision Making 2013;33(5):679-691.

30. EUnetHTA. Comparators & Comparisons: Direct and indirect comparisons. 2013. (Guideline).

31. CADTH. Second-Line Therapy for Patients with Diabetes Inadequately controlled on Metformin: A Systematic Review and Cost-Effectiveness Analysis. 2010. (Optimal Therapy Report).

32. CADTH. Second-Line Pharmacotherapy for Type 2 Diabetes - Update. 2013. (Optimal Use Report).

Appendix

Project: Diabetes type 2, metformin in combination with other

Databases: Cochrane library; Cochrane Database of Systematic Reviews, Other Reviews, Technology Assessments. Centre for Reviews and Dissemination (CRD); DARE, HTA. Ovid MEDLINE and Embase, PubMed

Date: 2013.04.17

Design: Systematic reviews (SR); Ovid's clinical queries: "reviews (maximizes specificity)" and (systematic* review* or meta analys*).tw.
PubMed's filter: Systematic Reviews

Results: 227 Systematic reviews (275 including duplicates)

Searched by: Ingrid Harboe, research librarian

Search strategies

Syntax guide:

/	Used after a word, = MeSH
exp	Explode = explode MeSH, i.e. include all subheadings
*	Truncation, plural, other variations of a word
.tw	Search for word in title or abstract

Databases: **Embase** 1980 to 2013 Week 15
Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Date: 2013-04-16

Results: 211

Search strategy:

1	Diabetes Mellitus, Type 2/ use prmz	77013
2	Non insulin dependent diabetes mellitus/ use emez	123940
3	(diabetes type 2 or type 2 diabetes).tw.	137602

43

4	or/1-3	237961
5	Metformin/	34842
6	metformin.tw.	20424
7	or/5-6	38604
8	exp Sulfonylurea Compounds/ use prmz	15706
9	exp Sulfonylurea derivative/ use emez	43387
10	(Sulfonylurea or Sulphonylurea).tw.	11945
11	or/8-10	62383
12	4 and 7 and 11	10419
13	Dipeptidyl-Peptidase IV Inhibitors/ use prmz	1345
14	exp dipeptidyl peptidase IV inhibitor/ use emez	5484
15	(Dipeptidyl-Peptidase IV Inhibitors or gliptin*).tw.	561
16	or/13-15	6995
17	4 and 7 and 16	2821
18	Glucagon-Like Peptide 1/ use prmz	4578
19	glucagon like peptide 1/ use emez	7949
20	(Glucagon Like Peptide 1 or Glucagon-Like Peptide-1 or GLP-1 or GLP 1).tw.	14820
21	or/18-20	17516
22	4 and 7 and 21	1986
23	12 or 17 or 22	11678
24	limit 23 to yr="2009 -Current"	5296
25	remove duplicates from 24	4591
26	limit 25 to "reviews (maximizes specificity)"	168
27	25 and (systematic* review* or meta analys*).tw.	208
28	26 or 27	211

Database: Cochrane library
Date Run: 16/04/13
Results: 4 Cochrane Reviews
             7 Other reviews
             2 Technology Assessments
Search strategy:

#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees	7534
#2	(diabetes type 2):ti,ab,kw (Word variations have been searched)	11075
#3	#1 or #2	11076

#4	MeSH descriptor: [Metformin] this term only	1321
#5	Metformin:ti,ab,kw	1871
#6	#4 or #5	1871
#7	MeSH descriptor: [Sulfonylurea Compounds] explode all trees	1233
#8	(Sulfonylurea or Sulphonylurea):ti,ab,kw (Word variations have been searched)	1016
#9	#6 and (#7 or #8)	481
#10	MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] this term only	196
#11	(Dipeptidyl-Peptidase IV Inhibitors or gliptin*):ti,ab,kw	214
#12	#6 and (#10 or #11)	64
#13	MeSH descriptor: [Glucagon-Like Peptide 1] this term only	386
#14	(Glucagon Like Peptide 1 or Glucagon-Like Peptide-1 or GLP-1 or GLP 1):ti,ab,kw	561
#15	#6 and (#13 or #14)	63
#16	#3 and (#9 or #12 or #15) from 2009 to 2013	183

Database: CRD Dare, HTA

Date: 2013-04-16

Results: 31 SR, HTA

Search strategy:

1	MeSH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES	676
2	("diabetes type 2")	7
3	#1 OR #2	681
4	MeSH DESCRIPTOR Metformin EXPLODE ALL TREES	93
5	(metformin)	264
6	#4 OR #5	264
7	MeSH DESCRIPTOR Sulfonylurea Compounds EXPLODE ALL TREES	45
8	((Sulfonylurea or Sulphonylurea)	0
9	#7 OR #8	45
10	MeSH DESCRIPTOR Dipeptidyl-Peptidase IV Inhibitors EXPLODE ALL TREES	25
11	("Dipeptidyl-Peptidase IV Inhibitors" or gliptin*)	40
12	#10 OR #11	40
13	MeSH DESCRIPTOR Glucagon-Like Peptide 1 EXPLODE ALL TREES	25
14	("Glucagon Like Peptide 1" or "Glucagon-Like Peptide-1" or "GLP-1" or "GLP 1")	46
15	#13 OR #14	46
16	#6 AND #9	28
17	((Sulfonylurea or Sulphonylurea))	106
18	MeSH DESCRIPTOR Sulfonylurea Compounds EXPLODE ALL TREES	45
19	#17 OR #18	116
20	#3 AND #6 AND #19	73
21	#3 AND #6 AND #12	14
22	#3 AND #6 AND #15	18
23	#20 OR #21 OR #22	81
24	(#23) IN DARE, HTA	55
25	(#23) IN DARE, HTA FROM 2009 TO 2013	31

46

#11	Search (#9) AND ("2012"[Date - Publication] : "3000"[Date - Publication])Filters: Systematic Reviews	20
#10	Search (#9) AND pubstatusaheadofprint	0
#9	Search (((#6) OR #7) OR #8) AND ("2009/01/01"[Date - Publication] : "3000"[Date - Publication])	652
#8	Search ((#1) AND #2) AND #5	306
#7	Search ((#1) AND #2) AND #4	355
#6	Search ((#1) AND #2) AND #3	1290
#5	Search ("glucagon like peptide 1"[MeSH Terms]) OR (Glucagon Like Peptide 1 or Glucagon-Like Peptide-1 or GLP-1 or GLP 1[Title/Abstract])	6378
#4	Search ("dipeptidyl peptidase iv inhibitors"[MeSH Terms]) OR (Dipeptidyl-Peptidase IV Inhibitors or gliptin*[Title/Abstract])	2168
#3	Search (sulfonylurea compounds[MeSH Terms]) OR (Sulfonylurea or Sulphonylurea[Title/Abstract])	18037
#2	Search (metformin[MeSH Terms]) OR metformin[Title/Abstract]	9118
#1	Search (diabetes mellitus, type 2[MeSH Terms]) OR diabetes type 2[Title/Abstract]	75986

Appendix 2 – Statistical methods and terminology

Meta-analysis versus network meta-analysis

Meta-analysis uses statistical techniques to combine evidence from multiple trials of the same direct comparison into an aggregate effect estimate. Network meta-analysis is a newer technique that estimates effect using both direct and indirect evidence. While direct evidence is generally considered more reliable, evidence from a network meta-analysis can be useful when the number of direct comparisons for a particular outcome is small. Both meta-analyses and network meta-analysis can be performed using standard statistical methods, often called "frequentist" statistics, or Bayesian statistical methods.

Frequentist versus Bayesian statistical methods

Frequentist and Bayesian methods provide two different approaches to making statistical inference. They are based on different assumptions and the effect estimates and confidence intervals they produce have slightly different interpretations.

Frequentist statistical methods begin with the assumptions that within a given population there is a "true" but unknown parameter associated with a given variable of interest and that there is a specific form for the distribution of sample parameters that could be observed by drawing all possible samples of a given size from the total population. For example, we might be interested in finding the mean height in a population assuming a normal distribution. We can estimate the value of the "true" mean by drawing a random sample of individuals from the population and observing height for each person. The sample data is then used to calculate the mean height for the sample and an associated confidence interval (CI).

The confidence interval provides information about the margin of error around the estimated parameter for a specified probability (often 95%). Many people inaccurately interpret the CI as indicating that there is a 95% probability that the true population mean falls within this range. In fact, the meaning of the confidence interval is that if we repeatedly drew samples of the same size as our sample from the original population, 95% of those samples would have a CI that included the true population mean. Our sample, in fact, could be one of the 5% that doesn't include the true mean, but we can be reasonably confident that it does. To be more confident that the true mean lies within the sample CI, we could use a higher probability level, for example 99%. However, doing so will make the CI wider and we will be less certain about the accuracy of our estimated mean. Similarly a CI interval constructed for a lower probability, for example 90%, will be narrower, providing a more precise estimate of the sample mean, but increasing the chance that our sample CI may not be one of those that actually includes the true population mean.

Bayesian statistics takes a very different approach to statistical inference that focuses on updating evidence. Bayesian methods begin with a "prior distribution," which captures current beliefs about the size of the parameter of interest and the uncertainty around it, but makes no assumptions about the form of the distribution. New data is combined with the prior distribution to generate a "posterior distribution." The prior distribution can be a subjective belief about the size of the parameter, evidence from previous samples or an "uninformative prior" that assumes all values in a range are equally likely. The posterior distribution provides an updated estimate of the parameter and a "credible interval," sometimes called a Bayesian confidence interval. The credible interval around the estimated effect provides an estimate of the degree of confidence (often 95%) one has in the reliability of the result. Unlike a frequentist confidence interval, it can be interpreted as describing the range within which we are 95% certain that the parameter lies.

Interpreting statistical significance

Statistical significance is a term frequently used in reporting results of hypothesis testing. If, for example, we test the hypothesis that there is a difference in treatment effect between two groups against the null hypothesis that there is no difference, the result is often said to be "statistically significant" if the 95% CI excludes the null hypothesis value (for example, an odds ratio=1 or a risk difference =0) or the p-value is ≤ 0.05. When the reverse is true, the result if frequently described as "statistically insignificant."

There are several issues that should be considered when interpreting the meaning of statistical significance or insignificance:

- The choice of probability attached to the CI, while conventionally set to 95%, is arbitrary. Varying the probability could change our determination of whether an effect is statistically significant or not.
- A statistically significant result is not necessarily a clinically important result. A very low p-value or a confidence interval that excludes the null value indicates that we are quite certain that there is a difference between two groups, but the size of that difference may be too small to be relevant.
- A statistically insignificant result is not necessarily evidence of no effect, or expressed slightly differently, no evidence of effect is not the same as evidence of no effect. A large p-value or a confidence interval that includes the null value may mean that the evidence is inadequate, for example, too few events to detect a difference, rather than that no effect exists.

This appendix borrows heavily from the Cochrane Handbook for Systematic Reviews of Interventions (2008). More detailed information can be found there.

Appendix 3 – List of excluded studies

Study	Cause for exclusion
1. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: Acute pancreatitis and cancer. Diabetes Research and Clinical Practice 2012;98(2):271-284.	Not relevant endpoints
2. Aroda VR, Henry RR, Han J, Huang W, DeYoung MB, Darsow T, et al. Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-Analysis and Systematic Review. Clinical Therapeutics 2012;34(6):1247-1258.(Bellinger DC 1775-83)	Not in combination with metformin
3. Bennett WL, Maruther NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Annals of Internal Medicine 2011;154:602-613.	More recent review, no direct comparisons
4. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassai B, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: Meta-analysis of randomised controlled trials. BMJ (Online) 2011;343(7817).	Not in combination with metformin
5. Cai L, Cai Y, Lu ZJ, Zhang Y, Liu P. The efficacy and safety of vildagliptin in patients with type 2 diabetes: A meta-analysis of randomized clinical trials. Journal of Clinical Pharmacy and Therapeutics 2012;37(4):386-398.	Not in combination with metformin
6. Canadian Agency for Drugs and Technologies in Health. Second-line therapy for patients with diabetes inadequately controlled on metformin: a systematic review and cost-effectiveness analysis. 2010.	More recent review
7. Cornell S. Differentiating among incretin therapies: A multiple-target approach to type 2 diabetes. Journal of Clinical Pharmacy and Therapeutics 2012;37(5):510-524.	Not in combination with metformin; limited search
8. Jonas DE, Van scoyoc EE, Gerrald K, Wines R, Amick H, Triplette M, et al. Comparative effectiveness of newer diabetes medications. Journal of General Internal Medicine 2011;Conference(var.pagings):S300.	No direct comparisons
9. McIntosh B, Cameron C, Singh SR, Yu C, Ahuja T, Welton NJ, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Medicine 2011;5(1):e35-e48.	Duplicate of CADTH, 2011
10. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 2010;303(14):1410-1418.	No direct comparisons
11. Robinson LE, Holt TA, Rees K, Randeva HS, O'Hare JP. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: Systematic review and meta-analysis. BMJ Open 2013;3(1):e001986.	Net relevant endpoints
12. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, et al. Newer agents for blood glucose control in type 2 diabetes: Systematic review and economic evaluation. Health Technology Assessment 2010;14(36):3-247.	More recent review

Appendix 4 – Evaluation of systematic reviews included in report

Sjekkliste for systematiske oversikter*		Ja	Uklart	Nei
1	Beskriver forfatterne klart hvilke metoder de brukte for å finne primærstudiene?			
Kommentar				
2	Ble det utført et tilfredsstillende litteratursøk? (bruk hjelpespørsmål på neste side for å besvare dette spørsmålet)			
Kommentar				
3	Beskriver forfatterne hvilke kriterier som ble brukt for å bestemme hvilke studier som skulle inkluderes (studiedesign, deltakere, tiltak, ev. endepunkter)?			
Kommentar				
4	Ble det sikret mot systematiske skjevheter (bias) ved seleksjon av studier (eksplisitte seleksjonskriterier brukt, vurdering gjort av flere personer uavhengig av hverandre)?			
Kommentar				
5	Er det klart beskrevet et sett av kriterier for å vurdere intern validitet?			
Kommentar				
6	Er validiteten til studiene vurdert (enten ved inklusjon av primærstudier eller i analysen av primærstudier) ved bruk av relevante kriterier?			
Kommentar				
7	Er metodene som ble brukt da resultatene ble sammenfattet, klart beskrevet?			
Kommentar				
8	Ble resultatene fra studiene sammenfattet på forsvarlig måte?			
Kommentar				
9	Er forfatternes konklusjoner støttet av data og/eller analysen som er rapportert i oversikten?			
Kommentar				
10	Hvordan vil du rangere den vitenskapelige kvaliteten i denne oversikten?			
Kommentar				

*Basert på EPOC Checklist for Refereeing Protocols for Reviews. EPOC, Effective Practice and Organisation of Care group, Guide for review authors. www.epoc.cochrane.org

Evaluation of included systematic reviews with reference to questions 1-10, above.

Study	1	2	3	4	5	6	7	8	9	10
Karagiannis	yes	yes	yes	yes	yes	yes	yes	yes	yes	High
Liu	yes	yes	yes	yes	yes	yes[1]	yes	yes[2]	yes	High

[1] Systematic review reported using the Jadad scale for risk of bias evaluation but did not report details of the results.
[2] Systematic review is based on network meta-analysis (NMA). It did not meet all of the criteria suggested in NICE guidelines for evaluating an NMA, however, the new methodology is relatively new and widely accepted evaluation criteria are still under development

Appendix 5 – Risk of bias assessments for primary GLP-1 versus sulfonylurea studies in Liu

Appendix 5.1 Risk of bias assessment for Nauck (2009)

Bias	Assessment
Random sequence (selection bias)	Low risk: "patients randomly assigned", detailed description of randomization process
Allocation concealment (selection bias)	Low risk: "telephone-based or web-based randomization system" "subjects randomly assigned to lowest available randomization number ..."
Blinding of participants and personnel (performance bias)	Low risk: "double-blind, double dummy design required that subjects within the liraglutide and placebo groups received a glimepiride placebo whereas subjects in the glimepiride and placebo groups received an injection of liraglutide placebo."
Blinding of outcome assessment: HbA1c [at end of study] (detection bias)	Low risk: "HbA1c assayed by a method certified by ...."
Blinding of outcome assessment: Weight (detection bias)	Low risk: patients blinded; objective measure
Blinding of outcome assessment: Hypoglycemic incidents (detection bias)	Low risk: "subject reported hypoglycemic episodes (based on symptoms and plasma glucose <3.1)" ; "minor episodes self-treated, major required 3rd party assistance"
Incomplete outcome data: long term outcomes (attrition bias)	Low: Intention to treat; missing data imputed using last observation carried forward
Selective reporting	Low risk: seems like all outcomes are reported
Other notes	dose (once per day): 0.6, 1.2, 1.8 mg liraglutide, glimepiride 4 mg (once per day, a.m.); metformin 1000 mg twice daily

Appendix 5.2 Risk of bias assessment for Derosa (2011)

Bias	Assessment
Random sequence (selection bias)	Low: "randomized"
Allocation concealment (selection bias)	Low: "Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician"
Blinding of participants and personnel (performance bias)	High: "single blind"; unclear who is blinded
Blinding of outcome assessment: HbA1c [at end of study] (detection bias)	Low: "We measured these [the baseline parameters] after 3, 6, 9 and 12 month"; "All measurements [of plasmatic parameters] were performed in a central laboratory"; methods described for plasmatic measurements
Blinding of outcome assessment: Weight (detection bias)	Unclear: objective measure; patients probably not blinded, unclear effect on outcome
Blinding of outcome assessment: Hypoglycemic incidents (detection bias)	Uncertain: Presumably patient reported; no definition of a hypoglycemic event; unclear how lack of blinding may effect reporting of outcome
Incomplete outcome data: long term outcomes (attrition bias)	Low: Intention to treat
Selective reporting	Low risk: seems like all outcome are reported
Other notes	Doses: exanetide 10 μg twice daily; glimepiride 2 mg 3 times daily); metformin 1000-2000 per day (intolerant to 2500-3000); all had diet and exercise

Appendix 5.3 Risk of bias assessment for Yang (2012)

Bias	Assessment
Random sequence (selection bias)	Low: "16-week, randomized"
Allocation concealment (selection bias)	Uncertain: details of randomization not provided except that study "patterned after LEAD protocols"
Blinding of participants	Low: "double-blind, double dummy" "Subjects randomized

and personnel (performance bias)	to liraglutide treament received blinded gimeperide placebo tablet(s) in addition to blinded liraglutide injection, while those randomized to glimepiride also received blinded liraglutide placebo injections."
Blinding of outcome assessment: HbA1c [at end of study] (detection bias)	Low: "primary endpoint was change in HbA1c from baseline to the end of the trial"
Blinding of outcome assessment: Weight (detection bias)	Low risk: patients blinded; objective measure
Blinding of outcome assessment: Hypoglycemic incidents (detection bias)	Low risk: "self-reported hypoglycemic episodes (based on symptoms & HbA1c < 3.1 mmol/l)": "minor events self-treated, major required 3rd party assisstance"
Incomplete outcome data: long term outcomes (attrition bias)	Low: subject flow reported; missing data imputed using last observation carried forward
Selective reporting	Low: Seems like all outcomes are reported
Other notes	Asian population: China, South Korea, India; 16-weeks; statistical methods involved replacing missing post-baseline values with LOCF approach; doses see LEAD