



**Fixed Dose Combination Drug Products
for the Treatment of
Type 2 Diabetes and Hyperlipidemia**

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Produced by:
The Health Resources Commission
Office for Oregon Health Policy & Research
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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

The Oregon Health Resources Commission (HRC) appointed standing Pharmaceutical subcommittee performed an evidence-based review of Fixed Dose Combination Products for the treatment of Type 2 Diabetes and Hyperlipidemia. Members of the subcommittee are listed above. The subcommittee had one meeting. All HRC and HRC subcommittee

meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria. The EPC's report, "Fixed Dose Combination Products for the Treatment of Type 2 Diabetes and Hyperlipidemia" was completed in October, 2007, circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene the subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *Fixed Dose Combination Products for the treatment of Type 2 Diabetes and Hyperlipidemia* is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Introduction

In many situations, drug therapy using a single drug (monotherapy) is inadequate to control the disease or leads to unacceptable adverse effects when the dose is increased to improve control. In such cases, the clinician can opt to add a second drug to improve the control, reducing the dose of the first drug to reduce the adverse events. Typically the second drug is one that has a different mechanism of action, allowing potential for improved control of the disease symptoms and a different adverse event profile. Many treatment guidelines recommend adding a second drug in such situations^{1,2}. The choice to prescribe 2 drugs to treat the same disease does increase the number of drug administrations the patient must take each day and at least in theory may reduce adherence. While there is evidence that multiple (3-4) administrations per day results in lower adherence than fewer per day (1-2), evidence regarding switching from twice daily dosing to once daily indicates an improvement in adherence, but not in treatment outcomes. Importantly, the impact of reducing the number of tablets taken only once or twice per day is not clear. For example, many medications used to treat type 2 diabetes or hyperlipidemia can be administered once per day. In this situation, adding a second drug that is also taken once per day may not lead to reduced adherence. The combination of 2 drug entities in one dosage form is known as a fixed-dose combination product (FDCP). The main advantage of such a combination product is purported to be convenience, with the suggestion that adherence or persistence with the medication regimen is improved. A

recent Cochrane review of interventions to improve adherence found that for long-term treatments, only complex interventions resulted in improvements in health, and that those improvements were small.³ Observational evidence of different levels of adherence among groups of patients must be interpreted cautiously. Another scenario for using a FDCP is when 2 diseases are commonly found together, such as hypertension and hyperlipidemia. In this case 2 drugs treating 2 different diseases are combined. This review will not be addressing this particular situation.

FDA approval of FDCPs is based primarily on evidence that the product is bio-equivalent to the component drugs co-administered, provided the component drugs co-administered have been previously shown to be safe and effective. FDA approval establishes that a FDCP is safe and effective. We are not interested in repeating this assessment, but rather in assessing the comparative benefits and harms of the FDCP versus the relevant comparator interventions: component drugs co-administered or monotherapy.

Our primary interest is in long-term health benefits, although we recognize that for some short-term benefits a link has been established to the longer-term benefits, and as such we are including those outcomes here also. For Type 2 diabetes, for example, a relationship between lower glycated hemoglobin (<7.0%) and decreased mortality and cardiovascular events was shown in the UK Prospective Diabetes Study (UK PDS) which included sulfonylureas and metformin. Many studies have shown a relationship between lower LDLc and decreased mortality and cardiovascular events in patients with dyslipidemia being treated with statins.

Although the individual components of the FDCPs in this report have been shown to improve health outcomes, it is still important to show whether outcomes are the same under the conditions of the FDCP. Naturally, the anticipated benefit of using 2 drugs is that lower doses of each component drug can be used, leading to similar health outcomes but fewer adverse events overall. However, in the case of a FDCP it is not entirely clear that this assumption can be made. The evidence related to LDLc and health outcomes comes from drug classes with many long-term studies such that the balance of benefits and harms are known. In the case of ezetimibe however, long-term studies are not available; only extrapolation of effects from other drug classes are available. Clinicians indicate that their major concern over FDCPs is the limitation in dose adjustment or titration, potentially leading to increased adverse events. For example, with FDCPs including sulfonylureas, excess hypoglycemia is a concern and clinicians indicate that among those patients approaching goal glucose, the increased efficacy is masked by the need to curtail titration to avoid hypoglycemia (DERP peer reviewer communication September 2007). We are also interested in the comparison of these FDCPs to monotherapy. Guidelines for Type 2 diabetes and hyperlipidemia do not provide clear cut recommendations for first- or second-line approaches, but rather suggest various methods that can be applied, including using 1 or 2 drugs.^{1,2} Evidence about the comparative benefits and harms of FDCPs to monotherapy can provide useful information to guide practice in these cases.

We recognize that an advantage of FDCPs may be convenience, including convenience to the patient in having to take only 1 pill instead of 2 and to fill only 1 prescription instead of 2, to the prescriber in having to write only 1 prescription instead of 2, to the prescription benefit manager in having to handle 1 claim instead of 2, and so on.

These potential benefits are not directly considered here, other than as they may be reflected in adherence, persistence and short and long-term health outcomes. Another aspect of convenience that is not directly considered here is that when dose adjustments are made in component drugs that are co-administered, a patient may be able to split tablets to reduce the dose or take 2 tablets to increase the dose depending on the situation. This would delay the need for filling a new prescription, but with a FDCP a change in dose of one component drug requires a new prescription. The advent of FDCPs may have impact on prescriber behavior, but this issue is outside the scope of this report.

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on the following criteria as well as others determined by DERP. Please see the DERP report for full details

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on the following criteria as well as others determined by DERP. Please see the DERP report for full details:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

Scope and Key Questions

The purpose of this review is to review the evidence surrounding the FDCPs currently on the market to treat hyperlipidemia or type 2 diabetes. We want to examine the clinical evidence available for these products in drug naïve patients and patients who have failed first-line therapy compared to a single drug or to the individual component drugs of the FDCP taken simultaneously in producing their clinical effects. This includes long-term health outcomes such as reducing mortality as well as short-term outcomes such as reducing hemoglobin A1C or serum lipids. We are also interested in the comparison of

adverse events. Lastly, when comparing the FDCP to its individual component drugs taken simultaneously, we are also interested in the impact on adherence. Is adherence improved with the FDCP and importantly, are there known links between an improvement in adherence and short- or long-term outcomes?

Key Questions

1. What is the evidence that each combination product improves long-term health outcomes compared to monotherapy?
 - 1a. When used as first-line treatment for type 2 diabetes or hyperlipidemia in drug-naïve patients?
 - 1b. When used as second-line treatment for type 2 diabetes or hyperlipidemia in a patient who has failed monotherapy?

2. What is the evidence that each combination product improves HbA_{1c} or serum lipids compared to monotherapy?
 - 2a. When used as first-line treatment for type 2 diabetes or hyperlipidemia in drug-naïve patients?
 - 2b. When used as second-line treatment for type 2 diabetes or hyperlipidemia in a patient who has failed monotherapy?

3. What is the evidence that each combination product improves long-term health outcomes compared to the 2 individual drugs taken simultaneously in a type 2 diabetic or hyperlipidemic population?
 - 3a. How many patients with type 2 diabetes or hyperlipidemia must receive a combination product rather than 2 individual products to avoid one adverse health outcome, e.g. myocardial infarction?

4. What is the evidence that each combination product improves HbA_{1c} or serum lipids compared to the 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?

5. What is the evidence that each combination product improves adherence compared to the 2 individual drugs taken simultaneously in a type 2 diabetic or hyperlipidemic population?
 - 5a. What is the evidence that changing from 2 tablets per dose to 1 tablet per dose improves adherence in a Type-2 diabetic or hyperlipidemic population with complicated drug regimens (e.g. > 3 drugs in regimen, some administered multiple times per day)?

6. How do the adverse events associated with a combination product compare to:
 - 6a. Monotherapy in a population of patients with type 2 diabetes or hyperlipidemia?
 - 6b. The 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?
 - 6c. In the natural setting, with dose adjustment allowed, how do the adverse events and adverse event-related withdrawals associated with a combination product compare to the 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?

7. What is the evidence that there is a correlation between adherence (in general) and long term health outcomes in a Type 2 diabetic or hyperlipidemic population?
- 7a. What is the evidence that improved adherence after changing from 2 tablets per dose to 1 tablet per dose results in improved long term health outcomes in a Type 2 diabetic or hyperlipidemic population?
 - 7b. What is the evidence that improved adherence improves long term health outcomes in a Type 2 diabetic or hyperlipidemic population with complicated drug regimens (e.g. > 3 drugs in regimen)?
8. What is the evidence that there is a correlation between adherence (in general) and HbA_{1c} in a Type 2 diabetic population and between adherence (in general) and improvement in serum lipids in patients with hyperlipidemia?
- 8a. What is the evidence that improved adherence after changing from 2 tablets once daily to 1 tablet once daily results in improved HbA_{1c} in a Type 2 diabetic population or serum lipids in patients with hyperlipidemia?
 - 8b. What is the evidence that improved adherence improves HbA_{1c} in a Type 2 diabetic population or serum lipids in patients with hyperlipidemia with complicated drug regimens (e.g. > 3 drugs in regimen)?
9. What is the evidence that adherence, short-term outcomes, long-term health outcomes or adverse events differ based on the characteristics of patients with type 2 diabetes or hyperlipidemia taking a fixed-dose combination product?
- 9a. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on the patients' age (older versus younger), gender, or race/ethnicity?
 - 9b. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on the complexity of the overall drug regimen (e.g., multiple drugs per day, multiple times per day)?
 - 9c. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on comorbidities (e.g. renal dysfunction, cardiovascular disease, depression) or variations in baseline HbA_{1c} or serum lipids?

Methods

In our reports, we traditionally refer to the drug products by their generic names wherever possible. For this report, however, we are using the trade names for the FDCPs in an effort to make reading easier. Drugs for type 2 diabetes will be discussed separately from drugs for hyperlipidemia.

Inclusion Criteria

Type 2 diabetes

Population(s)

Adults (age \geq 18 years) with type 2 diabetes.

First-line treatment refers to patients who have not previously been treated with drug therapy. Second-line treatment refers to patients who have previously been treated with drug therapy, but who have had insufficient response.

Interventions

The drugs of interest are the fixed-dose combination products listed in Table 1 below. Comparators can be any oral drug used to treat type 2 diabetes mellitus.

Table 1. Included drugs for type 2 diabetes

Fixed-dose Combination Products	Individual drugs in combination	Monotherapy
Metformin plus Sulfonylurea		glimepiride glipizide glyburide repaglinide nateglinide rosiglitazone maleate pioglitazone hydrochloride metformin hydrochloride sitagliptin
Metaglip® 2.5/250mg	glipizide; metformin hydrochloride	
Glucovance® 2.5/500mg	glyburide; metformin hydrochloride	
Metformin plus Thiazolidinedione		
Avandamet® 2/1000mg, 4/1000mg*, 2/500mg*, 1/500mg*, 4/500mg*	metformin hydrochloride; rosiglitazone maleate	
Actoplus Met® 15/850mg	metformin hydrochloride; pioglitazone hydrochloride	
Metformin plus Meglitinide		
Janumet® 500/50mg, 100/50mg	metformin hydrochloride; sitagliptin	
Sulfonylurea plus Thiazolidinedione		
Avandaryl® 4/2mg, 4/1mg*, 4/4mg*	glimepiride; rosiglitazone maleate	
Duetact® 2/30mg, 4/30mg	glimepiride; pioglitazone hydrochloride	

Outcomes

Health Outcomes

- Mortality and morbidity from cardiovascular disease
- Hospitalizations, emergency department visits (e.g., number, length)
- Nephropathy
- Neuropathy
- Retinopathy
- Composite outcomes of above as defined by study authors

Short-term (Intermediate) Outcomes

- Glycosylated hemoglobin (HbA_{1c})
- Adherence/persistence

Harms

- Overall adverse events

Major: those that are life-threatening, result in long-term morbidity, or require medical intervention to treat (e.g., lactic acidosis, hepatotoxicity, macular retinal edema, heart failure)

General: (e.g., weight gain, headache, diarrhea, nausea and vomiting, dizziness)

Withdrawals due to adverse events, time to withdrawal due to adverse events

Hyperlipidemia

Population(s)

Adults (age \geq 18 years) at significantly increased risk for atherosclerotic disease due to primary hypercholesterolemia, mixed hyperlipidemia/dyslipidemia, homozygous familial hypercholesterolemia.

First-line treatment refers to patients who have not previously been treated with drug therapy. Second-line treatment refers to patients who have previously been treated with drug therapy, but who have had insufficient response.

Interventions

Table 2 details the included drugs for hyperlipidemia.

Table 2. Included drugs for hyperlipidemia

Fixed-dose Combination Products	Individual drugs in combination	Monotherapy
Vytorin® 10/10mg, 10/20mg, 10/40mg, 10/80mg	Ezetimibe; simvastatin	Lovastatin, Simvastatin, Fluvastatin, Rosuvastatin, Niacin, Atorvastatin, Pravastatin, Ezetimibe
Advicor® 750/20mg, 500/20mg*, 1000/20*	lovastatin; niacin	

* Canadian Product

Outcomes

Health Outcomes

Mortality and/or morbidity from cardiovascular disease

Mortality and/or morbidity from cerebrovascular disease (individual and composite outcomes)

Nonfatal myocardial infarction, angina, cardiovascular death, all-cause mortality, stroke, and need for revascularization (coronary artery bypass graft, angioplasty and stenting)

Short-term (Intermediate) Outcomes

Serum lipids: LDL-c reduction or the percent of patients meeting NCEP goals; HDL-c increase

Adherence/persistence

Harms

Overall adverse events

Withdrawals due to adverse events, time to withdrawal due to adverse events

Specific adverse events

Major: those that are life-threatening, result in long-term morbidity, or require medical intervention to treat (e.g., rhabdomyolysis, hepatotoxicity, angioedema,

elevations in liver enzymes or creatine phosphokinase levels, proteinuria, decline in renal function, increased risk of cancer)

General: (e.g., myalgia, headache, upper respiratory infection, flushing, pruritus, hyperglycemia, diarrhea, nausea)

Drugs for Type 2 Diabetes

KQ1: What is the evidence that each combination product improves long-term health outcomes compared to monotherapy?

1a. When used as first-line treatment for type 2 diabetes or hyperlipidemia in drug-naive patients?

1b. When used as second-line treatment for type 2 diabetes or hyperlipidemia in a patient who has failed monotherapy?

We found no studies that evaluated long-term health outcomes for any available FDCP for type 2 diabetes.

KQ1 Consensus for Type 2 Diabetes:

We found no evidence evaluating long-term health outcomes for any available FDCP for type 2 diabetes.

KQ2: What is the evidence that each combination product improves HbA_{1c} or serum lipids compared to monotherapy?

2a. When used as first-line treatment for type 2 diabetes or hyperlipidemia in drug-naive patients?

2b. When used as second-line treatment for type 2 diabetes or hyperlipidemia in a patient who has failed monotherapy?

Glucovance®

Glucovance® was the first type 2 diabetes combination tablet product to be FDA-approved for the U.S. market and is the most well-studied among its competitors. The majority of this research consists of randomized controlled trials comparing Glucovance® to monotherapy with either glyburide or metformin. So far, only retrospective, nonrandomized studies of prescription data from pharmacy databases have compared patient outcomes following co-administration of glyburide and metformin versus taking both ingredients in the form of a fixed-dose combination tablet product.

We included six trials of Glucovance® compared to monotherapy with glyburide or metformin specifically as initial therapy for patients with Type 2 diabetes poorly controlled with diet and exercise alone^{4,5,6} or as second-line therapy for patients inadequately controlled by previous oral antidiabetic medications.^{7,8} Prior treatment failure criteria were not specified in one trial and it is not clear whether it was aimed at evaluating patients for use as first- or second-line therapy.⁹ In two trials conducted in European countries, Glucovance® and monotherapy comparator tablets used the

ingredient glibenclamide, which is another name used for glyburide, outside of the U.S. All but one trial were rated fair quality and the other was rated poor quality.

Overall, patients receiving Glucovance® achieved superior HbA_{1c} control using lower dosages of glyburide and metformin than patients receiving monotherapy with either of the component ingredients. Primary efficacy was pre-specified as the mean change from baseline in HbA_{1c} (% units) in the initial therapy trials and was described as 16-week HbA_{1c} concentration⁷ or HbA_{1c}⁸ in the second-line therapy trials. HbA_{1c} reductions were consistently greater with Glucovance® versus glyburide or metformin monotherapies. Baseline HbA_{1c} appeared to have some association with outcome in that groups with greater mean HbA_{1c} levels at baseline were noted to achieve greater reductions during follow-up. Three trials also reported the proportions of patients that reached the American Diabetes Association (ADA) treatment goal of an HbA_{1c} concentration of 7% or lower.^{5,6,8} Overall, there were more patients taking Glucovance® that achieved an HbA_{1c} of 7% or lower (mean=71.6% of patients; range=63.8% to 75.5%) compared to patients taking glyburide (mean=58% of patients; range=41.9% to 68%) or metformin (mean=51.5% of patients; range=37.6% to 62%), regardless of dosage or whether administered as initial or second-line treatment.

Metaglip®

We found 2 randomized controlled trials that evaluated the efficacy and safety of Metaglip® (glipizide/metformin) compared to monotherapy with either glipizide or metformin in a total of 1,115 patients with type 2 diabetes.^{10,11} One trial that evaluated Metaglip® as first-line therapy has not yet been published, but extensive details are available within the Center for Drug Evaluation and Research Medical Review.¹¹ The other trials evaluated Metaglip® compared to glipizide or metformin monotherapy when used as second-line therapy in patients who had previously failed a trial of monotherapy of at least half the maximum labeled dose of a sulfonylurea.¹⁰ Criteria used for diagnosis of Type 2 diabetes was not reported in either trial.

Change in HbA_{1c} was pre-specified as the primary outcome in both trials of Metaglip®. Compared to monotherapy with either glipizide or metformin, mean HbA_{1c} reductions were greater for all Metaglip® treatment groups, with the exception of patients who started first-line therapy at the lowest dose of 1.25/250mg. Additionally, there were more patients treated with Metaglip® than either glipizide or metformin monotherapy with HbA_{1c} < 7% at week 18 (36.3% vs. 8.9% vs. 9.9%; p-value NR).¹¹

Avandamet®

We found only 2 studies of Avandamet®.^{12,13} One randomized controlled trial compared Avandamet® to monotherapy with either rosiglitazone or metformin when used as first-line therapy in patients with type 2 diabetes that was inadequately controlled with diet and exercise alone. *The study did not evaluate Avandamet® as a second line therapy.*

First-line therapy with Avandamet® was compared to monotherapy with either rosiglitazone or metformin in a fair-quality, 32-week trial of 468 patients with uncontrolled type 2 diabetes.¹² Criteria used for diagnosis of Type 2 diabetes was not reported. Patients were randomized to double-blinded treatment if both their HbA_{1c} was greater than 7.5%, but less than or equal to 11%, and their FPG was 15 mmol/l or below

after a 2-week screening period of diet and exercise alone. Medication dosages were started at 2/500mg for Avandamet®, 4mg for rosiglitazone, or 500mg for metformin and were increased based on a mean daily glucose target of 6.1 mmol/l or below. Final mean dosages were 7.2/1799mg for Avandamet®, 7.7mg with rosiglitazone, and 1847mg for metformin. Methods of randomization and allocation concealment were not described, but resulted in treatment groups that were well-balanced with regard to important baseline patient characteristics that may influence outcome. Eleven patients (2.3%) with no valid on-therapy assessment data were excluded from the primary efficacy analysis, but these level of exclusions were not judged to pose a serious threat to study results. Overall, efficacy findings from this trial favored Avandamet® over monotherapy with either rosiglitazone or metformin when used as first-line therapy in adults with uncontrolled type 2 diabetes. On the primary outcome of change in HbA_{1c}, reductions were statistically significantly greater for patients taking Avandamet® (-2.3%) compared to reductions in patients taking monotherapy with rosiglitazone (-1.6%; p<0.0001) or metformin (-1.8%; p=0.0008). Additionally, more patients taking Avandamet® (77%) reached HbA_{1c} levels of less than 7% as compared to 58.1% of patients taking rosiglitazone (p<0.0001) and 57.3% taking metformin (p<0.001).

Avandaryl®

Evidence for Avandaryl® comes from one, fair quality 28-week randomized controlled trial specifically of drug-naïve patients with type 2 diabetes involving comparison to monotherapy with either glimepiride or rosiglitazone.¹⁴ *The study did not evaluate Avandaryl® as a second line therapy.*

Patients were randomized to double-blinded treatment if they had a diagnosis of type 2 diabetes⁵⁰ and an HbA_{1c} of 7.5% to 12% after a 2-week screening period of diet and exercise alone (n=901). Medication was titrated based on a mean daily glucose target of below 110 mg/dL and final mean dosages were 4.0/3.2mg for Avandaryl® Regimen A, 6.8/2.9mg for Avandaryl® Regimen B, 3.5mg for glimepiride monotherapy, and 7.5mg for rosiglitazone monotherapy.

Overall, efficacy findings from this trial favored Avandaryl® over monotherapy with either glimepiride or rosiglitazone when used as first-line therapy in drug-naïve adults with type 2 diabetes. On the primary outcome of change in HbA_{1c}, reductions were statistically significantly greater for patients taking Avandaryl® Regimen A (-2.41%) or Regimen B (-2.52%) compared to reductions in patients taking monotherapy with either glimepiride (-1.72; p<0.0001) or rosiglitazone (-1.75%; p<0.0001). Also, statistically significantly more patients taking Avandaryl® Regimen A (74.7%) or Regimen B (72.4%) reached HbA_{1c} levels of less than 7% as compared to 49.1% of patients taking glimepiride (p<0.0001) or 46.2% of patients taking rosiglitazone (p<0.0001). Proportions of patients reaching the American Association of Clinical Endocrinologists (AACE) goal of ≤ 6.5% were also reported and again Avandaryl® Regimen A (56.1%) and Regimen B (53.8%) were associated with higher rates than glimepiride (32.1%; p<0.0001) or rosiglitazone monotherapy (30.7%; p<0.0001).

Duetact®, Actoplus Met®

Studies for these Medications were rated poor quality and are not included.

KQ 2 Consensus for Type 2 Diabetes:

1. Based on *small short term* studies Glucovance®, Metaglip®, Avandaryl® or Avandamet® consistently produced statistically significantly greater reductions in HbA1c compared to monotherapy with either of their respective components. Numbers needed to treat for these comparisons are: Glucovance® vs. metformin = NNT of 4 - 6, Glucovance® vs. glyburide = NNT of 8 - 9, Avandamet® vs. rosiglitazone or metformin = NNT of 5, Avandaryl® vs. glimepiride or rosiglitazone = NNT of 3 - 4.
2. Based on *small short term* studies for second line therapy Glucovance® and Metaglip® improved HbA1c control and used lower mean dosages compared to each of either of their respective component monotherapies. NNT = 3-4 for an additional patient to reach the ADA goal within 18-24 weeks of treatment.

KQ 3 What is the evidence that each combination product improves long-term health outcomes compared to the 2 individual drugs taken simultaneously in a type 2 diabetic or hyperlipidemic population?

3a. How many patients with type 2 diabetes or hyperlipidemia must receive a combination product rather than 2 individual products to avoid one adverse health outcome, e.g. myocardial infarction?

We found no studies that evaluated long-term health outcomes for any available FDCP for type 2 diabetes.

KQ 3 Consensus for Type 2 Diabetes:

We found no evidence evaluating long-term health outcomes for any available FDCP for type 2 diabetes

KQ 4 What is the evidence that each combination product improves HbA_{1c} or serum lipids compared to the 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?

We found no studies that evaluated improvement of HbA_{1c} for any FDCP for Type 2 diabetes compared to concomitant administration of that FDCP's component drugs.

KQ 4 Consensus Statements for Type 2 Diabetes:

We found no evidence that compared HbA_{1C} control and co-administration of its components.

KQ 5 What is the evidence that each combination product improves adherence compared to the 2 individual drugs taken simultaneously in a type 2 diabetic or hyperlipidemic population?

5a. What is the evidence that changing from 2 tablets per dose to 1 tablet per dose improves adherence in a Type-2 diabetic or hyperlipidemic population with complicated drug regimens (e.g. > 3 drugs in regimen, some administered multiple times per day)?

Glucovance®

We found no randomized controlled trials that compared Glucovance® to co-administration of glyburide and metformin. The only evidence regarding the comparison of Glucovance® versus co-administration of glyburide and metformin comes from three retrospective database studies.

Results were mixed across studies for the comparison of adherence rates between Glucovance® or glyburide co-administered with metformin in newly treated patients. Mean adherence rates were not provided for patients in the smaller cohort (n=306), but it was reported that there were no statistically significant differences between patients receiving co-administration of glyburide and metformin and those receiving Glucovance®.¹⁵ In the larger cohort (n=1421), adjusted adherence rates were statistically significantly greater for patients taking Glucovance® compared to those taking glyburide co-administered with metformin (84% vs. 76% of days with drug supply; p<0.0001).¹⁶

Adherence rates in previously treated patients switched from monotherapy to Glucovance® had statistically significantly higher adherence rates than those switched to co-administration of glyburide and metformin (77% vs. 54%; p<0.001).¹⁵ Additionally, adherence rates increased statistically significantly when previously treated patients were switched from co-administration of glyburide and metformin to Glucovance® (71% vs. 87%; p<0.001).¹⁵

Avandamet®

The only evidence we found regarding the comparison between Avandamet® and co-administration of rosiglitazone and metformin comes from a retrospective database study that focused on medication adherence.¹³ We rated this study fair quality. The primary concern is the validity of calculating medication adherence based on prescription refill data. The main limitation of any refill-based adherence calculation method is the potential for inaccuracy in reflecting whether the medication was actually ingested by the patient. Another concern related to the systematic exclusion of patients with lapses in therapy > 60 days. It seems plausible that patients with lapses in therapy of > 60 days

could have represented extreme cases of nonadherence and exclusion of their data could have skewed results in the direction of higher compliance.

The primary outcome was change in MPR (Medication Possession Ratio) and between-group differences were analyzed using analysis of covariance methods that adjusted for a number of demographic and disease-related factors. Results of this analysis suggest that switching from rosiglitazone/metformin co-administration was associated with an increase in adherence (MPR change +3.5%), whereas adherence rates for patients in ongoing treatment with rosiglitazone/metformin co-administration actually dropped by -1.3%. After adjustment for all covariates, results suggest that the difference between mean change in adherence rates was statistically significant (4.8%; 95% CI 1.0%-8.6%). However, although statistically significant, no clinical events outcomes were reported, so it is not clear if a 4.8% increase in MPR has a clinically important impact. No information was provided about whether changes in MPR were affected by variations in total pill burden.

There were no studies found that evaluated adherence compared to simultaneous administration of the component drugs for any of the other included FDCP's. No evidence was found on the implications of using a FDCP in simple or complicated drug regimens

KQ 5 Consensus for Type 2 Diabetes:

1. There is insufficient evidence to determine that the use of Glucovance® or Avandamet® may improve adherence. Better quality studies are needed.
2. No evidence was found on the implications of using a FDCP in simple or complicated drug regimens.

- KQ 6 How do the adverse events associated with a combination product compare to:**
- 6a. Monotherapy in a population of patients with type 2 diabetes or hyperlipidemia?**
 - 6b. The 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?**
 - 6c. In the natural setting, with dose adjustment allowed, how do the adverse events and adverse event-related withdrawals associated with a combination product compare to the 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?**

Glucovance®

No unexpected increases in risk of hypoglycemia were seen for Glucovance® compared to glyburide monotherapy at dosages not exceeding 7.6mg. However, risk of hypoglycemia was significantly increased for Glucovance® compared to glyburide monotherapy when both were used second-line at higher dosages in order to attain glycemic control in patients with higher baseline mean HbA_{1c} levels (9.5%).⁷ Rates of all-cause adverse events, withdrawals due to adverse events, serious adverse events, death, overall gastrointestinal adverse events, diarrhea, upper respiratory infection, nausea/vomiting, musculoskeletal pain, headache, and abdominal pain for Glucovance®

were generally comparable or lower than monotherapy with either glyburide or metformin.

Metaglip®

Unexpectedly, risk of hypoglycemia for Metaglip® 2.5/250mg and above was increased beyond what was seen for glipizide monotherapy at 5mg. In both trials of Metaglip®, incidence of hypoglycemia was objectively measured using a fingerstick blood glucose measurement of ≤ 50 mg/dL. In the trial of second-line therapy, incidence of hypoglycemia was statistically significantly greater in patients taking Metaglip® (12.6%) compared to metformin (1.3%; $p=0.0086$) and glipizide (0%; $p=0.0006$).³¹ In the trial of first-line therapy, hypoglycemia was also statistically significantly more common in patients starting Metaglip® at 2.5/250mg (8%; $p<0.05$) or 2.5/500mg (9%; $p<0.0001$) than in those on glipizide (3%) or metformin (0%) monotherapy.¹¹

Higher rates of withdrawal due to adverse events were seen in patients randomized to second-line therapy with the highest dosage of Metaglip® (mean final dose of 17.5/1747mg) compared to rates for patients taking either glipizide or metformin monotherapy (12.6% vs. 3.6% vs. 5.3%).¹⁰ The differences in adverse event withdrawal rates reached statistical significance only for the comparison between second-line therapy with Metaglip® versus glipizide ($p=0.0337$). There was a trend toward higher rates of headache for patients using Metaglip® as second-line therapy (12.6%) compared to those using glipizide (6%) or metformin (5%),¹⁰ but otherwise adverse events rates for Metaglip® were comparable to or lower than in the monotherapy treatment groups.

Avandamet®

Avandamet® was not associated with any unexpected adverse effects compared to its monotherapy components. There were no significant increases in gastrointestinal adverse effects for Avandamet® compared to metformin monotherapy and no significant increases in edema or weight gain for Avandamet®. Rates of withdrawal due to adverse events were similar for Avandamet®, metformin, and rosiglitazone (1% vs. 2% vs. 3%).

Avandaryl®

Statistically significantly more patients gained weight taking either Regimen A (3.1%; $p=0.03$) or Regimen B (3.2%; $p=0.03$) of Avandaryl® when compared to rosiglitazone monotherapy (0.4%).¹⁴ The clinical significance of this finding is unclear, however, as weight gain criteria were not reported and resulted in treatment withdrawal for only 1 patient in the Avandaryl® Regimen A group. There were no significant differences between either regimen of Avandaryl® and rosiglitazone monotherapy for rates of edema or cardiac-ischemic events. One patient in each of the rosiglitazone monotherapy and Avandaryl® groups experienced congestive heart failure, but these events were considered unrelated to study medication. Incidence of confirmed hypoglycemia (<50 mg/dL) did not differ significantly between either Regimen A (3.6%) or Regimen B (5.5%) of Avandaryl® and glimepiride monotherapy (4.1%).¹⁴

KQ 6 Consensus for Type 2 Diabetes:

Based on small size short duration studies (see table below) for FDCP's containing sulfonylurea compared to sulfonylurea monotherapy, improved glycemic control was associated with an increase in frequency of hypoglycemia for Glucovance® and Metaglip® but not for Avandaryl®.

Hypoglycemia Rates*: FDCP vs. sulfonylurea monotherapy**

FDCP	Initial Therapy	Second Line Therapy
Glucovance®	11% vs 8%, NS	7% vs 2%, (p< 0.01)
Metaglip®	7% vs 3%, (p= 0.03)	13% vs 0%, (p=0.0086)
Avandaryl®	4% vs 4%, NS	NA

*Hypoglycemia defined as ≤ 60 mg/dl for the second line trial of Glucovance®, ≤ 50 mg/dl in the others.

** Table from Oregon EPC.

KQ 7 What is the evidence that there is a correlation between adherence (in general) and long term health outcomes in a Type 2 diabetic or hyperlipidemic population?

7a. What is the evidence that improved adherence after changing from 2 tablets per dose to 1 tablet per dose results in improved long term health outcomes in a Type 2 diabetic or hyperlipidemic population?

7b. What is the evidence that improved adherence improves long term health outcomes in a Type 2 diabetic or hyperlipidemic population with complicated drug regimens (e.g. > 3 drugs in regimen)?

Decreased antidiabetic medication adherence was not consistently found to be a statistically significant predictor of increased risk of hospitalizations across two fair quality retrospective studies that used administrative claims data from patients with type 2 diabetes enrolled in different health care organizations in the U.S.^{17,18}

The impact of medication adherence on health outcomes was evaluated as part of the nonrandomized, prospective Medical Outcomes Study (MOS).^{17,19} DERP had major concerns about the validity of the methods used to measure adherence and health outcomes. It is unclear what proportion of patients were type 2 diabetics and no information about baseline characteristics were provided for this subgroup.

KQ 7 Consensus for Type 2 Diabetes:

1. There is insufficient evidence to determine if there is a correlation between adherence (in general) and long term health outcomes in Type 2 diabetics.

KQ 8 . What is the evidence that there is a correlation between adherence (in general) and HbA_{1c} in a Type 2 diabetic population and between adherence (in general) and improvement in serum lipids in patients with hyperlipidemia?

8a. What is the evidence that improved adherence after changing from 2 tablets once daily to 1 tablet once daily results in improved HbA_{1c} in a Type 2 diabetic population or serum lipids in patients with hyperlipidemia?

8b. What is the evidence that improved adherence improves HbA_{1c} in a Type 2 diabetic population or serum lipids in patients with hyperlipidemia with complicated drug regimens (e.g. > 3 drugs in regimen)?

The only evidence pertaining to the association between antidiabetic medication adherence and HbA_{1c} control comes from 6 nonrandomized studies with conflicting results. Notably, this body of evidence was characterized by extreme heterogeneity in patient population characteristics, methods used to quantify medication adherence, duration of observation periods, and statistical analysis methods. Although the majority of studies reported positive associations between improved medication adherence and improved HbA_{1c} control, serious concerns about the internal validity of these studies limit the strength of their findings.^{39, 40, 42, 45} Taken as a whole, findings from these studies were difficult to interpret. The main insight provided by this body of evidence is that further research is needed in this area with an emphasis on use of improved methodologies.

Formal meta-analyses were not possible due to heterogeneity in methods of outcome assessment, but we subjectively considered whether differences between studies as to whether or not they found a statistically significant association between adherence and HbA_{1c} control could be attributed to any of the variations described above. No clear patterns were interpreted and reasons for the conflicting results remain unclear.

KQ 8 Consensus for Type 2 Diabetes:

1. There is insufficient evidence to determine if there is a correlation between adherence (in general) and HbA _{1c} in a Type 2 diabetic population.
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KQ 9 What is the evidence that adherence, short-term outcomes, long-term health outcomes or adverse events differ based on the characteristics of patients with type 2 diabetes or hyperlipidemia taking a fixed-dose combination product?

9a. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on the patients' age (older versus younger), gender, or race/ethnicity?

9b. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on the complexity of the overall drug regimen (e.g., multiple drugs per day, multiple times per day)?

9c. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on comorbidities (e.g. renal dysfunction, cardiovascular disease, depression) or variations in baseline HbA_{1c} or serum lipids?

Glucovance®

When subgroup analyses based on patient demographics were performed based on outcome data from the one trial that compared the efficacy and safety of second-line therapy with Glucovance® or monotherapy with either glyburide or metformin, no differences in changes from baseline in HbA_{1c} based on gender, race, and age were found for any of the treatment groups.⁷ Additionally, a meta-analysis²⁰ was conducted that combined data from three⁶⁻⁸ of the six trials discussed above and looked at the comparative efficacy and safety of Glucovance® versus monotherapy with either metformin or glyburide/glibenclamide based on potential influences of baseline HbA_{1c}, weight, or age. The main findings were that Glucovance® was associated with significantly greater reductions in HbA_{1c} and comparable tolerability compared to metformin or glyburide/glibenclamide, irrespective of baseline HbA_{1c}, age, or BMI. No trials addressed how complexity of overall drug regimens or comorbidities could impact outcome.

Metaglip®

Subgroup analyses of reductions in HbA_{1c} based on differences in baseline patient characteristics were only available from the first-line therapy trial.¹¹ In patients taking Metaglip®, there were no statistically significant differences in HbA_{1c} reductions based on age, gender, or race. Subgroup analyses did not appear to explore differences in patient outcomes based on variations in the complexity of the overall drug regimen or based on comorbidities.

No subgroup analyses of efficacy or safety outcomes based on differences in patient demographics, overall pill burden, or comorbidities were reported for any of the other FDCP's used for treatment of Type 2 Diabetes that were included in this study.

KQ 9 Consensus for Type 2 Diabetes:

1. There is limited evidence that for subgroups of race, age and gender there is no difference in effect on HbA_{1c} for Glucovance® or Metaglip®.
2. No subgroup analyses of efficacy or safety outcomes based on differences in patient demographics, overall pill burden, or comorbidities were reported for any of the other FDCP's used for treatment of Type 2 Diabetes that were included in this study.

Drugs for Hyperlipidemia

For treatment of hyperlipidemia, 2 FDCPs are available, Vytorin® and Advicor®. Advicor® is a combination of an HMG-CoA Reductase Inhibitor (statin), lovastatin, with an extended release formulation of niacin, while Vytorin® is a combination of another statin, simvastatin, and a newer drug ezetimibe. All of the individual products are available separately and can be administered once daily. The FDCPs have multiple strengths available, although the dose of ezetimibe is constant at 10mg in Vytorin®.

KQ1: What is the evidence that each combination product improves long-term health outcomes compared to monotherapy?

1a. When used as first-line treatment for type 2 diabetes or hyperlipidemia in drug-naive patients?

1b. When used as second-line treatment for type 2 diabetes or hyperlipidemia in a patient who has failed monotherapy?

We found no studies that evaluated long-term health outcomes for any available FDCP for hyperlipidemia.

KQ 1 Consensus for Hyperlipidemia:

1. We found no evidence evaluating long-term health outcomes for any available FDCP for hyperlipidemia.
2. Dates of included studies for this report are 1996 to May, week 4 2007. This is prior to the publication of the ENHANCE study which is not included in this summary.

KQ2: What is the evidence that each combination product improves HbA_{1c} or serum lipids compared to monotherapy?

2a. When used as first-line treatment for type 2 diabetes or hyperlipidemia in drug-naive patients?

2b. When used as second-line treatment for type 2 diabetes or hyperlipidemia in a patient who has failed monotherapy?

Advicor®

The evidence for Advicor® is limited to 3 fair quality, short term trials (16 to 28 weeks) comparing Advicor® to its individual components as monotherapy (lovastatin or niacin alone, 2 trials)^{21,22} or to atorvastatin or simvastatin (1 trial).²³ While our questions were stratified into first and second-line populations, the trials appear to have potentially included either. It is presumed that most patients in these trials were being treated as second-line, and that the choice to enroll in the study indicates some type of dissatisfaction with prior therapy.

Two dose-ranging studies assessed Advicor® compared to lovastatin or niacin monotherapy.^{21,22} Both found that there was a dose-response for all three drugs in LDLc reduction, but only for Advicor® and niacin in HDLc elevation. The higher doses (2000mg/40mg or 1500mg/20mg) of Advicor® were found superior to either drug alone for LDLc reduction. These studies also found that the addition of a second drug provided additional benefit compared to a single drug based on lipoprotein A and triglyceride levels. In the third study, ADVOCATE,²³ moderate doses of a highly potent statin, atorvastatin 40mg, was superior to Advicor® in reducing LDLc, while 40mg of simvastatin, considered less potent than atorvastatin on a mg per mg basis, was not superior. Similar to the other 2 studies, this study found that the addition of niacin brought about statistically significant benefits in HDLc increases not found with the statins alone. Apolipoprotein B was more reduced in the atorvastatin 40mg group at 16 weeks compared to the simvastatin or Advicor® 1000/40 group (p<0.05), and Apolipoprotein A1 was more elevated with Advicor® group (2000/40) than with either statin

Vytorin®

A single fair quality study compared the component drugs as monotherapy to Vytorin®;⁶³ this study was also identified in the FDA medical review documents.²⁴ While the study randomized patients to 1 of 10 groups, the primary analysis presented is based on pooling all doses of Vytorin® and all doses of simvastatin. Vytorin® was found to be superior (p<0.001) to either drug taken as monotherapy in reducing LDLc, total cholesterol, and triglycerides, with no statistically significant differences in HDLc elevation found between treatments

Three studies compared Vytorin® and atorvastatin at various doses, but in differing populations. The first was a dose-ranging study in a general population with CHD or CHD risk equivalent and LDLc ≥ 130 mg/dL.²⁵ In this study the combination product was superior to monotherapy in combined dose analysis for change in LDLc, total cholesterol, and HDLc. LDLc and HDLc were statistically significantly better for Vytorin® across individual statin dose level comparisons while total cholesterol was improved significantly more with only the 10, 20, and 40mg statin doses of Vytorin®. A difference in effect on triglycerides was not found. In a combined dose analysis, patients receiving Vytorin® were more likely to have achieved their personal NCEP ATP III goals, 89.7% with Vytorin® versus 81.1% with atorvastatin, with an NNT 12 (95% CI 9-19). combined Vytorin® groups (10% vs. 0%; p=0.002 and 11% vs. 1%; p=0.006, respectively).

The second study was that of patients with CHD previously treated with atorvastatin 10mg/day, without complete success (LDL-C between 100 to 160 mg/dL), who were being considered for a dose increase.²⁶ These patients were randomized to the next dose of atorvastatin (20mg/day) compared to Vytorin® at the second level dose 10/20mg/day. The study did find that Vytorin® 10/20mg per day was superior to atorvastatin 20mg per day in reducing LDLc and total cholesterol and in elevating HDLc. A difference in the impact on triglycerides was not found.

The third study treated patients with hypercholesterolemia and type 2 diabetes randomized to low to moderate doses of atorvastatin (10mg, 20mg or 40mg) or moderate doses of Vytorin® (10/20mg, 10/40mg).²⁷ Again, the dose comparisons are not directly

comparable to the doses of Vytorin® used. The analysis compares 10 or 20mg of atorvastatin to Vytorin® 10/20mg and 40mg of atorvastatin to Vytorin® 10/40mg. The study found that adding a second drug (ezetimibe) resulted in additional benefit in LDLc and total cholesterol reduction and HDLc elevations, although triglyceride reduction was only statistically significantly different between the atorvastatin 10mg and Vytorin® 10/20mg groups (p=0.02). Additionally, the proportions of patients achieving the NCEP ATP III goal of < 70 mg/dL were statistically significantly greater in the Vytorin® groups. Those achieving a NCEP ATP III goal of < 100 mg/dL were statistically significant when comparing the lower dose groups, but not the 40mg statin groups.

A recent study compared Vytorin® to rosuvastatin at varying doses. The study compared rosuvastatin at starting (10mg), intermediate (20mg), and high (40mg) daily doses to Vytorin® at corresponding doses. This good quality study (n=2959) found that reduction of LDLc and total cholesterol was greater with Vytorin® than rosuvastatin across all dose groups, although changes in HDLc were not found to be different. Changes in triglycerides were greater with Vytorin® in all dosage comparisons except rosuvastatin 40mg. A higher percentage of patients achieved NCEP ATP III goals with Vytorin® low dose than with rosuvastatin low dose and when all dose groups were combined.²⁸

An observational study using data collected prospectively from general practitioners and internists in the UK and Germany, the effect of switching patients with LDLc > 100 mg/dL during pretreatment with a statin at low to moderate doses (10-20mg/d) to Vytorin® was evaluated.²⁹ In this fair quality before-after study, patients also had to have either CHD or type 2 diabetes, and both groups were large. Most patients (93%) had been previously treated with statin monotherapy, most commonly simvastatin. Switch to a 2 drug regimen from low to moderate dose statin therapy (depending on specific drug) resulted in additional reductions in LDLc, total cholesterol, and triglycerides and elevation in HDLc. These changes were smaller than the changes seen in the switching trial reported above, where Vytorin® resulted in an LDLc reduction of 32.8%, compared to 27-28% here.²⁶ These data reflect a broader patient population, specifically patients with CHD or type 2 diabetes, co-morbid with hypercholesterolemia despite statin monotherapy. However, because it is a before-after study design, the strength of this evidence is lower because it is open to more biases and confounding.

KQ 2 Consensus for Hyperlipidemia:

1. Studies in this section are based on short term (12-24 weeks duration) studies.
2. Addition of a second lipid lowering compound can lead to additional lowering of LDLc and total cholesterol but is dependant on the specific dose and specific statin being compared (atorvastatin resulted in better lipid lowering by a difference of 7 - 10% compared to Advicor®). More potent statins may result in greater lipid lowering than FDCP's.. There were no studies to evaluate Avandamet or Avandaryl as second line therapy
3. Triglyceride reduction is also affected by adding niacin, but statistically significant improvements in HDLc are not often seen when compared to statin monotherapy.
4. NCEP Adult Treatment Panel III (ATP III) goal was reached in more patients randomized to Vytorin® compared to atorvastatin or rosuvastatin across all doses: Vytorin® 89.7% versus atorvastatin 81.1%, NNT 12 (95% confidence interval (CI) 9-19)
Vytorin® 95.9% versus rosuvastatin 93%, NNT 35 (95% CI 22-80).

KQ 3 What is the evidence that each combination product improves long-term health outcomes compared to the 2 individual drugs taken simultaneously in a type 2 diabetic or hyperlipidemic population?

3a. How many patients with type 2 diabetes or hyperlipidemia must receive a combination product rather than 2 individual products to avoid one adverse health outcome, e.g. myocardial infarction?

We found no studies that evaluated long-term health outcomes for any available FDCP for hyperlipidemia.

1. We found no evidence evaluating long-term health outcomes for any available FDCP for hyperlipidemia.

KQ 3 Consensus for Hyperlipidemia:

KQ 4 What is the evidence that each combination product improves HbA_{1c} or serum lipids compared to the 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?

We found no studies that evaluated improvement in serum lipids for any FDCP compared to co-administration of its component drugs.

KQ 4 Consensus for Hyperlipidemia

1. We found no evidence that that compared serum lipids between any FDCP and co-administration its components.

KQ 5 What is the evidence that each combination product improves adherence compared to the 2 individual drugs taken simultaneously in a type 2 diabetic or hyperlipidemic population?

5a. What is the evidence that changing from 2 tablets per dose to 1 tablet per dose improves adherence in a Type-2 diabetic or hyperlipidemic population with complicated drug regimens (e.g. > 3 drugs in regimen, some administered multiple times per day)?

Advicor®

A fair quality study designed to assess medication adherence and persistence with Advicor® compared to either drug as monotherapy or the 2 taken simultaneously found no benefit in using the combination product.³⁰ The study used prescription claims data from 2,389 patients over a 1 year period, and defined adherence as a ‘medication possession rate’ of ≥ 0.80 , and persistence as a ‘proportion of days covered’, also ≥ 0.80 . For the adherence measure, all drugs were adhered to well, with scores of 0.88 for Advicor® and 0.90 for the co-administration (NS).

Vytorin®

No evidence was found on adherence or persistence with Vytorin® compared to the two drugs taken together in a hyperlipidemic population.

Advicor® and Vytorin®

No evidence was found on the implications of using a FDCP in simple or complicated drug regimens.

KQ 5 Consensus for Hyperlipidemia:

1. A single study (of 1 year duration based on medication possession rates based on prescription claims data) indicated that the Advicor® did not result in higher adherence rates compared to co-administration of individual drug components.

KQ 6 How do the adverse events associated with a combination product compare to:

6a. Monotherapy in a population of patients with type 2 diabetes or hyperlipidemia?

6b. The 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?

6c. In the natural setting, with dose adjustment allowed, how do the adverse events and adverse event-related withdrawals associated with a combination product compare to the 2 individual drugs taken together in a type 2 diabetic or hyperlipidemic population?

Advicor®

In the studies of Advicor® compared to niacin ER or lovastatin monotherapy, withdrawal due to adverse events was higher in the groups of patients receiving niacin (23% and 20% with niacin ER and 18% and 19% with Advicor®) compared to lovastatin alone (9% and 10%).^{21,22} Flushing was reported by 63% of those receiving niacin in some formulation, compared to 15% in the statin group in one of the studies,²² and was described as the most common adverse event leading to withdrawal in the other.²¹

Adverse events and withdrawals from the study were poorly described in the ADVOCATE study where withdrawals due to adverse events were greater in the Advicor® group (estimated to be 15.5 to 19%) compared to the statin groups (estimated to be 8.5% for atorvastatin and 2.6% for simvastatin). Dizziness and flushing were reported more often with Advicor® than the statins.

Additional evidence on potential harms related to Advicor® from broader populations of patients was found in 2 open-label, single arm studies of Advicor® (Table 3).^{31,32} The discontinuation rates and adverse event patterns were very similar to those seen in the trials, with some small differences.

Table 3. Uncontrolled, open-label studies of Advicor®

Study, N, FU, interventions	Patient population lipid parameters	Baseline characteristics
Rubenfire 2004 N = 4499; 12 weeks Advicor® 1000/40mg Fair quality	Hyperlipidemia requiring pharmacotherapy according to NCEP III guidelines	Mean age 57 LDL 135 HDL 44 Triglycerides 243 Total Cholesterol 225
Kashyap 2002 N = 814; 52 weeks Advicor® 2000/40mg, down-titration allowed Fair quality	Type IIA or Type IIB hyperlipidemia LDL-C ≥ 130 mg/dL with CAD or type 2 diabetes ≥ 160 mg/dL without CAD or type 2 diabetes but with ≥ 2 additional risk factors for CAD ≥ 190 mg/dL with and < 2 CAD risk factors	Mean age 59 LDL 195 HDL 48 Triglycerides 199 Total Cholesterol 283 CAD 37% ≥ 2 CHD risk factors 65%

Withdrawal from study occurred in 23% of the Rubenfire study and in 30% of the Kashyap study,^{31,32} and discontinuation due to adverse events was reported in 16% and 23%, respectively. In both studies, flushing was the most common reason for discontinuation and the most commonly reported adverse event followed by gastrointestinal adverse effects. In neither study, nor the 2 trials above, was a case of myalgia reported, although the definitions differed across the studies somewhat. Rates of discontinuation due to elevated CPK enzymes were 0.86% in the shorter study,³¹ and 0.04% in the longer study compared to none in the other trials.³² The rate of withdrawal due to treatment emergent elevations of liver transaminases was 0.37% and 0.04% in the shorter and longer studies, respectively. This compares to a rate of 0.32% in the

ADVOCATE study²³ and was not reported in the other trial.²² The rate of elevations > 3 times the normal limit of either AST or ALT was 0.25% and 0.5% in these 2 open-label studies, compared to 2.4%²² and 0%²³ in the trials.

Vytorin®

In a single fair quality study which compared the component drugs as monotherapy to Vytorin®; discontinuation from the study due to adverse events slightly was more common, but not statistically significantly different, among the simvastatin-exposed groups. This study was identified in the FDA Medical review documents²⁴ In the three studies comparing Vytorin® vs. atorvastatin no patient had CPK elevations or myopathy. However, in one study²⁵ patients with ALT elevations and combined ALT or AST elevations was statistically significantly higher in the combined atorvastatin groups compared to the combined Vytorin® groups (10% vs. 0%; p=0.002 and 11% vs. 1%; p=0.006, respectively). In the study of Vytorin® vs. rosuvastatin discontinuations due to adverse events were equal between Vytorin® and rosuvastatin groups (2.2% each), analysis by dose not presented. Elevations in serum transaminases, elevations in CPK, and cases of myopathy were not found to be different between the groups. In the observational study (Hildemann) small proportions of patients reported adverse events, with the most serious being related to statin therapy (Table 4 below). These data reflect a broader patient population, specifically patients with CHD or type 2 diabetes, co-morbid with hypercholesterolemia despite statin monotherapy. However, because it is a before-after study design, the strength of this evidence is lower because it is open to more biases and confounding.

Table 4. Results after switch from statin monotherapy to Vytorin®⁶⁴

Hildemann 2007	LDLc reduction	HDLc elevation	Adverse event rate	Myalgia or CK elevations
n = 19,194 CHD n = 19,848 type 2 diabetes Mean 13 weeks follow-up	CHD: -27.9% DM: -27.3%	CHD: +9.3% DM: +10.1%	CHD: 0.3% DM: 0.16%	CHD: 0.12% DM: 0.08%*

*1 serious case

KQ 6 Consensus Statements:

1. There was no benefit in reduction of statin related adverse events for Advicor® or Vytorin®.
2. The addition of niacin to the therapeutic regimen for Advicor® caused an increase in withdrawals due to flushing.

KQ 7 What is the evidence that there is a correlation between adherence (in general) and long term health outcomes in a Type 2 diabetic or hyperlipidemic population?

7a. What is the evidence that improved adherence after changing from 2 tablets per dose to 1 tablet per dose results in improved long term health outcomes in a Type 2 diabetic or hyperlipidemic population?

7b. What is the evidence that improved adherence improves long term health outcomes in a Type 2 diabetic or hyperlipidemic population with complicated drug regimens (e.g. > 3 drugs in regimen)?

No evidence was found for long term health outcomes for any FDCP for hyperlipidemia.

KQ 7 Consensus Statements:

1. No evidence was found for long term health outcomes for any FDCP for hyperlipidemia.

KQ 8 . What is the evidence that there is a correlation between adherence (in general) and HbA_{1c} in a Type 2 diabetic population and between adherence (in general) and improvement in serum lipids in patients with hyperlipidemia?

8a. What is the evidence that improved adherence after changing from 2 tablets once daily to 1 tablet once daily results in improved HbA_{1c} in a Type 2 diabetic population or serum lipids in patients with hyperlipidemia?

8b. What is the evidence that improved adherence improves HbA_{1c} in a Type 2 diabetic population or serum lipids in patients with hyperlipidemia with complicated drug regimens (e.g. > 3 drugs in regimen)?

We identified a single fair quality study (n=653) assessing the link between adherence to antihyperlipidemic drug treatments and health outcomes.³³ In particular, this study assessed the relationship between adherence to statin therapy and attainment of LDLc goals among diabetics. Overall, the mean MPR (medication possession rate) was 70%, although the rates were higher among men (75%) than women (66%). This study found that the choice of statin had a statistically significant impact on achieving LDLc goal (with atorvastatin being significantly more likely), but not on adherence. Unfortunately, the study did not examine other aspects of the patient's drug regimen to assess impact of complicated versus simple therapeutic regimens. In fact, other than stratifying some data by gender, the study does not control for potential confounding factors. Also, this study assesses only statin use, primarily given once daily. As such, the study sheds only minimal light on the question of improved adherence using fewer administrations per day, such as a FDCP.

KQ 8 Consensus for Hyperlipidemia:

1. No evidence was found that there is a correlation between adherence (in general) and improvement in serum lipids in patients with hyperlipidemia.

KQ 9 What is the evidence that adherence, short-term outcomes, long-term health outcomes or adverse events differ based on the characteristics of patients with type 2 diabetes or hyperlipidemia taking a fixed-dose combination product?

9a. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on the patients' age (older versus younger), gender, or race/ethnicity?

9b. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on the complexity of the overall drug regimen (e.g., multiple drugs per day, multiple times per day)?

9c. What is the evidence that included outcomes are different when taking a combination drug product compared to the 2 individual drugs based on comorbidities (e.g. renal dysfunction, cardiovascular disease, depression) or variations in baseline HbA_{1c} or serum lipids?

Advicor®

No comparative evidence in subgroups was found for Advicor® versus co-administration of the 2 drugs, although one of the trials found that changes in lipid parameters with niacin-containing regimens tended to be greater in women and that combination regimens produced the greatest lipid changes in patients > 65 years compared to monotherapies.²¹ One open-label, uncontrolled study reported geographic and medical specialty differences, with those living in the southeast US and those under the care of an endocrinologist having the lowest compliance and the highest adverse event rates.³¹

Vytorin®

Gender

Compared to rosuvastatin, Vytorin® had a larger effect on men than women in the study by Catapano.³⁴ The difference in the mean change in LDLc was somewhat larger in men than women (-5.7% vs. -3.2%), although both were statistically significant compared to baseline (p<0.001). The interaction between drug and gender (using ANOVA) was statistically significant, p = 0.005.

Comorbidity

Data from the Goldberg study of diabetic patients (Vytorin® vs. atorvastatin),²⁷ the Hildemann study of patients with CHD or type 2 diabetes as well as other co-morbidities (Vytorin® only),²⁹ and subgroup analysis from the Bays study (Vytorin® vs. simvastatin)³⁵ indicate that Vytorin® is effective in reducing LDLc, total cholesterol, and triglycerides in these subgroups, similar to the pattern seen in the overall study populations. These studies do not provide evidence of a higher rate of adverse events among the groups compared to the narrower trial populations.

In the study of rosuvastatin monotherapy compared to Vytorin®, similar patterns of greater LDLc lowering with Vytorin® were found in various comorbidity groups (CHD, ≥ or < 2 risk factors for CHD, type 2 diabetes, metabolic syndrome =/- diabetes,

baseline LDLc).²⁸ In all of these groups the difference in the mean change in LDLc favored Vytorin®, with the difference being statistically significant (P=0.001). ANOVA did not reveal statistically significant relationships between these covariates and the difference in mean change in LDLc.

The Hildemann study did show additional reductions in LDLc, total cholesterol, and triglycerides and elevation in HDLc when switching to a 2 drug regimen from low to moderate dose statin therapy (depending on specific drug).

KQ 9 Consensus statements for Hyperlipidemia:

1. There is very limited evidence (n=237, duration=28weeks) indicating changes in lipid parameters with niacin-containing regimens (Advicor®) tended to be greater in women and that combination regimens produced the greatest lipid changes in patients > 65 years compared to monotherapy.

Conclusions:

1. Limitations of the Study:
 - a. There were no studies that evaluated long-term health outcomes for any available FDCP.
 - b. There were no RCTs that compared any FDCP and co-administration of their respective components.
2. The addition of a second, non-statin drug did not appear to reduce the incidence of statin-related AEs compared to monotherapy.
3. Evidence for FDCP's in subpopulations is limited and inconclusive.

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