Drug Class Review
on
Fixed Dose Combination Drug Products for the Treatment of Type 2 Diabetes and Hyperlipidemia

Final Report
Evidence Tables

October 2007

The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports

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Note: The medical literature related to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). The Drug Effectiveness Review Project governance group elected to archive this report. It has been superseded by Newer Diabetes Medications, TZDs and Combinations report. Please see timeline for details on the date of its release.

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Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Goldstein 2003 US	ACT 108 outpatient clinics	Patients with type 2 DM and inadequate blood glucose control (HbA ≥7.5% and ≤12.0%) despite monotherapy with at least half the maximum labeled daily dose of a sulphonylurea. Inclusion criteria at screening included confirmed type 2 DM of >3 months' duration, a fasting plasma glucose (FPG) level that was <300 mg/dL, an HbA level ≥7.5% and ≤12.0%, a body mass index (BMI) ≥25 kg/m² and ≤40 kg/m², the ability to give written informed consent, and the willingness and ability to perform self-moitoring of blood glucose.	Included symptomatic DM (marked polyuria and polydipsia or >10.0% weight loss); significant renal, hepatic, or cardiovascular disease; administration of antihyperglycemic agents other than sulfonylureas in the 8 weeks preceding screening; and a history of diabetic ketoacidosis, hyperosmolar nonketotic coma, or long-term insulin therapy.	glipizide/metformin 5/500mg up to 20/2000mg

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Goldstein 2003 US	glipizide 30mg (no titration) metformin 500mg up to 2000mg	2 wk glipizide 15mg run-in; DC sulfonylurea monotherapy 8wk DC antihyperglycemic agents other than sulfonylureas	NR	Blood measures (primary endpoint HbA1c) at 18 wks	Total: 56.2 yrs (SD 10.1) 61.5% male 70.0% white G/M group: 54.6 yrs (SD 11.3) 58.6% male 72.4% white G group: 57.4 yrs (SD 9.2) 64.3% male 71.4% white M group: 56.6 yrs (SD 9.7) 61.8% male 65.8% white

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Goldstein 2003 US	Duration of diabetes: Total 6.5 yrs (SD 4.9) G/M 5.9 yrs (SD 5.3) G 6.5 yrs (SD 4.4) M 7.3 yrs (SD 4.9) BMI Total 31.3 (SD 4.7) G/M 31.7 (SD 4.9) G 30.6 (SD 4.8) M 31.3 (SD 4.7)	NR/298/247	69/NR/246 (? unclear; all pts who received at least 1 dose included in analysis, one pt described as being randomized but not receiving treatment)	Primary outcome: change in HbA1c % HbA1c G/M vs G vs M (SE) 7.4 (0.1) vs 8.5 (0.1) vs 8.4 (0.1) % Mean change from baseline G/M vs G vs M -1.3 vs -0.4 vs -0.2 Mean diff HbA1c: G/M vs G -1.06 (SE 0.15; p<0.001) G/M vs M -0.98 (SE 0.15; p<0.001) Secondary outcomes: 18 wks FPG mean change (data interpolated from graph) G/M vs G vs M -30 mg/dl vs 6 mg/dl vs 5/mg/dl G/M vs G: p<0.001; G/M vs M: p=0.002 Body weight change G/M vs G vs M -0.3kg vs -0.4kg vs -2.7kg (M vs G/M - p<0.001)	Medical review of clinical AEs or lab abnormalities by blinded assessor

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Goldstein 2003 US	No deaths, treatment-related serious AEs or cases of lactic acidosis Withdrawals due to AEs G/M vs G vs M 12.6% vs 3.6% vs 5.3% Symptomatic hypoglycemia G/M vs G vs M 12.6% vs 0(NR) vs 1.3% Specific AEs G/M (n=87) vs G (n=84) vs M (n=75) Any AE 63.2% vs 67.9% vs 73.3% Diarrhea 18.4% vs 13.1% vs 17.3% Headache 12.6% vs 6.0% vs 5.3% (p=NR) Upper respiratory infection 10.3% vs 13.1% vs 10.7% Musculoskeletal pain 8.0% vs 7.1% vs 6.7% Nausea/vomiting 8.0% vs 6.0% vs 8.0% Abdominal pain 5.7% vs 8.3% vs 6.7%	69/18		

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Marre 2002 France, Belgium, The Netherlands, Denmark and Portugal	ACT multicenter	Patients were eligible for the study if their fasting plasma glucose (FPG) was ≥7 mmol/L (126 mg/dl) despite treatment with monotherapy with metformin at a dose of ≥850 mg b.i.d. or ≥500 mg t.i.d., diet and exercise for the 2-month period immediately before enrollment. Additional inclusion criteria included age >18 years and body mass index (BMI) <40 kg/m². Premenopausal female patients were included subject to reliable contraception, a negative pregnancy test, or having undergone documented surgical sterilization.	Patients were excluded for renal disease or dysfunction (serum creatinine >127µmol/L) of if they suffered from hypoxic states, such as cardiovascular collapse, acute heart failure, myocardial infarction, or any condition characterized by hypoxaemia (e.g. any severe respiratory disturbance or infection). Further exclusion criteria were hepatic dysfunction (serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) above twice the upper normal level), history of metabolic acidosis including diabetic ketoacidosis, known hypersensitivity to metformin or glibenclamide, a history of cancer or (of?) any type (excepting basocellular cancer that had been treated successfully at least 2 years prior to the study), pregnancy or lactation, excessive alcohol intake, major disease problems, drug addiction, or concomitant treatment with other anti-diabetic drugs.	glibenclamide/metformin 2.5/500mg or 5/500mg up to 4x/day

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Marre 2002 France, Belgium, The Netherlands, Denmark and Portugal	glibenclamide 5mg up to 4x/day metformin 500mg up to 4x/day	2 wk run-in stabilized metformin	NR	Blood measures (primary endpoint HbA1c) at 16wks	G/M 2.5/500 group (SD) 58.0 yrs (13.0) 50% male race NR G/M 5/500 group (SD) 60.7 yrs (11.2) 54% male race NR G group 58.7 yrs (11.4) 55% male race NR M group (SD) 57.5 yrs (11.5) 60% male race NR

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Marre 2002 France, Belgium, The Netherlands, Denmark and Portugal	Duration of diabetes (SD) G/M 2.5/500 5.9 yrs (5.4) G/M 5/500 6.7yrs (7.0) G 6.6 yrs (6.3) M 5.4 yrs (4.9) BMI (SD) G/M 2.5/500 30.1 (4.6) G/M 5/500 29.7 (4.2) G 29.3 (4.2) M 29.9 (4.7)	NR/NR/411	55/NR/unclear, reported as ITT	Primary outcome: 16 wks Mean change from baseline HbA1c G/M 2.5/500 vs G/M 5/500 vs G vs M -1.2% vs -0.9% vs -0.3% vs -0.2% FPG mean change from baseline G/M 2.5/500 vs G/M 5/500 vs G vs M -2.6 mmol/L vs -2.3 mmol/L vs -0.7 mmol/L vs -0.6 mmol/L	Identified and documented at each visit and evaluated by investigator

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Marre 2002 France, Belgium, The Netherlands, Denmark and Portugal	G/M 2.5/500 vs G/M 5/500 vs G vs M Withdrawals due to AEs: 3% vs 7% vs 4% vs 5% Any AE 38% vs 52% vs 43% vs 40% Serious AEs 4% vs 4% vs 8% vs 3% Specific AEs: G/M 2.5/500 vs G/M 5/500 vs G vs M Hypoglycemia 11% vs 14% vs 8% vs 1% GI symptoms 6.9% vs 18.4% vs 11.7% vs 14.4%	55/19		

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Blonde 2002	ACT NR	Men and women with type 2 diabetes who had failed to achieve glycemic control despite diet, exercise and sulfonylurea therapy at a minimum of half the maximal recommended dose. Inclusion requirements included age 30-75 years, presence of established type 2 diabetes, fasting serum C-peptide concentration ≥0.5 ng/mL and HbA ≥7.4% at screening, and FPG concentration ≥7.0 mmol/L (≥126 mg/dl) at screening and week 2 of the lead-in period. Patients were also required to have normal liver function and a body mass index (BMI) of ≤40 kg/m².	Symptomatic type 2 diabetes mellitus (i.e. >10% weight loss accompanied by marked polyuria and polydipsia), FPG >16.7 mmol/L (>300 mg/dl), liver disease, renal disease, renal impairment, heart failure, left ventricular ejection fraction ≤45%, history of drug or alcohol abuse, history of diabetic ketoacidosis, hyperglycaemic hyperosmolar non-ketotic coma, known hypersensitivity to glyburide or metformin, pregnancy, breastfeeding or any medical condition that would render the patient unable to complete the study or pose a significant risk to the patient. Use of any antihyperglycaemic agents other than sulphonylureas or troglitazone (the only thiazolidinedione available at the time of this study) was to be discontinued at least 4 weeks before study entry. Use of troglitazone had to be discontinued at least 8 weeks before enrollment.	glyburide/metformin 2.5/500mg or 5/500mg (titration to 20/2000mg allowed)

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Blonde 2002	glyburide 10mg metformin 500mg (titration to 2000mg allowed)	2 wk run-in glyburide 5mg bid 1st wk followed by 10mg bid 2nd wk 4wk DC any antihyperglycemic agents other than sulphonylureas 8wk DC troglitazone	NR (presumably sulphonylureas)	HbA1c measured at baseline, day 15, wks 8, 12, 16 (final timepoint)	G/M 2.5/500 group: 55.4 (SD 10.4) yrs 55.6% male 70% white G/M 5/500mg group 55.6 (SD 10.7) yrs 63.6% male 67.9% white G group: 55.8 (SD 8.9) yrs 57.3% male 66.5% white M group: 57.6 (SD 9.4) yrs 62.1% male 69.3% white

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Blonde 2002	DM duration: G/M 2.5/500 - 7.36 (SD 5.7) yrs G/M 5/500 - 6.97(SD 6.0) yrs G - 7.01 (SD 5.8) yrs M - 8.18 (SD 6.5) yrs BMI: G/M 2.5/500 - 30.7 (SD 4.8) G/M 5/500 - 30.6 (SD 4.9) G - 30.3 (SD 4.4) M - 30.6 (SD 4.4)	NR/717/639	118/unclear, reported as 2.3% of patients/ unclear, all randomized pts included in safety analysis	Primary outcome: 16 wks HbA1c concentration - mean diff G/M groups vs G or M groups: 1.7% vs 1.9% (p<0.001) Secondary outcomes significantly lower for G/M groups vs G or M at 16 wks FPG concentrations: p<0.0001 PPG concentrations: p<0.0001 No SS differences in lipid values Mean weight increase of <1kg in G mono and G/M groups; mean decrease of 2-3kg M group	Any illness, sign, symptom (unclear if patient or physician assessed); also lab evaluated

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Blonde 2002	Withdrawals due to AEs: G/M groups vs G vs M - 3.4% vs 3.0% vs 5.2% Serious AEs - 20 reported, no further data on intervention or nature of AE Deaths - 4 deaths reported (1 G, 1 M, 2 G/M 2.5/500mg) 1 considered to be possibly related to intervention (MI in G/M 2.5/500 group) Specific AEs: G/M 2.5/500mg vs G/M 5/500mg vs G vs M Diarrhea - 23.1% vs 16.7% vs 6.1% vs 24.8% Musculoskeletal pain - 8.8% vs 9.9% vs 9.8% vs 7.2% Upper resp infection - 11.3% vs 6.8% vs 9.1% vs 8.5% Nausea/vomiting - 10.0% vs 6.8% vs 5.5% vs 12.4% Headache - 6.9% vs 6.2% vs 8.5% vs 6.5% Abdominal pain - 7.5% vs 4.3% vs 2.4% vs 8.5% Fatigue - 4.4% vs 5.6% vs 5.5% vs 5.9% Dyspepsia/heartburn - 5.0% vs 3.7% vs 4.6% vs 3.0%	118/24		

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Bruce 2006	ACT NR	Aged 20-75 years, with a diagnosis of type 2 diabetes mellitus within the previous 5 years, and HbA >6.7% but ≤9.5% on diet and exercise. Subjects were either drug naïve or did not receive antihyperglycaemic therapy during the 8 weeks prior to screening. Women of childbearing potential were required to practice a reliable method of contraception.	Patients with a body mass index (BMI) >40 kg/m², symptomatic diabetes (marked polyuria and polydipsia with >10% weight loss within 3 months prior to screening), history of chronic insulin use, renal dysfunction [serum creatinine ≥124 µmol/L (1.5 mg/dl) for men and ≥133 µmol/L (1.4 mg/dl) for women], morbid cardiovascular events within 6 months of screening, or other significant renal, hepatic, cardiac or psychiatric disease.	metformin/glibenclamide 250/1.25mg QD additional doses up to 4/day permitted if indicated by self-monitored blood glucose
Erle 1999 Italy	crossover, ACT single-center hospital clinic	Patients with type 2 diabetes	Patients were excluded if contraindications to oral antidiabetic drugs were present.	glyburide/metformin dose ranging 5-10mg/800-1600mg

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Bruce 2006	metformin 500mg glienclamide 2.5mg additional doses up to 4/day permitted if indicated by self-monitored blood glucose	1 wk run-in eucaloric weight-maintaining diet 8wk DC antihyperglycemic therapy	NR	NR	M/G group: 49 (SD 12) yrs 39% male race NR M group: 48 (SD 9) yrs 47% male race NR G group: 51 (SD 8) yrs 29% male race NR
Erle 1999 Italy	glyburide 5-15mg	30 diet therapy run-in 2 wks oral hypoglycemics DC	NR	method NR/assessments after 1, 2, and 3 months followed by 2 wk washout and crossover	60 yrs (SD 7) 52.5% male race NR

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Bruce 2006	Mean BMI: G/M 33 (SD 5) M 33(SD 6) G 36 (SD 4) Mean diabetes duration: G/M 2.6 yrs (SD 1.3) M 2.7 yrs (SD 2.2) G 2.4 yrs (SD 1.6)	NR/NR/50	5/1/46 (efficacy analysis; # for safety analysis unclear)	G/M vs G vs M at 20wks (final timepoint) Mean HbA1c 7.0% vs 7.1% vs 7.4% FPG and plasma glucose described as similar in all three groups (figures not provided; data presented in graphical form only)	NR
Erle 1999 Italy	Mean BMI 30.5 Mean weight 86kg Obese 58% Hypertension 50%	NR/NR/40	7/0/33	G/M vs G at 6 mos (final timepoint) HbA1c 6.85 (SD 1.43) vs 7.58 (SD 1.69); p<0.01 Body weight 84.8 kg (13.6) vs 85.2 kg (SD 13.7) FPG 9.66 (SD 3.11) vs 11.22 (SD 3.33); p<0.05 Postprandial plasma glucose (mmol/L) 230 (SD 77) vs 258 (SD 63); p<0.05 no major effect on total cholesterol and triglycerides	NR

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Bruce 2006	AE results appear to be based on all randomized patients - only percentages presented for most AEs G/M vs G vs M Withdrawals due to AEs - 1 in G group; none in other groups Serious AEs - 1 in G/M group (CHD unrelated to intervention) Any AE - 44% vs 65% vs 87% Hypoglycemic events - 11% vs 29% vs 0 (? no data provided) GI - 17% vs 24% vs 53%	5/1		Multiple other results presented in paper; these appeared to be pharmacokinetic rather than clinical outcomes
Erle 1999 Italy	No reports of AEs No significant changes reported for the following parameters: urea, creatinine, electrolytes, bilirubin, alkaline phosphatase, aspartate dehydrogenase, red and white blood cell counts, ECG, fundus examination	7/none		

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Garber 2003 US	ACT multicenter	Confirmed type 2 diabetes mellitus, screening fasting plasma glucose (FPG) concentration ≤13.3 mmol/l (240 mg/dl), HbA between 7% and 11%, normal renal and liver function and body mass index (b.m.i.) < 38 kg/m².	Marked polyuria and polydipsia with greater than 10% weight loss, current therapy with antihyperglycaemic agents or previous use in the 8 weeks preceding study entry, or a history of diabetic ketoacidosis, hyperosmolar non-ketotic coma or insulin therapy.	glyburide/metformin 1.25/500mg up to 5/1000mg

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Garber 2003 US	glyburide 2.5mg up to 10mg metformin 500mg up to 2000mg	2wk placebo run-in 8wk antihyperglycemics	Medications known to affect carbohydrate mechanism (corticosteroids, endocrine replacement therapy, oral contraceptives, diuretics, lipid lowering agents	Physical exam, lab measures/16 wks	G/M group: 55.6 yrs (SD 11.2) 44.4% male 77.2% white G group: 55.3 yrs (SD 12.2) 43.7% male 81.5% white M group: 54.7 yrs (SD 11.8) 43.3% male 80.5% white

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Garber 2003 US	Diabetes duration G/M 3.0 yrs (SD 3.0) G 3.0 yrs (SD 2.6) M 2.6 yrs (SD 2.3) BMI G/M 31.4 (SD 4.6) G 31.1 (SD 4.3) M 31.4 (SD 4.0)	NR/513/486	57/NR/485 (safety analysis; unclear number efficacy analysis - all pts with baseline data and at least one post-baseline assessment included)	G/M vs M vs G A1C % change from baseline -2.27% vs -1.53% vs -1.90% (G/M vs M: p<0.0001; G/M vs G: p=0.0003) FPG change from baseline (mg/dl) -64.2 vs -43.8 vs -52.8 (G/M vs M: p<0.001; G/M vs G: p=0.007) Body weight mean change 1.6 kg vs -1.1kg vs 2.0kg (G/M vs M: p<0.0001; G/M vs G: NSD)	NR

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Garber 2003 US	G/M vs M vs G % of pts reporting any AE: 79% vs 73% vs 76% Serious AEs - 14 pts, none related to intervention (results not stratified by group) Deaths - 2 in G/M group, not related to intervention Specific AEs G/m vs M vs G Diarrhea 7.6% vs 18.3% vs 5.3% Upper respiratory infection 8.8% vs 11.0% vs 9.9% Nausea/vomiting 4.7% vs 10.4% vs 6.6% Musculoskeletal pain 6.5% vs 9.8% vs 8.6% Headache 9.4% vs 4.9% vs 5.3% Abdominal pain 4.1% vs 6.1% vs 4.0%	57/17		

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Garber 2002 US	glyburide 2.5mg up to 4x/day metformin 500mg up to 4x/day placebo	2 wk placebo run-in 8 wk antihyperglycemic agents	NR	Blood measures (primary endpoint HbA1c) at 20 wks	G/M 1.25/250mg (SD) 56.9 yrs (12.0) 57.6% male 74.1 % white G/M 2.5/500mg (SD) 58.1 yrs (9.8) 58.2% male 79.4% whilte G (SD) 56.5 yrs (10.5) 50.9% male 78.3% white M (SD) 56.0 yrs (11.0) 57.8% male 80.7% white placebo (SD) 55.4 yrs (10.5) 47.2% male 75.8% white

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Garber 2002 US	Duration of diabetes: G/M 1.25/250mg 3.52 yrs G/M 2.5/500mg 3.30 yrs G 2.81 yrs M 2.98 yrs placebo 2.76 yrs Mean BMI G/M 2.5/250mg 30.1 G/M 5/500mg 29.6 G 30.3 M 30.4 placebo 30.2	847/NR/806	273/NR/800	Primary endpoint - mean change in HbA1c G/M 1.25/250 vs G/M 2.5/500 vs G vs M vs placebo -1.48 vs -1.53 vs -1.24 vs -1.03 vs -0.21 (G/M 1.25/250 vs G: p<0.016, vs M: <0.001; G/M 2.5/500 vs G: p<0.004, vs M: <0.001) Secondary endpoints - change in body weight G/M 1.25/250 vs G/M 2.5/500 vs G vs M vs placebo 1.4kg vs 1.9kg vs 1.7kg vs -0.6kg vs -0.7kg (G/M groups vs placebo; p=reported as SS in text but data not provided)	Medical review of clinical AEs, lab results and physical exams

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Garber 2002 US	Withdrawals due to AEs: G/M 1.25/250 vs G/M 2.5/500 vs G vs M vs placebo 3.8% vs 11.1% vs 6.9% vs 6.3% vs 1.9% Specific AEs: G/M 1.25/250 vs G/M 2.5/500 vs G vs M vs placebo Diarrhea 7.6% vs 12.3% vs 4.4% vs 15.1% vs 3.1% Nausea/vomiting 1.9% vs 4.9% vs 0.6% vs 6.3% vs 4.3% Abdominal pain 5.7% vs 5.6% vs 3.1% vs 5.0% vs 1.9% Dyspepsia 2.5% vs 3.1% vs 2.5% vs 5.0% vs 3.7% No deaths in any active treatment groups No cases of lactic acidosis Study-related AEs in 1 G/M 1.25/250 pt (angina) and 1 G pt (chest pain)	273/48		

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Unpublished Study (#138-50) (source: FDA)	ACT NR	Either drug naïve or have have discontinued antihyperglycemic therapy for at least 8 weeks, or thiazolidinedione therapy for at least 12 weeks, prior to screening. On diet and exercise, subjects must have had inadequate glycemic control with HbA1c > 7.5% to ≤ 12.0% but FPG < 300mg/dL	NR	metformin/glipizide 250/1.25mg up to 1000/5mg Mean dose: glipizide = 9.0mg metformin = 1209.9mg

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Garber 2002 US	ACT 158 centers	Eligible patients were 20-78 yrs old, had a diagnosis of type 2 diabetes for at least 3 months but no longer than 10 yrs, had a body mass index of 23-40 kg/m², gave informed consent, and were able to perform self-monitoring or blood glucose concentrations. Patients had not been previously treated with glucose-lowering agents or had been free from antihyperglycemic therapy for at least 8 wks before screening. Medications known to affect carbohydrate metabolism (e.g. corticosteroids, endocrine replacement therapy, oral contraceptives, diuretics, and lipid-lowering agents) were permitted concomitantly if patients were maintained on stable doses.	Marked polyuria and polydipsia with greater than 10% weight loss; administration of antihyperglycemic agents within 8 wks before screening; a history of chronic insulin therapy, diabetic ketoacidosis, or hyperosmolar nonketotic coma; significant abnormal renal function defined by a serum creatinine concentration greater than or equal to 1.5 mg/dl (133 µmol/L) for men and greater than or equal to 1.4 mg/dl (124 µmol/L) for women; significant abnormal liver function defined as aspartate aminotransferase or alanine aminotransferase levels greater than or equal to twice the upper limit of normal or total serum bilirubin concentration greater than or equal to twice the upper limit of normal; alcohol and/or substance abuse within the year before screening; and cardiac or cerebral events within 6 months before screening.	glyburide/metformin 1.25/250mg or 2.5/500mg up to 4x/day

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Unpublished Study (#138-50) (source: FDA)	metformin/glipizide 250/2.5mg up to 1000/10mg metformin/glipizide 500/2.5mg up to 2000mg/10mg metformin 500mg up to 2000mg glipizide 5mg up to 20mg	8 wk washout antihyperlipidemic therapy 12 wk washout TZDs 2 wk run-in placebo to test compliance	NR	Blood measures (primary endpoint change in HbA1c) wks 2, 4, 6, 9, 12, 18, 24	Total: 56 yrs 43% male 95% white

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Unpublished Study (#138-50) (source: FDA)	Duration of diabetes: 3.3 yrs Mean BMI: 30.8 Class naïve: 58% Mean HbA1c 9.1%	1631/919/868	131/8/841	Primary outcome - HbA1c Unadjusted mean change from baseline: M/G 250/1.25mg -1.83 vs M/G 250/2.5mg -2.13 vs M/G 500/2.5mg -2.15 vs M -1.49 vs G -1.81 SS differences b/t M/G doses 250/2.5mg and 500/2.5mg vs M monotherapy (p<0.001) and G monotherapy (p<0.001) Proportion of patients with final HbA1c <7.0%: M/G 250/1.25mg 54.3% vs M/G 250/2.5mg 59.6% vs M/G 500/2.5mg 57.1% vs M 35.1% vs 43.5% Secondary outcome - Cholesterol Total cholesterol mean change from baseline (SE): M/G 250/1.25mg -2.6 (2.2) vs M/G 250/2.5mg -5.8 (2.5) vs M/G 500/2.5mg -6.0 (2.3) vs M -10.8 (3.0) vs G -4.1 (2.4) M/G doses vs M: p<0.001; M/G 500/2.5 vs G: p=0.013 (other M/G doses: NSD vs G) Mean change in LDL (SD; CI): M/G 250/1.25mg -9.6 (1.8; -13.2 to -5.9) vs M/G 250/2.5mg -12.0 (2.0; -15.9 to -8.1) vs M/G 500/2.5mg -12.1 (2.0; -16.1 to -8.1) vs M -11.9 (2.2; -16.2 to -7.6) vs G -6.6 (2.0; -10.6 to -2.7) Mean change in HDL (SD; CI): M/G 250/1.25mg 7.8 (0.6; 6.7 to 8.9) vs M/G 250/2.5mg 7.0 (0.6; 5.8 to 8.3) vs M/G 500/2.5mg 7.7 (0.6; 6.5 to 8.9) vs M 7.2 (0.6; 5.9 to 8.5) vs G 6.1 (0.7; 4.7 to 7.4)	Method NR

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Unpublished Study (#138-50) (source: FDA)	Withdrawals due to AEs: M/G 250/1.25mg 6/176 (3.4%) vs M/G 250/2.5mg 7/172 (4.1%) vs M/G 500/2.5mg 11/173 (6.4%) vs M 11/177 (6.2%) vs G 6/170 (3.5%)	131/41		

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Rosenstock 2006 US, Canada, Mexico, Australia, Korea, Brazil, New Zealand	ACT multicenter	Adults aged 18–70 years with type 2 diabetes and inadequate glycaemic control [A1c > 7.5% and ≤11% with fasting plasma glucose (FPG) ≤15 mmol/l1] on diet and exercise alone were screened over a 2-week period. Patients were not permitted to take more than a short-term course of antidiabetic medication (≤15 days) for 12 weeks prior to screening. Any patient who received a short-term course of antidiabetic medication or insulin was required to complete a 2-week washout period prior to screening assessments	Clinically significant renal, hepatic or haematological disease; uncontrolled hypertension while on antihypertensive treatment; intermittent or chronic use of oral or intravenous corticosteroids; presence of unstable or severe angina, coronary insufficiency, or congestive heart failure requiring pharmacological treatment; any clinically significant abnormality judged by the investigator to preclude inclusion in the trial; use of an investigational agent within 30 days of the study (or five half-lives of the investigational drug if longer than 30 days); prior history of severe oedema or medically serious fluid-related event associated with any TZD; or presence of acute or chronic metabolic acidosis or history of diabetic ketoacidosis	RSG/MET 2/500mg up to 8/2000mg Mean dose: RSG = 7.5mg MET = 1822mg

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Rosenstock 2006 US, Canada, Mexico, Australia, Korea, Brazil, New Zealand	MET 500mg up to 2000mg RSG 4mg up to 8mg	2 wk washout short-term antidiabetic medication or insulin 12 wk washout long-term antidiabetic medication	Lipid lowering agents at stable doses; dose adjustment allowed	Blood measures (primary endpoint change in HbA1c) every 4 wks	Total: 51 yrs 57% male 57% white RSG/MET group: 50.1 yrs (SD 10.7) 57% male 54% white MET group: 51.5 yrs (SD 10.4) 56% male 58% white RSG group: 50.6 yrs (SD 10.26) 58% male 59% white

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Rosenstock 2006 US, Canada, Mexico, Australia, Korea, Brazil, New Zealand	Duration of diabetes (mean): 2.6 yrs (SD 3.1) BMI: 32.8 (SD 7.3)	NR/NR/468	72/23/unclear* *for efficacy, the number analyzed is reported as being all pts who received at least one dose and had at least one valid on-therapy observation; for safety, all pts who received at least one dose were included in analysis	Primary outcome - change in A1c Mean reduction: R 1.6% vs M 1.8% vs R/M 2.3% (R vs R/M: p<0.0001; M vs R/M: p=0.0008) Proportion of pts achieving A1c <7%: R 58.1% vs M 57.3% vs R/M 77.0% (R vs R/M: p<0.0001; M vs R/M: p< 0.001) Secondary outcomes - Mean decrease in FPG: R 2.6 mmol/L vs M 2.8 mmol/L vs R/M 4.1 mmol/L (R vs R/M: p<0.0001; M vs R/M: p<0.0001) Proportion of pts reaching FPG <7.0 mmol/L: R 38.1% vs M 36.7% vs R/M 63.2% (R vs R/M: p <0.0001; M vs R/M: p<0.0001) Mean decrease in fasting insulin: R -35.5% vs M -24.0% vs R/M -45.9% (R vs R/M: p=NSD; M vs R/M: p=0.01) Total cholesterol % change from baseline: R 5.3% (CI 3.5-7.2) vs M -9% (CI -10.5--7.5) vs R/M -2.2% (CI -3.8--0.5); R vs R/M: p=0.0006; M vs R/M: p=0.009 HDL % change from baseline: R 3.1% (CI 1.4-4.7) vs M 0.0% (CI -1.3-1.3) vs R/M 5.8% (CI 4.2-7.3); R vs R/M: p=0.25; M vs R/M: p=0.01 LDL % change from baseline: R 4.5% (CI 0.8-8.4) vs M -10.7% (CI -13.1--8.2) vs R/M -0.2% (CI -2.8-2.4); R vs R/M: p=0.16; M vs R/M: p=0.02 Triglycerides % change from baseline: R -4.8% (CI -8.6--0.9) vs M -15.4% (CI -18.4--12.2) vs R/M -	Method NR

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Rosenstock 2006 US, Canada, Mexico, Australia, Korea, Brazil, New Zealand	Withdrawals due to AEs: R 5/159 (3%) vs M 3/154 (2%) vs R/M 2/155 (1%) Serious AEs: Ischemic heart disease - R 2/159 vs M 2/154 vs R/M 1/155 Angina - M 1/154; none for other interventions MI - R 1/159; none for other interventions Specific AEs: Non-serious edema: R 11/159 (7%) vs M 5/154 (3%) vs R/M 9/155 (6%) Self-reported hypoglycemic symptoms: R 13/159 (8%) vs M 14/154 (9%) vs R/M 19/155 (12%) Nausea/vomiting: R 13/159 (8%) vs M 20/154 (13% vs R/M 25/155 (16%) Diarrhea: R 11/159 (7%) vs M 32/154 (21%) vs R/M 22/155 (14%) Headache: R 16/159 (10%) vs M 18/154 (12%) vs R/M 17/155 (11%) Dyspepsia: R 14/159 (9%) vs 12/154 (8%) vs 15/155 (10%)	72/10		

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Study design and setting	Inclusion criteria	Exclusion Criteria	Fixed dose combination product
Unpublished study (GSK dossier, pgs 9-12) 2007	ACT multicenter	Age 18-75 yrs w/type 2 DM and screening HbA1c of 7.5-12.0%	Unstable or severe angina, known CHF requiring pharmacologic treatment, use of OAD or insulin ≥15 days within 4 mos of study entry. Pts entered into study in European centers excluded for NYHA class I-IV heart failure.	rosiglitazone/glimepiride 4/1mg up to 4/4mg qd (R/G Group A) rosiglitazone/glimepiride 4/1mg up to 8/4mg qd (R/G Group B)

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Unpublished study (GSK dossier, pgs 9-12) 2007	rosiglitazone 4mg up to 8mg qd glimepiride 1mg up to 4mg qd	2 wk screening run-in (not further described) 2 wk washout OAD and insulin (in pts using <15 days)	NR	Blood measures (primary endpoint change in HbA1c) at 28 wks	54 yrs 59% male (532/901) 77% white (694/901)

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Unpublished study (GSK dossier, pgs 9-12) 2007	Duration of diabetes: 3 yrs Mean BMI: 32 Mean baseline HbA1c: 8.97-9.15% Mean FPG: 206.9-214.1 mg/dL	NR/NR/901	NR/NR/varied - HbA1c outcome: n=874 FPG outcome: n=878 AEs: n=894	Primary outcome: change in HbA1c at 28 wks Mean change from baseline R/G Group A vs R/G Group B vs R vs G (HbA1c %) -2.41% vs -2.52% vs -1.75% vs -1.72% (p<0.0001 R/G groups vs R and vs G; total n analyzed: 874/901) Secondary outcome: change in FPG at 28 wks Mean change from baseline R/G Group A vs R/G Group B vs R vs G (mg/dL) -69.5 vs -79.9 vs -56.5 vs -42.2 (p<0.0001 R/G groups vs R and vs G; total n analyzed: 878/901)	Method NR

Evidence Table 1. Diabetes RCT

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Unpublished study (GSK dossier, pgs 9-12) 2007	Total n analyzed for AEs: 894/901 R/G Group A (n=224) vs R/G Group B (n=218) vs R (n=230) vs G (n=222) Pts reporting any AE: 49.1% vs 52.3% vs 50.4% vs 46.4% Hypoglycemia: 29% vs 22.5% vs 5.2% vs 21.6%; text reported no serious AEs or withdrawals due to hypoglycemia Headache: 3.1% vs 6.0% vs 6.1% vs 2.3% Upper RTI: 4.0% vs 3.2% vs 3.9% vs 1.8% Hypertension: 3.1% vs 2.3% vs 5.2% vs 3.6% UTI: 1.8% vs 1.3% vs 0% vs 3.2% Sinusitis: 0.9% vs 1.8% vs 2.2% vs 3.2% Diarrhea 0.9% vs 0.9% vs 3.0% vs 2.7%	NR		

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Goldstein 2003 US	yes	yes	yes	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	yes
Marre 2002 France, Belgium, The Netherlands, Denmark and Portugal	Method NR	Method NR	yes	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating	Number screened/eligible/ enrolled
Goldstein 2003 US	no	no	no; 17 randomized pts not included in analysis	yes, 1 pt	fair	NR/298/247
Marre 2002 France, Belgium, The Netherlands, Denmark and Portugal	no	no	Unclear for efficacy, reported as ITT; yes for safety	no	fair	NR/NR/411

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Exclusion criteria	Run-in/washout	Funding
Goldstein 2003 US	Included symptomatic DM (marked polyuria and polydipsia or >10.0% weight loss); significant renal, hepatic, or cardiovascular disease; administration of antihyperglycemic agents other than sulfonylureas in the 8 weeks preceding screening; and a history of diabetic ketoacidosis, hyperosmolar nonketotic coma, or long-term insulin therapy.	2 wk glipizide 15mg run-in; DC sulfonylurea monotherapy 8wk DC antihyperglycemic agents other than sulfonylureas	NR (Bristol Myers Squibb?)
Marre 2002 France, Belgium, The Netherlands, Denmark and Portugal	Patients were excluded for renal disease or dysfunction (serum creatinine > 127µmol/l) of if they suffered from hypoxic states, such as cardiovascular collapse, acute heart failure, myocardial infarction, or any condition characterized by hypoxaemia (e.g. any severe respiratory disturbance or infection). Further exclusion criteria were hepatic dysfunction (serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) above twice the upper normal level), history of metabolic acidosis including diabetic ketoacidosis, known hypersensitivity to metformin or glibenclamide, a history of cancer of any type (excepting basocellular cancer that had been treated successfully at least 2 years prior to the study), pregnancy or lactation, excessive alcohol intake, major disease problems, drug addiction, or concomitant treatment with other anti-diabetic drugs.	2 wk run-in stabilized metformin	Merck Lipha

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Blonde 2002	Method NR	Method NR	yes	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Bruce 2006	Method NR	Method NR	No, more women in glibenclamide group (71%) vs the metformin (53%) or Glucovance (61%) groups	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Erle 1999 Italy	Method NR	Method NR	no baseline demographic data stratified by intervention provided	yes (minimal)	Unclear, reported as double-blind	Unclear, reported as double-blind	yes

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating	Number screened/eligible/ enrolled
Blonde 2002	no	no	Unclear for efficacy; yes for safety	no	fair	NR/717/639
Bruce 2006	no	no	No; 5 withdrawals (10%) not included in analysis	no	fair	NR/NR/50
Erle 1999 Italy	no	no	no; 7 withdrawals (17.5%) not included in analysis	no	poor	NR/NR/40

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Exclusion criteria	Run-in/washout	Funding
Blonde 2002	Symptomatic type 2 diabetes mellitus (i.e. > 10% weight loss accompanied by marked polyuria and polydipsia), FPG > 16.7 mmol/l (>300 mg/dl), liver disease, renal disease, renal impairment, heart failure, left ventricular ejection fraction ≤ 45%, history of drug or alcohol abuse, history of diabetic ketoacidosis, hyperglycaemic hyperosmolar non-ketotic coma, known hypersensitivity to glyburide or metformin, pregnancy, breastfeeding or any medical condition that would render the patient unable to complete the study or pose a significant risk to the patient. Use of any antihyperglycaemic agents other than sulphonylureas or troglitazone (the only thiazolidinedione available at the time of this study) was to be discontinued at least 4 weeks before study entry. Use of troglitazone had to be discontinued at least 8 weeks before enrolment.	2 wk run-in glyburide 5mg bid 1st wk followed by 10mg bid 2nd wk 4wk DC any antihyperglycemic agents other than sulphonylureas 8wk DC troglitazone	Bristol-Myers Squibb
Bruce 2006	Patients with a body mass index (BMI) >40 kg/m², symptomatic diabetes (marked polyuria and polydipsia with >10% weight loss within 3 months prior to screening), history of chronic insulin use, renal dysfunction [serum creatinine ≥124 µmol/l (1.5 mg/dl) for men and ≥ µmol/l (1.4 mg/dl) for women] morbid cardiovascular events within 6 months of screening, or other significant renal, hepatic, cardiac or psychiatric disease.	1 wk run-in eucaloric weight-maintaining diet 8wk DC antihyperglycemic therapy	Bristol-Myers Squibb
Erle 1999 Italy	Patients were excluded if contraindications to oral antidiabetic drugs were present.	30 diet therapy run-in 2 wks oral hypoglycemics DC	Laboratori Guidotti SpA

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Garber 2003 US	yes	yes	yes	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	yes
Garber 2002 US	Method NR	Method NR	yes	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	yes

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating	Number screened/eligible/ enrolled
Garber 2003 US	no	no	Unclear how many of 57(11.7%) noncompleters didn't have at least one post-baseline and were excluded from efficacy analyses, or from what groups they came from	no	Fair	NR/513/486
Garber 2002 US	no	no	yes* (see post-randomization exclusions)	yes; 6 (0.7%) randomized pts excluded prior to receiving any study medication	fair	847/NR/806

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Exclusion criteria	Run-in/washout	Funding
Garber 2003 US	Marked polyuria and polydipsia with greater than 10% weight loss, current therapy with antihyperglycaemic agents or previous use in the 8 weeks preceding study entry, or a history of diabetic ketoacidosis, hyperosmolar non-ketotic coma or insulin therapy.	2wk placebo run-in 8wk antihyperglycemics	Bristol-Myers Squibb
Garber 2002 US	Marked polyuria and polydipsia with greater than 10% weight loss; administration of antihyperglycemic agents within 8 wk before screening; a history of chronic insulin therapy, diabetic ketoacidosis, or hyperosmolar nonketotic coma; significant abnormal renal function defined by a serum creatinine concentration greater than or equal to 1.5 mg/dl (133 µmol/liter) for men and greater than or equal to 1.4 mg/dl (124 µmol/liter) for women; significant abnormal liver function defined as aspartate aminotransferase or alanine aminotransferase levels greater than or equal to twice the upper limit of normal or total serum bilirubin concentration greater than or equal to twice the upper limit of normal; alcohol and/or substance abuse within the year before screening; and cardiac or cerebral events within 6 months before screening.	2 wk placebo run-in 8 wk antihyperglycemics	Bristol-Myers Squibb

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Rosenstock 2006 US, Canada, Mexico, Australia, Korea, Brazil, New Zealand	Method NR; pts randomized 'with equal probability'	Method NR	yes	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	yes
Unpublished Study (#138-50)	Method NR	Method NR	yes	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	yes
Unpublished study (GSK dossier, pgs 9-12) 2007	Method NR	Method NR	Text reports baseline disease characteristics and demographics as being similar; no detailed table provided	yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating	Number screened/eligible/ enrolled
Rosenstock 2006 US, Canada, Mexico, Australia, Korea, Brazil, New Zealand	no	no	unclear for efficacy; apparently yes for safety	no	fair	NR/NR/468
Unpublished Study (#138-50)	no	no	no; 27 randomized patients not included in analysis	no	fair	1631/919/868
Unpublished study (GSK dossier, pgs 9-12) 2007	no	Unclear, disposition of all randomized patients NR	no; number of analyzed pts varied by outcome	NR	fair	NR/NR/901

Evidence Table 2. Diabetes RCT_Quality

Author, Year Country	Exclusion criteria	Run-in/washout	Funding
Rosenstock 2006 US, Canada, Mexico, Australia, Korea, Brazil, New Zealand	Clinically significant renal, hepatic or haematological disease; uncontrolled hypertension while on antihypertensive treatment; intermittent or chronic use of oral or intravenous corticosteroids; presence of unstable or severe angina, coronary insufficiency, or congestive heart failure requiring pharmacological treatment; any clinically significant abnormality judged by the investigator to preclude inclusion in the trial; use of an investigational agent within 30 days of the study (or five half-lives of the investigational drug if longer than 30 days); prior history of severe oedema or medically serious fluid-related event associated with any TZD; or presence of acute or chronic metabolic acidosis or history of diabetic ketoacidosis	2 wk washout short-term antidiabetic medication or insulin 12 wk washout long-term antidiabetic medication	GlaxoSmithKline
Unpublished Study (#138-50)	NR	8 wk washout antihyperlipidemic therapy 12 wk washout TZDs 2 wk run-in placebo to test compliance	Bristol-Myers Squibb
Unpublished study (GSK dossier, pgs 9-12) 2007	Unstable or severe angina, known CHF requiring pharmacologic treatment, use of OAD or insulin ≥15 days within 4 mos of study entry. Pts entered into study in European centers excluded for NYHA class I-IV heart failure.	2 wk screening run-in (not further described) 2 wk washout OAD and insulin (in pts using <15 days)	GlaxoSmithKline

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Schectman 2002 Retrospective cohort	Prescription refill data from pharmacy of University of Virginia Health (UVA) System's principal internal medicine primary care site serving primarily indigent patients in Central Virginia	At least one oral agent (sulfonylureas, metformin, α-glucosidase inhibitors, and thiazolidinediones) for type 2 diabetes	January 2000 through March 2001	N/A	Proportional adherence (mean for all diabetes drugs): number of days dispensed (based on refill data) divided by number of days in treatment interval (dates of first and last prescriptions)
Blonde 2003 Retrospective cohort	Administrative claims database containing pharmacy (Medco Health Solutions) and clinical laboratory testing (Quest Diagnostics) information for patients in all of the contiguous US	**Glucovance** (glyburide/metformin) ≤ 20 mg/2000 mg **Co-administration:** glyburide ≤ overlaps of ≤ 15 days of ≤ 20 mg and ≤ metformin 2550 mg/day	Initiated between August 2000 and June 2001	No combination antidiabetic therapy of any kind within 6 months of index; no other antidiabetic medications during study period	Total days' supply of medication divided by the number of days in the study period

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Schectman 2002 Retrospective cohort	NR	(1) Metabolic control: Most recent HbA1c; (2) Improvement in HbA1c: difference between first and last HbA1c during 20-month time frame	NR	NR	Adherence=15 months HbA1c=20 months	Simple and multivariate linear regression
Blonde 2003 Retrospective cohort	≤ 1 A1c test between 7/00 and 12/01; baseline measurement occurred ≤ 30 days prior to index and ≤ 14 subsequent; follow-up measurement during window of 76-194 days subsequent to index	Change in glycemic control: difference between follow-up and baseline measurements	NR	Continuously eligible for pharmacy benefits for at least 6 months prior to and subsequent to the index prescription date	**Mean days:** Glucovance=128.5, Co-administration=134.8 (Sum of days' supply of medication for index; for co-administration, only overlapping days were counted)	Multiple variable linear regression

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Schectman 2002 Retrospective cohort	Eligible: 844 Analyzed: 810 (98%) for metabolic control; 726 (88%) for improvement in metabolic control model	Mean age: 59 yrs 39.5% male 58.3% White 41.7% African-American	HbA1c: 8.1% HbA1c decrease: 0.52% Oral agent adherence: 79.7%
Blonde 2003 Retrospective cohort	Final cohort=1421	Mean age: 57 yrs 60% male Race NR	Chronic disease score: 7.9 % pts with previous antidiabetic monotherapy: 67% A1c: 9.2%

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Schectman 2002 Retrospective cohort	Adjusted values: Most recent HbA1c: parameter estimate=-0.016 (0.16% lower for every 10% increase in adherence), p<0.0001, partial R^2=2.7% Change in HbA1c: parameter estimate=0.013 (0.13% greater for each 10% increment in adherence); p<0.0001, partial R^2=1.5%	Poor Risk of reduced reliability due to use of prescription refill-based data to estimate drug adherence; overall exclusion of 118 (14%) patients with missing data (ethnicity or HbA1c) has potential of biasing results; reasons for missing data were not reported and can't be ruled out as relating to outcome; no specific temporal criteria for HbA1c measurements in relation to therapy dates, which could lead to skewing of results if there were systematic differences between temporal relationship of HbA1c measurements relative to therapy dates (e.g., the "first" and "last" HbA1c could have occurred only weeks apart, which would reflect minimal change. This coupled with lower adherence could give the result of a negative correlation.)
Blonde 2003 Retrospective cohort	% patients achieved A1c < 7%: 55.9% vs 31.2%; p-value NR Adjusted mean change in A1c: -2% vs -1.5%; p<0.0001 Adherence (% days with drug supply): 84% vs 76%; p<0.0001 (unclear whether adjusted) Correlation: "Patient adherence was not a significant predictor of decrease in A1c"	Fair Prescription refill-based assessments don't take into account that patients could have had other medication sources and low adherence may not reflect actual medication use patterns - requiring continuous eligibility for pharmacy benefits would reduce this risk, but couldn't eliminate it entirely; can't rule out publication bias due to lack of prespecification of subgroup categorization (e.g., above or below 80% adherent); can't rule out bias in patient selection methods as no information was provided about selection results; total pill burden was not taken into account - may have been systematic differences between groups in levels of complication of drug regimens - unclear if FDCT vs co-administration has as much impact on adherence in populations with high overall pill burdens

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Vanderpoel 2004 Retrospective cohort KQ5	Pharmacy claims database of a large health benefits company encompassing ~3.5 million covered members enrolled in health maintenance organizations, preferred-provider organizations, independent plans, or Medicare risk	**Dual/Dual** (co-administration throughout the whole study period) vs **Dual/Fixed-Dose Combination Therapy (FDCT)** (pre-index therapy=co-administration of rosiglitazone and metformin, post-index therapy=Avandamet)	≥ 1 pharmacy claim for dual therapy with rosiglitazone and metformin between 11/1/02 and 8/31/03 Dual/FDCT index=first fill date for Avandamet Dual/Dual index=first fill date for dual therapy	No restrictions	Compare changes in adherence rates using medication possession ratio (MPR) as a proxy: (total days' supply obtained)/(date of last claim - date of first claim + days' supply of last claim) (scale 0% to 100%)

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Vanderpoel 2004 Retrospective cohort KQ5	N/A	N/A	NR	Aged ≥ 18 with continuous, traditional plan enrollment during the duration of the study period; patients with generic-only plans were excluded; required maintenance of "continuous" medication therapy, defined as therapy without a lapse of > 60 days between date of days' supply expiration of any prescription fill and the subsequent claim date	12 months: 6 months pre-index and 6 months post-index	Analysis of covariance (ANCOVA) using a general linear model

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Vanderpoel 2004 Retrospective cohort KQ5	Dual/Dual=1230 Dual/FDCT=127	Mean age=55.8 yrs (56 vs 53.69) 41.5% male (40.7% vs 50.4%) Race NR	Total pill burden (# pills): 4.7 Insulin use (% pts): 83% Nonstudy oral hypoglycemic agent use: 67%

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Vanderpoel 2004 Retrospective cohort KQ5	Adjusted least-square mean of MPR change: -1.3% vs +3.5%; difference of mean change=4.8%; 95% CI 1.0%-8.6%, p<0.005	Fair Prescription refill-based assessments don't take into account that patients could have had other medication sources and low adherence may not reflect actual medication use patterns - requiring continuous eligibility for pharmacy benefits would reduce this risk, but couldn't eliminate it entirely; patients with lapses in therapy > 60 days may have been cases of "noncompliance" and exclusion of their data could have skewed results in direction of higher compliance; in the dual/dual group there were more male patients and they had a higher mean age - these factors were adjusted for, but there could have been other associated differences

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Melikian 2002 Retrospective cohort KQ5	Pharmacy claims from a pharmacy-benefit and medical-management company serving a large managed care organization (~2.5 million covered individuals in OR, WA, TX, OK)	**Newly Treated Patients** Co-administration with metformin and glyburide vs Glucovance **Previously Treated Patients** **(A)** Comparison of those switched from monotherapy to co-administration vs those switched from monotherapy to Glucovance **(B)** Those receiving co-administered metformin+glyburide and were switched to Glucovance at index date (before-after)	Pharmacy claim for an oral antidiabetic medication between 8/1/00-12/31/00 Index dates: newly treated=first prescription fill; previously-treated=date of switch	Insulin use was one of the covariates adjusted for in the statistical model and this implies insulin use was allowed	Rate of adherence: sum of days' supply of oral antidiabetic medication divided by the total number of days in the follow-up period Medication Possession Ratio (MPR): (total days' supply obtained)/(date of last claim - date of first claim + days' supply of last claim) (scale 0% to 100%)

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Melikian 2002 Retrospective cohort KQ5	N/A	N/A	NR	Continuous plan enrollment; aged ≥ 18 yrs	180 days post-index date	Analysis of covariance (ANCOVA)

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Melikian 2002 Retrospective cohort KQ5	**Newly treated:** co-administration =219; Glucovance=87 **Previously treated:** monotherapy to co-administration =patients switched from monotherapy to co-administration= 1815; patients switched from monotherapy to Glucovance=105; patients switched from co-administration to Glucovance=59	Only provided overall data, including monotherapy cohorts that are not relevant to KQ of this review and not described here **Newly treated:** 49.5% male; 62.5 yrs; race NR **Previously treated:** 50.1% male; 67 yrs; race NR	**Newly treated:** Chronic disease score: 6.1; total medication burden=3.8 at index, 4.5 at end of study **Previously treated:** Chronic disease score: 6.8

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Melikian 2002 Retrospective cohort KQ5	**Newly treated:** no significant differences over the initial 6 months between patients receiving co-administration or Glucovance **Previously treated** (adjusted rates) **(A)** Switched from monotherapy to either co-administration (Group 1) or Glucovance (Group 2): 54% vs 77%; p<0.001 **(B)** Before (co-administration) vs after (switch to Glucovance): 71% vs 87%; p<0.001	Fair Prescription refill-based assessments don't take into account that patients could have had other medication sources and low adherence may not reflect actual medication use patterns - requiring continuous eligibility for pharmacy benefits would reduce this risk, but couldn't eliminate it entirely; no information about average numbers of actual days of observation data - observation period was 180 days, but the actual number of days could have been much lower and would render these findings less meaningful - or the number of days could have differed among cohorts, which could potentially bias the results

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Krapek 2004 Prospective cohort KQ8	Self-report data from patients at 6 practicing sites participating in the Diabetes Goals Project from April 2001 to September 2002	Stratified by number of antidiabetic agents, defined as the number of distinct categories that physicians prescribed before HbA1c test	Maintenance on a stable antidiabetic regimen (unchanged over 2-3 months or considered stable by the primary care provider)	No restrictions; concomitant antidiabetic medications was a covariate in the statistical model	Morisky Scale Score ▪Calculated by totaling the number of "no" responses (0-4) to questions: 1. Do you ever forget to take your medications; 2. Are you careless at times about taking your medicine; 3. When you feel better, do you sometimes stop taking your medicine; 4. Sometimes if you feel worse when you take the medicine, do you stop taking it ▪Higher score indicates better adherence ▪When response missing, default was "yes" ▪For analyses, patients separated into two groups: those scoring 0-2 and those scoring 3-4 (determined post-hoc based on natural break-point of HbA1c's)

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Krapek 2004 Prospective cohort KQ8	HbA1c determination available that corresponded to the time on stable drug therapy	Absolute value	NR	Diagnosis of type 2 diabetes; a registered nurse, nurse practitioner, or certified diabetes educator acting as the primary care provider; patient-signed informed consent; age ≥ 18 years; information available on the length of current medication therapy	2-3 months; mean NR	Multiplicative regression model

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Krapek 2004 Prospective cohort KQ8	384 enrolled; 83 (21.6%) excluded due to invalid HbA1c test or inconsistencies with protocol; 301 analyzed	Age 18-44: 13% 45-54: 21.9% 55-65: 35.5% 66-75: 17.3% ≥ 76: 12.3% Gender: 40.2% male Race Hispanic: 12.6% Black: 36.9% White: 46.8% Other: 3.7%	**MMAS score:** 0 or 1=13.0% 2=14.0% 3=24.3% 4=48.8% **Antidiabetic agents:** 1=49.2% 2=38.2% ≥3=12.6% **Diabetes complications:** 0=54.5% 1=36.5% 2=6.6% ≥3=2.3% **Length of time with diabetes:** <2=19.3% 2–4.9=22.3% 5–9.9=24.6% 10–14.9=12.0% ≥15=21.9% **BMI group:** underweight=0.7% ideal weight or marginally over =22.3% overweight=21.3% obese or morbidly obese=55.8% **HbA1c:** 4%=0% 5%=9% 6%=23.7% 7%=24% 8%=21% 9%=9% 10%=6.7% 11%=2.5% 12%=1.8% 13%=2.2% 14%=0% 15%=0% 16%=0% 17%=0% 18%=0.5%

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Krapek 2004 Prospective cohort KQ8	"Good adherence" (Morisky score ≥ 3) was associated with a 10% lower total HbA1c; p=0.0003 (adjusted) HbA1c for Morisky score levels: 0-1: 8.92% 2=8.67% 3=7.74% 4=7.60% Significant variables in model: total antidiabetic pill burden (p=0.04), number of diabetes-related complications (p=0.002), black in ethnicity (p<0.001), practice site (p<0.001)	Poor Patient selection may have been biased as no information was provided about the total number of potentially eligible patients relative to the actual number enrolled; reasons for missing HbA1c data/protocol inconsistencies for 83 (21.6%) patients could have been related to low adherence and exclusion of these data could have skewed the results; 2-3 months may not have been a long-enough treatment interval for HbA1c's to stabilize; at least moderate risk of bias associated with method of adherence assessment due to being based on patient report using a rating scale that has been validated only against a clinical measure of blood pressure and it was unclear if patients were blinded to study hypothesis

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Lau 2004 Retrospective cohort KQ8	Data from 2000 and 2001 from the medical and pharmacy claims of a commercially-insured population of a Managed Care Organization in the Midwestern US with ~200,000 covered lives	Monotherapy or "multiple drugs simultaneously"	Pharmacy claim data (≥ 2 refills) for oral antihyperglycemic agents in 2000	Insulin users excluded	(A) Nonadherence=MPR < 80%; medication possession ratio (MPR) as a proxy: (total days' supply obtained)/(date of last claim - date of first claim + days' supply of last claim) (scale 0% to 100%) (B) Categorical variable with 3 levels: no drug prescribed, drug prescribed but nonadherent, drug prescribed but good adherence

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Lau 2004 Retrospective cohort KQ8	NR	NR	Hospitalization=inpatient admission with a primary diagnosis code related to diabetes or cardiovascular/cerebrovascular causes	Aged ≥ 18 years; pharmacy benefit; ICD-9-CM codes for type 2 diabetes (250.xx)	Medication adherence in 2000; Hospitalizations in 2001; no information about actual duration of therapy	Multivariate logistic regression analysis

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Lau 2004 Retrospective cohort KQ8	900	Age <45=19.7% 45-54=38.5% 55-64=32.9% ≥ 65: 8.9% Gender: 55.2% male Race NR	Single therapy=54.2% Multiple therapies=45.8% Nonadherence (MPR<80%) to antihyperglycemics in 2000: 28.8% Charlson comorbidity index: 1=67.1%; 2-3=25.3%; ≥ 4=7.6% Hospitalizations: in 2000 (all cause)=11.4%; in 2001 (diabetes/CVD)=6.7%

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Lau 2004 Retrospective cohort KQ8	Hospitalization rates in 2001 stratified by MPR% in 2000: 100% MPR = 4.1% patients hospitalized 99-80%=5.2% 79-60%=10.3% 59-40%=11.9% < 40=14.8% OR of hospitalization in 2001 for nonadherents compared to adherents: 2.53; 95% CI 1.38-4.64	Poor Results of this analysis are at risk of bias as it does not take into consideration differences in index date of therapy initiation and overall duration of therapy (2 refills versus 8 refills) as MPR based on the number of days that patient possessed a supply of medication, with the minimum requirement being 2 refills in all of 2000. For example, with all other things being equal, 2 patients that both had an index refill in January of 2000 and a hospitalization in February of 2001 could be classified very differently. If one took 100% of medications across 2 consecutive refills (Jan-Feb), but went 10 other months of 2000 without medications, he/she would be classified with high adherence. However, if the other only took medications in January and June, but went just as many other months in 2000 without medication, he/she would get a very low adherence score; use of prescription refill-based assessment method may not have accurately reflected actual medication use patterns as patients could have had other medication sources and low adherence may not reflect actual medication use patterns; patient selection may have bee

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Brown 1999 Retrospective cohort KQ8	Administrative and clinical electronic databases of data from members of Kaiser Permanente Northwest Division that were entered into the Diabetes Registry in 1988; serves 20% of population in and around Portland, OR	Antidiabetic drug use: remaining on or switching to non-use; reviewed annually for the months of January, February, and March	Purchase of a sulfonylurea, insulin or both in incident year of 1988	NR	Switch to non-use: failure to purchase antidiabetic drugs in Jan-Mar after having purchased an antidiabetic agent in the previous year

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Brown 1999 Retrospective cohort KQ8	NR	NR	NR	Newly diagnosed or presumed DM2 (registered after age of 45 or registered < 46 years but no insulin until ≥ 2 years after diagnosis); ≥ 12 full months of health-plan eligibility prior to entry into Diabetes Registry; previously had received no services or products associated with the diagnosis or treatment of diabetes; health insurance had to include continuous pharmaceutical coverage	10 years	NR; chi-square test performed to assess differences in HbA1c values for "remained" vs "switched", but no information about the characteristics of the groups being compared and whether they were similar

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Brown 1999 Retrospective cohort KQ8	693	NR	Drugs used SU only=79.2% Insulin only=7.1% SU+insulin=1.9% No drug=11.8% Metformin=0%

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Brown 1999 Retrospective cohort KQ8	Remained vs switched 1994 (year 7) N=110/29 HbA1c: Excellent (< 7%)=12.7% vs 21.7%, p<0.05; Good (7%-7.9%)=12.7% vs 6.9%, p<0.05; no test=65.5% vs 44.8%; p<0.05 1995 (year 8) N=94/25 HbA1c: Excellent=12.8% vs 8%; p=NS; Good=14.9% vs 32%, p=NS; no test=52.1% vs 36%, p=NS 1996 (year 9) N=68/26 HbA1c: Excellent=19.1% vs 11.5%, p=NS; Good=17.7% vs 23.1%, p=NS; no test=50% vs 38.5%; p=NS 1997 (year 10) N=60/32 HbA1c: Excellent=36.7% vs 15.6%; Good=13.3% vs 28.1%, p=NS; no test=28.3% vs 25%, p=NS Conclusion: "..avoidance of therapy and slow transitioning from failing therapies may compromise long-term glycemic control."	Poor Potential patients selection bias due to exclusion of 76 (8.2%) of patients who disenrolled but later re-enrolled, which may have been related to adherence as they may have "switched to non-use"; level of missing data (96.4% by year 10) serious threat to study results; high risk of bias in statistical analysis as chi-square test to detect potential differences between "remained" and "switched" groups did not control for potential between-groups differences in demographics or clinical characteristics, which weren't reported at all

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Mateo 2006 Prospective cohort KQ8	Pill counts and laboratory test data from all patients with type 2 diabetes living in Rafelcofer, Valencia, therefore registered with the only family doctor practicing in the village	Current treatment with one or more oral drugs for associated vascular risks in patients with type 2 diabetes: hypoglycemic, antihypertensive, lipid-lowering, and antiplatelets agents	Between September 2001 and August 2002	NR	Pill count Adherence percentage (AP)=(number of pills absent from the packet, supposedly taken by the patient)/(number of pills prescribed by the physician) x 100 "Adequate" adherence=AP of 80-110% "Poor" adherence=AP below 80% or more than 110%

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Mateo 2006 Prospective cohort KQ8	Inhibition turbidimetric method for whole blood (normal values: 4.3%-5.8%)	HbA1c<7%	N/A	Diagnosis of type 2 diabetes according to ADA and WHO-1999 criteria; registration with the only family doctor practicing in the village; age ≥ 18 years; no concurrent somatic or psychiatric diseases and/or serious social dysfunction that made the patient unsuitable for adequate administration of medications; no intercurrent acute diseases that required a change in the prescribed medication; acceptance of attending appointments	1 month	Binary logistic regression using the forward and backward, step-wise method

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Mateo 2006 Prospective cohort KQ8	90 enrolled 82 analyzed	Age=68.5 yrs 50% male Race NR	Disease duration=10.5 yrs Mean BMI=30.2 kg/m^2 Obese=45.1% Diabetes complications: macrovascular complications=28%; microvascular complications=32.6% Mean total daily pill burden=4.8

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Mateo 2006 Prospective cohort KQ8	% patients with HbA1c < 7%: adherent=68.8% vs nonadherent=31.3%, p=0.0007 Results of multiple logistic regression analysis: OR 2.32, 95% CI 1.09-4.95, p=0.030 (probability of being non-adherent to one or more drugs prescribed for vascular risk was 2.3% higher for each 1% increase in HbA1c)	Fair Risk of patient selection bias unclear as unclear if there were other types of doctors in the area that could have been managing other potentially eligible patients; 8 (8.9%) of patients who withdrew after the first appointment were excluded and it was not reported as to whether withdrawal could have been due to adherence-related issues, but this level of attrition was not a serious threat to the study results; risk of outcome assessment bias as "single researcher" who carried out all counts was not blinded to study objective or HbA1c's and there was no information about accuracy of pill counts; 4 weeks likely not an adequate treatment interval for HbA1c's to stabilize

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Grant 2003 Prospective cohort KQ8	Self-report data from patients in registry of chart-confirmed type 2 diabetes receiving primary care at Massachusetts General Hospital Revere HealthCare Center, an academically affiliated community health center serving a working class community 10 miles north of Boston; random selection of 231 patients from 462 that had at least one HbA1c and one cholesterol level measured in the previous year	Any oral hypoglycemic agents, insulin, antihypertensive agents, lipid-lowering medicines, and aspirin	NR, but interviews were conducted from May 2001 to May 2002	N/A	Structured telephone-based interviews of patient self-reported adherence using 2 questions: (1) On how many days in the past week were you able to take all of [specific medicine name] as prescribed by your doctor? (2) Did you take all of this medicine as prescribed by your doctor yesterday?

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Grant 2003 Prospective cohort KQ8	At least one hbA1c in the previous year; data collected from computerized databases; HbA1c value was taken from most recent measurement preceding the interview data, which was a mean of 84.6 days before the interview	Mean	N/A	No terminal illness or cognitive deficits; adequate communication level in spoken English	One interview in which patients were asked about adherence over the past week	Chi-square test for categorical variables; t tests for normally distributed continuous variables; Spearman's correlation coefficient

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Grant 2003 Prospective cohort KQ8	231 selected 128 analyzed	Mean age=66 yrs 39% male 88% white	Mean total daily pill burden specifically for diabetes and related comorbidities=4.1 Overall mean total daily pill burden=5.8 HbA1c=7.7% % patients HbA1c > 7%=60 Total cholesterol=180 mg/dl Blood pressure=136/73 mmHg

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Grant 2003 Prospective cohort KQ8	HbA1c for patients with perfect adherence was 7.6% vs 7.9% for patients without perfect adherence; p=0.5	Poor Risk of selection bias as unclear if there were other potentially eligible patients in the Massachusetts General system in addition to the 910 that formed the "registry"; 71 (33%) of potentially eligible patients excluded due to being unavailable by telephone and this level of exclusion presents a moderate risk of bias to overall study results; serious concern about validity of associating a temporal relationship between self-reported 7-day adherence and an HbA1c that was measured a mean of 84.6 days prior; risk of bias in ascertainment of adherence data as unclear if clinical pharmacist conducting interviews was blinded to study objective and patients' HbA1c's; concerns about use of unadjusted chi-square tests as a way to test differences in HbA1c between those with "perfect" adherence versus those with "less than perfect" adherence as it was not reported whether the groups were similar in other important demographic and clinical characteristics that could have affected HbA1c's

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Balkrishnan 2003 Retrospective cohort KQ7	Patients enrolled in Qual-choice, a Medical HMO in North Carolina; demographic, clinical and utilization-related economic variables retrieved from HMO administrative claims database	Any antidiabetic pharmacotherapy	HMO's internal medication coding system for receipt of antidiabetic medication prescriptions	N/A	Medication Possession Ratio: number of days prescription supply dispensed divided by the number of days between refills; number of days a person was in a hospital was subtraced from the denominator because any drug taken during this time was provided by the hospital

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Balkrishnan 2003 Retrospective cohort KQ7	NR	NR	Hospitalizations	Aged ≥ 65; diagnosis of type 2 diabetes based on ICD-9-CM codes (250.xx)	≤ 5 years	Random-effects generalized least squares regression with MPR as dependent variable

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Balkrishnan 2003 Retrospective cohort KQ7	Years 1/2/3/4/5=775/628/495/381/171	Mean age=75 yrs 40% male Race NR	Years 1/2/3/4/5/ Charlson index (severity of comorbidity index)=3.65/3.71/3.74/3.82/3.79 Center for Epidemiologic Studies Depression scale (CES-D) (0-100)=14/13/13/12/10 Prescription refills=48.62/53.1/56.18/55.25/56.90 Oral antidiabetic use (%)=84/85/84/82/77 Any alcohol consumption (%)=5/5/6/5/6 Current smoker (%)=11/11/11/11/13 Physically active (%)=27/30/32/33/35 Hospitalization during previous year (%)=21/20/19/17/16 ER visit during previous year (%)=25/25/23/21/22 SF-12 PCS score (Medical Outcomes Study 12-Item Short-Form Health Survey Physical Component Summary): 48.23/49.21/49.63/50.40/49.49

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Balkrishnan 2003 Retrospective cohort KQ7	Years 1/2/3/4/5 MPR (%): 71/78/77/75/70 Total days in hospital: 10.03/9.68/9.33/9.99/14.32 Total ER visits: 1.32/1.37/1.34/1.29/1.99 Total monthly outpatient visits: 1.25/1.23/1.24/1.26/1.42 Regression analysis (MPR-point decrease) complete data only available for N=667, included and excluded patients did not differ significantly on non-missing variable means Hospitalization during previous year= -0.0074, p=NS ER visit during previous year= -0.043, p=0.05	Fair Some risk of selection bias as no information was provided about results of selection process and it is unclear if there were other potentially eligible patients that were not included in final study sample; some risk of bias to study results due to exclusion of 14% of patients from analysis due to incomplete data - stated that a comparison of nonmissing variables found no differences between included and excluded patients, but there remains the possibility that the missing data was related to adherence; use of less reliable refill database-based methods based only on the assumption that a prescription filled was a prescription taken

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sampling source/methods of data collection	Medication groups	Medication index information	Other antidiabetic medications	Measures of adherence
Hays 1994/Tarlov 1989 (Methods) Prospective cohort KQ7	Adult patients who visited an enrolled Medical Outcomes Study (MOS) health care provider (internal medicine, family practice, endocrinology, cardiology) within 3 systems of care (HMO, large multispecialty groups, and solo practices) in 3 cities (Boston, Chicago, and LA) during a 9-day period beginning in February 1986; diabetes diagnosis initially confirmed from physician questionnaire and confirmed by physical/laboratory examination; enrollment determined in Fall of 1986 via follow-up telephone interview; overall data collection methods included telephone interviews and self-administered questionnaires/forms for providers and for patients, self-administered questionnaires and diaries, telephone interviews, face-to-face interviews, clinical exams, hospital records for episodes of inpatient care	Insulin-use, non-insulin use	NR	N/A	Self-report assessment instrument self-administered 3-4 months post-enrollment measuring the extent to which patients had followed recommendations for 8 specific treatment behaviors (e.g., take prescribed medications, follow a low-fat or weight loss diet, follow a diabetic diet, check blood for sugar, exercise regularly, check feet for minor cuts and bruises, carry source of glucose, and carry medical supplies for self-care) in past 4 weeks (from "none of the time" to "all of the time"); adherence score represented a composite of ratings across all 8 behaviors

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	HbA1c index information	Measures of HbA1c	Other dependent variable definitions	Other eligibility criteria	Observation period	Statistical methods
Hays 1994/Tarlov 1989 (Methods) Prospective cohort KQ7	NR	NR	Measures of health outcomes evaluated using an extensive self-report health-related quality of life battery of measure; RAND 36-Item health Survey 1.0 (8 multi-item measure of functioning and well-being, each scored from 0-100, with 100 representing optimal health)	Completion of a 42-item screening form; physician completion of 32-item form that included diagnosis; diagnosis checked by physical examination and laboratory tests performed by MOS staff; English-speaking	Adherence measured 3-4 months post-enrollment, and patient responses based on behavior in preceding 4 weeks; health outcomes measured 2 years post-enrollment	Multiple regression methods

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Sample size	Population demographics (means) Age % male % white	Clinical characteristics (means)
Hays 1994/Tarlov 1989 (Methods) Prospective cohort KQ7	2125	Mean age=56 yrs 41% male 80% white 20% nonwhite	NR

Evidence Table 3. Diabetes observational studies

Author, year Study design Key Question (KQ)	Results	Quality
Hays 1994/Tarlov 1989 (Methods) Prospective cohort KQ7	Adherence to medication recommendations for insulin-using diabetics was associated with *negative* effects on physical health (t = -2.47; p<0.05) (unclear how "physical health" score was determined - RAND 36-item Health Survey contains subscales for "physical functioning", "limitations due to physical health problems", "general health perceptions")	Poor Risk of selection bias as it is unclear whether patients approached during 9-day screening period represented ALL potentially eligible patients and also concern about discrepant numbers of patients screened across 2 companion publications; serious concern about validity of associating a temporal relationship between self-reported 7-day adherence and subjective reports of "physical health" outcome that was measured 2 years later; risk of bias in ascertainment of outcome data as unclear if patients and study personnel collecting data were blinded to study objectives; serious concern about reliability of using subjective patient self-report methods of outcome ascertainment; no information about how ambiguous data were handled

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Schectman 2002	Yes; 844 patients identified on one or more oral agents for diabetes during study period	15 (1.8%) patients excluded due to missing ethnicity data; 19 (2.2%) excluded from analysis of 'Most Recent HbA1c' parameter due to missing HbA1c value; 118 (12%) excluded from analysis of 'change in HbA1c' parameter	Yes	Unclear whether retrospective or prospective, but assume retrospective. No information about outcome assessors (e.g., qualifications, blinding to hypothesis), source of HbA1c data (e.g., patient chart, electronic medical records, etc.), whether source(s) same for all patients, or how ambiguous data was handled	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors
Blonde 2003	Unclear; only reported N for "final cohort"; details about patient selection results NR	Unclear; detailed patient selection results NR	Categories used for some outcome analyses not prespecified (e.g., comparing A1c decreases in patients with adherence above and below 80%)	Data collection was retrospective; use of less reliable refill database-based methods of assessing adherence (patients could have had alternative sources of medications); no information about how data were extracted from the databases and how reliable the methods were	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors

Evidence Table 4. Diabetes observational study quality

			External validity			
Author Year	**Adequate duration of follow-up?**	**Overall quality rating**	**Population characteristics**	**Sample size**	**Exclusion criteria**	**Funder**
Schectman 2002	Yes	Poor	Primarily indigent population in Virginia receiving oral medications for type 2 diabetes	844	Missing ethnicity data	NR
Blonde 2003	Yes	Fair	Patients new to combination therapy	1421	Ineligible for benefits with 6 months before after index date; concomitant use of other antidiabetic medications	Bristol-Myers Squibb

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Vanderpoel 2004	Yes; of 178,288 subjects with DM-2, data from the 16,928 who met inclusion criteria were used in analysis (there were 3 other cohorts that weren't relevant to the key questions of this review)	NR	Yes	Data collection was retrospective; use of less reliable refill database-based methods of assessing adherence (patients could have had alternative sources of medications); no information about how data were extracted from the databases and how reliable the process was	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Vanderpoel 2004	Yes	Fair	Patients with DM-2 enrolled in health maintenance organizations, preferred-provider organizations, independent plans, or Medicare risk	Overall=16,928; cohorts of interest=1,357	Aged < 18; lapse in continuous, traditional plan enrollment during the duration of the study period; patient with generic-only plans were excluded; required maintenance of "continuous" medication therapy, defined as therapy without a lapse of > 60 days between date of days' supply expiration of any prescription fill and the subsequent claim date	NR; last author affiliated with GSK

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Melikian 2002	Unclear; reported number of eligible patients included in the analyses, but it is not clear if there were other eligible patients that were not included in the analyses	NR	Yes, but no results of MPR analyses reported	Data collection was retrospective; use of less reliable refill database-based methods of assessing adherence (patients could have had alternative sources of medications); no information about how data were extracted from the databases and how reliable the process was	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Melikian 2002	Unclear; Planned observation period=180 days; no information about actual mean number of days of observation	Fair	Patients with continuous enrollment in a large managed care health plan	**Newly treated:** co-administration=219; Glucovance=87 **Previously treated:** monotherapy to co-administration=patients switched from monotherapy to co-administration=1815; patients switched from monotherapy to Glucovance=105; patients switched from co-administration to Glucovance=59	Age < 18 years; lapse in health plan enrollment during study period	Bristol-Myers Squibb

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Krapek 2004	Unclear; total number of potentially eligible patients in Diabetes Goals Project NR	83 (21.6%) patients excluded due to incomplete HbA1c data/protocol violations; reasons for incomplete data were NR and could have been related to outcome	Yes	Data collection prospective; assessment of adherence based on patient report, using a rating scale that has been validated only against a clinical measure of blood pressure; unclear if patients were blinded to study hypothesis	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Krapek 2004	Follow-up duration specified as "2-3 months", which may not have been an adequate interval for HbA1c stabilization	Poor	Patients participating in Diabetes Goals Project with registered nurse, nurse practitioner, or certified diabetes educator acting as primary care provider	384 enrolled; 301 analyzed	Age < 18 years; gestational or type 1 diabetes, active changes in the drug regimen during the study, HbA1c determination unavailable for the study period, lack of information on study period	NR

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Lau 2004	Unclear; total number of potentially eligible patients NR	Unclear if any potentially eligible patients with incomplete data and were excluded	Yes	Data collection was retrospective; use of less reliable refill database-based methods of assessing adherence (patients could have had alternative sources of medications); no information about how data were extracted from the databases and how reliable the process was	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Lau 2004	Unclear; observed medication adherence in 2000 and hospitalizations in 2001, but the observation window for some patients could have been limited to 11/00-1/01	Poor	Individuals with pharmacy benefits with a commercially-insured population of a Managed Care Organization in the Midwestern US who were over age 18 years	900	No	University of Michigan Health System; first author participant in Pfizer Research Fellowship Program

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Brown 1999	Excluded 76 (8.2%) of patients who disenrolled but later re-enrolled and this could have introduced bias in that those individuals could have been classified as "switched to non-use"	Data only provided for years 7-10 and only provided data for 139 patients (20%) of the original cohort for year 7, 119 (17%) for year 8, 94 (13.6%) for year 9, and 92 (13.3%) for year 10 and of those patients, HbA1c's were missing for 25%-65.5% of them	No; nothing in Methods about HbA1c; stated in Results that HbA1c's became available in 1994, but no information about categorizations of "Excellent", "Good", etc.	Data collection was retrospective; use of less reliable refill database-based methods of assessing adherence (patients could have had alternative sources of medications); no information about how data were extracted from the databases and how reliable the process was	Lacking actual statistical analysis of association between adherence and HbA1c; chi-square test to detect potential differences between "remained" and "switched" groups, without controlling for potential between-groups differences in demographics or clinical characteristics

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Brown 1999	Yes; 10 years	Poor	Newly diagnosed or presumed DM2 (registered after age of 45 or registered < 46 years but no insulin until ≥ 2 years after diagnosis); ≥ 12 full months of Kaiser Permanente Northwest Division health-plan eligibility prior to entry into Diabetes Registry; previously had received no services or products associated with the diagnosis or treatment of diabetes; health insurance had to include continuous pharmaceutical coverage	693	See 'Population Characteristics'	SmithKline Beecham Pharmaceuticals, Inc. and Kaiser Permanente Center for Health Research

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Mateo 2006	Unclear if there were other types of doctors in the area that could have been managing potentially eligible patients	8 (8.9%) of patients who withdrew after the first appointment were excluded; unclear if withdrawal was due to adherence-related issues	Yes	Data collection was prospective; used pill count, which was cited as being among the best indirect methods to assess adherence; patients were described as blinded to study objectives, but did not appear that "single researcher" who carried out all counts was blinded; no information about accuracy of pill counts	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Mateo 2006	No; 4 weeks	Fair	Elderly population (mean age=68.5) in small village (1,249) in Rafelcofer, Valencia where there was only one practicing family doctor	90 enrolled; 82 analyzed	Concurrent somatic or psychiatric diseases and/or serious social dysfunction that made the patient unsuitable for adequate administration of medications; intercurrent acute diseases that required a change in the prescribed medication; decline to attend appointments	NR

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Grant 2003	Unclear if 910 patients with chart-confirmed type 2 diabetes that formed the original registry represented ALL potentially eligible patients	71 (33%) of potentially eligible patients excluded due to being unavailable by telephone	Classification of "perfect" vs "less than perfect" adherence was not prespecified	Adherence was measured prospectively, but HbA1c was based on retrospective data; questionable reliability of self-report method of responding to 2 questions based on previous week's medication-taking behavior as measure of adherence; concerns over use of the previous week's adherence to generalize to longitudinal behavior and assume this pattern was consistent between then and the previous most recent HbA1c test; unclear if clinical pharmacist conducting phone interviews was blinded to HbA1c	Chi-square test to detect differences in HbA1c levels between patients with "perfect" and "less than perfect" adherence, which didn't account for any potential between-groups differences in patient demographics and clinical characteristics

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Grant 2003	No; adherence was rated only based on last week	Poor	Patients with chart-confirmed diabetes receiving primary care at academically-affiliated health care center	128	No terminal illness or cognitive deficits	Research grant from the Aetna Quality Care Research Fund

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Balkrishnan 2003	Unclear if there were other potentially eligible patients that were not included in final study sample; no information provided about selection process	Complete data for regression only available for 667 patients (14% excluded), but stated that a comparison of nonmissing variables found no differences between included and excluded patients; risk remains that the missing data was related to the dependent variable, adherence, but the level of missing data is not considered a serious threat to the study results	Yes	Data collection was retrospective; use of less reliable refill database-based methods of assessing adherence (patients could have had alternative sources of medications); no information about how data were extracted from the databases and how reliable the process was	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Balkrishnan 2003	Yes	Fair	Older population in a Medicare HMO population in North Carolina	775	Non-continuous enrollment in HMO for 1-5 years; non-continuous antidiabetic pharmacotherapy	Study conduct funded by Wake Forest University Baptist Medical Center; analysis of study data was funded by a research grant from Takeda pharmaceuticals

Evidence Table 4. Diabetes observational study quality

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up/incomplete data specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Non-biased and adequate ascertainment methods?**	**Potential for bias in analysis methods?**
Tarlov 1989/ Hays 1994	Unclear whether all potentially eligible patients seen during the 9-day screening period had equal opportunity to participate; Tarlov 1989 methods publication states that 22,785 adults were seen during the period and that only 96% of those were screened based on their clinicians' completion of a diagnostic questionnaire; Hays 1994 results publication states that 28,257 were approached and that 20,223 (71%) agreed to participate; unclear how the sample was narrowed down to 2125	Level of incomplete health outcome data available at 2-year follow-up NR; stated that a dummy variable was created indicating whether or not the patient had follow-up data available and this was adjusted for in the analysis	Yes	Data collection was prospective; serious concern about reliability of using subjective patient self-report methods of outcome ascertainment; no information about how ambiguous data were handled; serious concerns about validity of associating a temporal relationship between self-reported 7-day adherence and subjective reports of "physical health" outcome that was measured 2 years later	No information about statistical power, but methods were valid and appropriate and including controlling for confounding factors

Evidence Table 4. Diabetes observational study quality

External validity

Author Year	Adequate duration of follow-up?	Overall quality rating	Population characteristics	Sample size	Exclusion criteria	Funder
Tarlov 1989/ Hays 1994	Yes	Poor	Patients seen in internal medicine, family practice, endocrinology, or cardiology clinics within 3 systems of care (HMO, large multispecialty groups, and solo practices) in 3 cities (Boston, Chicago, and LA)	2125	Non-English speaking	AHRQ, National Institute on Aging, The Robert Wood Johnson Foundation, Henry J. Kaiser Family Foundation, National Institute of Mental Health, Pew Charitable Trusts, RAND, New England Medical Center

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Inclusion criteria	Exclusion criteria	Fixed dose combination product
Bays 2003a/Bays 2003b/Bays 2005 US (ADVOCATE)	Women and men, 18 to 70 years old, with 2 consecutive baseline low-density lipoprotein (LDL) cholesterol blood levels ≥160 mg/dl without coronary artery disease, or ≥130 mg/dl if coronary artery disease was present. Other lipid inclusion criteria included triglycerides <300 mg/dl and high-density lipoprotein (HDL) cholesterol <45 mg/dl in men and <50 mg/dl in women. Any lipid-altering drug treatment was discontinued ≥6 weeks before study randomization. Women of childbearing potential were eligible if they used an effective means of contraception for the study duration.	Known prior allergy or intolerability to any of the study drugs, history of substance abuse or dependence within 12 months of screening, consumption of >14 alcoholic drinks per week, uncontrolled psychiatric disease, participation in another investigational study within 30 days of screening, or probucol administration within the previous year. Subjects were also excluded if they had a history of the following diseases or laboratory abnormalities: active gallbladder disease; uncontrolled hypertension; renal insufficiency (serum creatinine ≥1.5 mg/dl); hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase >1.3 times the upper limit of normal); fasting glucose ≥115 mg/dl; New York Heart Association class III/IV congestive heart failure; active gout symptoms or uric acid >1.3 times the upper limit of normal; active peptic ulcer disease; type 1 or 2 diabetes; fibromyalgia; cancer within the previous 5 years (except for basal cell carcinoma); unstable angina, myocardial infarction, coronary artery bypass graft, percutaneous transluminal cor angioplasty, or stroke within prior 6 months; or any condition of laboratory abnormality which, in the opinion of the investigator, might be adversely affected by the study procedures or medications.	Niacin ER/lovastatin 1000/40mg or 2000/40mg

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Bays 2003a/Bays 2003b/Bays 2005 US (ADVOCATE)	Atorvastatin 10-40mg Simvastatin 10-40mg	6 wk DC lipid-altering drugs 4 wk DC: 3-isotretinoin, androgens/anabolic steroids, ciprofloxacin, corticosteroids, cycosporine, erythromycin, other macrolides, itraconazole, other oral -azole antifungals, margarine with plant stanol or sterol esters, nefazodone, orlistat, protease inhibitors, sibutramine, vitamins w/>50mg niacin, warfarin other other coumadin-derived anticoagulants.	Mean age 53 yrs (SE 1.1) 72% male 87% white	LDL 191.8 (SE 3.7) HDL 38.5 (SE 0.6) Mean BMI 29.0 CHD 21.5% (66/315) ≥2 CHD risk factors 50% (figures not provided)	NR/NR/315

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Bays 2003a/Bays 2003b/Bays 2005 US (ADVOCATE)	42/NR/NR* *reported as 'ITT'	Primary endpoint: N/L 1000/40 vs N/L 2000/40 vs A 40mg vs S 40mg at wk 16 (final timepoint and doses) Mean reduction in LDL-C: -39% vs -42% vs -49% vs -39% (both doses N/L vs A: p<0.05) Mean change in HDL-C: 17% vs 32% vs 6% vs 7% (both doses N/L vs A and S: p<0.05) Secondary endpoints: N/L 1000/40 vs N/L 2000/40 vs A 40mg vs S 40mg at wk 16 (final timepoint and doses) Mean reduction in trigylcerides: -29% vs -49% vs -31% vs -19% (N/L vs S: p<0.05) Mean reduction in lipoprotein(a): -19% vs -21% vs 0% vs 2% (N/L vs A and S: p<0.05) Compliance: N/L 1000/40 vs N/L 2000/40 vs A 40mg vs S 40mg at wk 16 (final timepoint and doses) 97% vs 94% vs 96% vs 96% SUBGROUP: CHD/CHD risk % achieving LDL-C goal <100mg/dl N/L 1000/40 vs N/L 2000/40 vs A 40mg vs S 40mg at wk 16 (final timepoint and doses) 67% vs 65% vs 68% vs 44% (from Bays 2005, Figure 4 pg 229)	Lab measures, diet recall and pill counts

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Bays 2003a/Bays 2003b/Bays 2005 US (ADVOCATE)	NSD for specific AEs (including rash, hyperglycemia, hyperuricemia, GI AEs) except for dizziness (p=0.025) and flushing (p=NR) reported more frequently in N/L groups (p=0.025) Elevated ALT in A and S groups significantly higher than N/L groups (p<0.04) No cases of myopathy in any group No treatment-emergent elevated ALT/AST >3x ULN	42/35		Figures in Bays 2005 very difficult to read (ILL copy)

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Inclusion criteria	Exclusion criteria	Fixed dose combination product
Hunninghake 2003 US	Women and men ≥ 18 years of age and to have type IIA hyperlipidemia (elevated LDL-C levels) or type IIB hyperlipidemia (elevated LDL-C and TG levels). Patients qualified for randomization based on LDL-C levels that were classified as elevated based on the guidelines developed by the second Adult Treatment Panel of the National Cholesterol Education Program (NCEP). Elevated LDL-C levels were defined as ≥ 130 mg/dl in patients with documented CAD or type 2 diabetes mellitus, ≥ 160 mg/dl in patients who had neither CAD nor diabetes but did have ≥ two additional risk factors for CAD, and ≥ 190 mg/dl in patients with < two CAD risk factors. To qualify, patients had to have a mean of two consecutive LDL-C levels that met NCEP criteria and LDL-C values that varied by ≤ 12% between measurements at least 7 to 10 days apart during screening. In patients previously treated with statins or resins, these drugs were required to be withdrawn at least 4 weeks prior to the first qualifying lipid determination.	Patients with TG > 800mg/dl, hypatic dysfunction, or hepatic enzyme levels > 1.3 X the upper limit of normal (ULN), renal disease, biliary disease, severe hypertension, a recent major cardiovascular or cerebrovascular event, active peptic ulcter disease or gout, type 1 or uncontrolled type 2 diabetes mellitus, or cancer. Additional grounds for exclusion were inability to withdraw concomitant lipid-altering drug therapy, probucol treatment within the last year, concurrent use of medications with hepatic or myopathic side effects, and, in women of childbearing potential, failure to use adequate contraceptive methods.	Niacin ER/lovastatin 500-1000mg/20-40mg (dose-ranging)

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Hunninghake 2003 US	Niacin ER 500-2000mg Lovastatin 20-40mg	4 wk run-in NCEP step 1 diet 4 wk DC lipid-altering drugs wash-out	Mean age 59.3 yrs 73% male 87% white	LDL 189.5 (SE 4.8) HDL 45.2 (SE 1.5)	NR/NR/237

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Hunninghake 2003 US	NR/NR/236	Primary endpoint: N/L 1000/20 vs N/L 2000/40 vs N 2000 vs L 40 mean % reduction in LDL-C at 28 wks -27.6% vs -41.9% vs 13.5% vs 32.2% SS difference in mean % reduction in LDL-C N/L 2000/40 vs L 40 vs N 2000 (in text; p<0.05) Secondary endpoints: N/L 1000/20 vs N/L 2000/40 vs N 2000 vs L 40 Mean change in HDL-C at 28 wks: 21.4% vs 30.4% vs 23.5% vs 6.4% Mean change in TG at 28 wks: -25.9% vs -42.9% vs 22.9% vs 20.0% Mean change in LP(a) at 29 wks: -15.7% vs -19.3% vs -24.5% vs -1.8% SUBGROUPS: Reported in text - Changes in lipid parameters w/niacin-containing regimens tended to be greater in women; combo regimens produced greatert lipid changes in patients >65yrs compared to monotherapies	Assessed by investigator following pt questioning

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Hunninghake 2003 US	N/L groups vs N mono vs L mono Death: 2 deaths reported (1 in N/L 1000/20mg group and 1 in L monotherapy group) neither attributed to intervention Withdrawals due to AEs: 19% vs 20% vs 10% (p=0.06) Withdrawal due to flushing: 11% vs 5% vs 2% (p=NR) Withdrawal due to muscle ache: 4% vs 2% vs 7% (p=NR) Other AEs: all except hyperglycemia reported more frequently in women Headache 9% vs 10% vs 3% Pruritus 7% vs 5% vs 2% Hyperglycemia 4% vs 5% vs 7% Myalgia 4% vs 5% vs 7% Rash 3% vs 8% vs 3% Elevated ALT and/or AST >3x ULN in 1N/L 2000/40 pt and 1 L mono pt Elevated CK >10x ULN NR by any pt	NR/60	Baseline groups - heterogeneity w/respect to TG led to adjusted analysis considering baseline TG, treatment, gender and treatment-by-gender interaction	

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Inclusion criteria	Exclusion criteria	Fixed dose combination product
Insull 2004 US	Patients 21 years or older with CHD or diabetes and LDL-C level of 130 mg/dL or greater (≥3.4 mmol/L); 2 or more CHD risk factors and LDL-C level of 160 mg/dL or greater (≥4.1 mmol/L); or less than 2 risk factors but LDL-C level greater than 190 mg/DL (>4.9 mmol/L). Baseline LDL-C levels needed to be within 12% of each other during 2 qualification visits 10 days or less apart. Baseline TG levels were required to be less than 800 mg/dL (<9.0 mmol/L). Dyslipidemia medications were withdrawn at least 6 weeks before qualifying lipid determinations. Medications with minor effects on lipoproteins were permitted if the dose remained stable. Vitamins or other preparations containing 30 mg of niacin or more were excluded.	Hepatic dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥1.3 X the upper limit of normal [ULN]); renal disease (serum creatinine >1.4 mg/dL [>123.8 µmol/L]); recent (within 6 months) myocardial infarction, unstable angina, stroke syndrome, or revascularization; congestive heart failure, arterial bleeding, severe hypertension, active peptic ulcer, or gallbladder disease; type 1 or uncontrolled type 2 diabetes mellitus; active gout; substance abuse; and breast-feeding women or women of childbearing potential using inadequate contraception. Concomitant agents with adverse effects on hepatic function, skeletal muscle, or creatine kinase and certain agents metabolized by the cytochrome P-450 enzyme system were prohibited.	Niacin ER/lovastatin 500-1500mg/10-40mg (dose-ranging)

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Comparator	Run-in/washout period	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Insull 2004 US	Niacin ER 500-1500mg Lovastatin 10-40mg	6 wk washout dyslipidemia medications 4 wk 'dietary lead-in/drug washout' 2 wk run-in requiring compliance w/National Cholesterol Education Program Step 1 diet	Mean age 59.3 yrs 52% male 82% white	Mean LDL-C 198.5 Mean HDL-C 44.4	299/NR/164

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Insull 2004 US	35/NR/NR	L/N (dose 10/500mg-40/2500mg) vs L monotherapy (dose 10mg-40mg) vs N monotherapy (dose 500mg-2500mg) Primary outcome: mean reduction in LDL-C -21.6%(SE 1.81) to -46.6%(SE 4.48) vs -18.9%(SE 1.80) to -24.4%(SE 2.41) vs -3.3%(SE 1.38) to -19.7%(SE 3.70) N/L vs L SS difference at 20mg and 40mg dose only (p≤0.001) Secondary outcomes: mean increase in HDL-C 8.6%(SE1.90) to 32.9%(SE 4.28) vs 5.4%(SE 2.18) to 9.5%(SE 2.07) vs 2.8%(SE 1.39) to 33.1%(SE 3.60)	Lab measures at each visit

Evidence Table 5. Advicor

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments	Internal comments
Insull 2004 US	N/L (range doses 10-40mg) vs N monotherapy vs L monotherapy Any AE 15-21% vs 21% vs 17% Asthenia 1-3% vs 2% vs 3% Headache 0-1% vs 1% vs 2% Infection 0-2% vs 0% vs 1% Pain 0-2% vs 2% vs 1% Abdominal pain 0-3% vs 1% vs 1% Digestive system AEs 3-10% vs 10% vs 4% Hyperglycemia 0-2% vs 1% vs 0% Elevated ALT and/or AST 1-2% vs 0% vs 0% Nervous system AEs 1-4% vs 1% vs 1% Skin AEs 4-7% vs 6% vs 3% No clinically significant myopathy observed (reported in text, no data)	35/164 total withdrawals 28/164 withdrawals due to AEs		

Evidence Table 6. Advicor_Quality

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Bays 2003a/Bays 2003b/Bays 2005 US (ADVOCATE)	method NR	method NR	yes	yes	yes - to results	yes - to results	no (open-label)
Hunninghake 2003 US	method NR	method NR	no - heterogeneous baseline TG; adjusted analysis attempted to correct for this difference	yes	unclear - reported as double blind	unclear - reported as double blind	yes
Insull 2004 US	method NR	method NR	yes	yes	unclear - reported as double blind	unclear - reported as double blind	unclear - reported as double blind

Evidence Table 6. Advicor_Quality

						External Validity	
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/enrolled**	**Funding**
Bays 2003a/Bays 2003b/Bays 2005 US (ADVOCATE)	no	no	yes for efficacy; unclear for safety	no	fair	NR/NR/315	Kos Pharmaceuticals
Hunninghake 2003 US	no	no	yes - 1 pt (0.4%) never received medication, not included in	no	fair	NR/NR/237	Kos Pharmaceuticals
Insull 2004 US	no	no	unclear for efficacy; yes for safety	no	fair	299/NR/164	Kos Pharmaceuticals

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Study design Setting	Inclusion criteria	Exclusion criteria
Barrios 2005 Europe (7 countries)	ACT NR	Eligible patients included men and women ≥ 18 years with documented hypercholesterolaemia and atherosclerotic or CHD. Patients had serum LDL-C between 2.5 and 4.2 mmol/l (100 to 160 mg/dl) and triglycerides (TG) <4.0 mmol/l (350 mg/dl) while on a stable dose of ATV 10 mg for ≥ 6 weeks prior to randomisation. Patients were considered to have CHD if they qualified as a CHD-risk equivalent by the National Cholesterol Education Program ATP III or ESC guidelines (e.g. diabetes) or if they presented with one or more of the following features: documented stable angina, history of myocardial infarction (MI) or percutaneous coronary intervention and/or documented history of unstable angina or non-Q wave MI. Atherosclerotic vascular disease included symptomatic peripheral vascular disease, documented history of atherosclerosis or atherothrombotic cerebrovascular disease. Patients of childbearing age were eligible to participate if they had negative pregnancy test results and were considered, by the study investigator, highly unlikely to conceive.	Key exclusion criteria included congestive heart failure; MI, coronary artery bypass surgery or angioplasty within the past 3 months; poorly controlled or newly diagnosed (within 3 months) Type I or II diabetes; uncontrolled hypertension (systolic > 160 mmHg or diastolic > 100 mmHg); uncontrolled endocrine or metabolic disease known to influence serum lipids, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels > 1.5 times the upper limit of normal (ULN) and creatine kinase (CK) levels > 1.5x ULN.

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Fixed dose combination product	Comparator	Run-in/washout period	Allowed other medications/ interventions
Barrios 2005 Europe (7 countries)	Ezetimibe/simvastatin 10/20mg	Atorvastatin 20mg	Run-in: 1 wk diet/stabilization period D/C all lipid-altering tx other than ator 10mg 6 wks; fibrates 8 wks	NR

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Barrios 2005 Europe (7 countries)	Lab blood measures; baseline, 6 wks, 8 wks (phone follow-up or visit if necessary)	Mean age 63.5 (SD 9.9) yrs 62% male 92% white	LDL 123.7 mg/dL HDL 54.5 mg/dL (SD 0.3)	752/NR/435

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Barrios 2005 Europe (7 countries)	16/NR/427	Mean change (SE) E/S vs ator: LDL-C -32.8% (1.2) vs -20.3% (1.2) Mean diff -12.6 (1.6) p<0.001 TC -20.3 (0.8) vs -13.0 (0.9) Mean diff -7.2 (1.2) p<0.001 TG (median) -8.4 (2.5) vs -6.5 (2.5) Mean diff -3.2 (3.7) p=NS HDL-C 1.8% (0.8) vs -0.4% (0.8) Mean diff 2.5 (1.2) p< 0.05	Lab blood measures AEs; patient reported and investigator assessed other AEs

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Barrios 2005 Europe (7 countries)	Specific AEs NR E/S vs ator: one or more serious clinical AE 5/221 vs 2/214 tx-related serious clinical AE 0/221 vs 0/214 ALT or AST elevations ≥3x ULN 1/221 vs 0/214	16/13	

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Study design Setting	Inclusion criteria	Exclusion criteria
Goldberg 2006 US VYTAL	ACT NR	Patients with type 2 diabetes (aged 18-80 years) with hemoglobin A_{1c} levels of 8.5% or less AND LDLc > 100mg/dL and triglycerides < 400 mg/dL	NR

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Fixed dose combination product	Comparator	Run-in/washout period	Allowed other medications/ interventions
Goldberg 2006 US VYTAL	Ezetimibe/simvastatin 10/20mg, or the next highest dose (10/40mg/d)	Atorvastatin 10 or 20mg, or the next highest dose (40mg/d)	4 wk run-in placebo 3-5 wk DC lipid-lowering medications	NR

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Goldberg 2006 US VYTAL	Lab assessed blood measures 6 wks	Mean age 59.5 yrs 47% male 73% white	LDL 145 HDL 45.8	2299/1491/1229

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Goldberg 2006 US VYTAL	44/4/1198	Primary endpoint: LDL-C% change from baseline E/S 10/20mg -53.6% vs ator 10mg -15.3% and ator 20mg -44.6%(p<0.0001 vs ator 10mg and 20 mg) E/S 10/40mg -57.6% vs ator 40mg -50.9% (p<0.0001 vs ator 40mg) Secondary endpoint: % pts attaining LDL-C <70 md/dL E/S 10/20mg 59.7% vs ator 10mg 21.5% and ator 20mg 35.0% (p<0.001 vs atol 10mg and 20 mg) E/S 40mg 74.4% vs ator 40mg 55.2% (p<0.001 vs ator 40mg) Secondary endpoint: % pts attaining LDL-C <100 mg/dL E/S 10/20mg 90.3% vs ator 10mg 70.0% and ator 20mg 82.1% (p<0.001 vs atol 10mg and p=0.007vs	NR (presumably lab measures)

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Goldberg 2006 US VYTAL	No SS differences b/t groups for all reported AEs, including serious AEs, death, GI, gallbladder, allergic reactions, rach, hepatitis, ALT or AST elevations, CK elevations	44/17	14 pts excluded from analysis due to AEs (Figure 1)

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Study design Setting	Inclusion criteria	Exclusion criteria
Ballantyne 2005	ACT NR	Men and women, 18 to 79 years, with an LDL-C level at or above drug treatment thresholds established by NCEP ATP III[1] were eligible for enrollment if they met the following criteria: established CHD or CHD risk equivalent with an LDL-C ≥130 mg/dL; other criteria included fasting serum triglyceride (TG) level ≤350 mg/dL, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatine kinase (CK) level ≤1.5 times the upper limit of normal, serum creatinine level ≤1.5 mg/dL, and hemoglobin A1C <9.0% in patients with diabetes.	No established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD ≥10% and ≥20% with an LDL-C ≥130 mg/dL; no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD <10% with an LDL-C ≥160 mg/dL; and no established CHD or CHD risk equivalent, with <2 risk factors, and with LDL-C ≥190 mg/dL.

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Fixed dose combination product	Comparator	Run-in/washout period	Allowed other medications/ interventions
Ballantyne 2005	Atorvastatin 10, 20, 40, or 80 mg	Ezetimibe/simvastatin 10/10, 10/20, 10/40, or 10/80 mg	4 wk run-in placebo/diet D/C 9 wk fibrate therapy; 7 wk all other lipid-lowering therapies	NR

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Ballantyne 2005	Lab assessed blood measures (LDL, HDL, TC, TG) 6 wks	Mean age 58.8 (SD 10.4) yrs 52.3% male 86.2% white	LDL 178.3 (SD 37.9) HDL 48.9 (SD 12.2) CHD/CHD risk equivalent (NCEP ATP III risk category): E/S 46.1% vs Ator 46.4%	4343/NR/1902

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Ballantyne 2005	55/5/1850	Primary endpoint: LDL-C % change from baseline - E/S vs ator: all doses combined: -53.4% vs -45.3% Secondary endpoints: LDL-C % change from baseline, individual dose comparisons - E/S vs ator: range -47.1(10mg) to -58.6(80mg) vs -36.1%(10mg) to -52.9%(80mg); p<0.001 for all same-dose comparisons HDL-C % change from baseline - E/S vs ator: all doses combined: 7.9% vs 4.3%; p<0.001 range 7.2%(20mg dose) to 9.0%(40mg dose) vs 1.4%(80mg dose) to 6.9%(10mg dose); p<0.001 for all same-dose comparisons TC % change from baseline - E/S vs ator: all doses combined: -27.4% vs -25.5% range -25.4%(20mg dose) to -30.8% (80mg dose) vs -21.3%(10mg dose) to -32.1%(80 mg dose); p<0.001 for all same-dose comparisons TG % change from baseline - E/S vs ator NSD all doses combined: -27.4% vs -25.5% range -25.4%(20mg dose) to -30.8% (80mg dose) vs -21.3%(10mg dose) to -32.1%(80 mg dose) % of pts achieving ATP III LDL-C goal: E/S 89.7% vs ator 81.1%; p<0.001 SUBGROUPS - CHD/CHD risk:	Lab assessment blood measures; investigator determined other AEs

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Ballantyne 2005	C-reactive protein: mean % reduction E/S vs ator 24.8% vs 25.1% (NSD) E/S vs ator mean difference: ALT ≥3x ULN -1.1 (CI -1.9 to -0.4; p=0.002) AST ≥3x ULN -0.6 (CI -1.4 to -0.0; p=0.07) CK ≥10x ULN -0.1 (-0.6 to 0.3; p=1.0)	55/32	

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Study design Setting	Inclusion criteria	Exclusion criteria
Catapano 2006 US	ACT NR	Men and women 18–81 years of age with LDL-C ≥ 145 mg/dL (3.7 mmol/L) and ≤ 250 mg/dL (6.5 mmol/L) were eligible for enrollment. Other eligibility criteria included fasting serum triglyceride (TG) level ≤ 350 mg/dL (4.0 mmol/L), alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatine kinase (CK) level ≤ 1.5 times the upper limit of normal (ULN), serum creatinine level ≤ 1.5 mg/dL (133 mmol/L), and hemoglobin A1c < 9.0% in patients with diabetes.	NR

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Fixed dose combination product	Comparator	Run-in/washout period	Allowed other medications/ interventions
Catapano 2006 US	Ezetimibe/simvastatin 10/20, 10/40, or 10/80 mg	Rosuvastatin 10, 20, or 40 mg	4 wk run-in placebo/diet D/C 9 wk fibrate therapy; 7 wk all other lipid-lowering therapies	NR

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Catapano 2006 US	Lab blood measures at baseline and wks 5/6	Mean age 55.7 (SD 10.4) yrs 44% male 86% white	LDL 172.5 (SD 4.5) HDL 50.2 (SD 1.3)	5269/NR/2959

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Catapano 2006 US	136/19/2855	All doses E/S vs all doses rosuvastatin Primary endpoint: Mean change LDL-C -55.8% vs -51.6% (mean diff -4.2%; p<0.001) Secondary endpoints: Mean change HDL-C 7.6% vs 7.6% (NSD) Mean change TC -40.0% vs -36.7% (mean diff -3.3%; p<0.001) SUBGROUP: NCEP AT III CHD/CHD risk equivalent Pts reaching LDL-C <70mg/dl 50.1% vs 29.4% (p<0.001) Pts reaching LDL-C <100mg/dl 90.1% vs 82.0% (p<0.011)	Blood measures lab assessed, others Investigator assessed. Drug related AEs assessed by blinded investigator as to liklihood of being related to therapy

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Catapano 2006 US	E/S vs rosuvastatin: Any clinical AE 29.2% vs 31.1% Drug related AE 8.1% vs 7.4% Serious AEs 1.2% vs 1.1% ≥1+ proteinuria 3.5% vs 6.6% (p<0.001) No SS differences b/t groups for the following AEs: GA, gallbladder, hepatitis, rash, allergy-related, ALT and/or AST elevations (≥3x ULN), CK elevations (≥10x ULN)	136; 73	

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Study design Setting	Inclusion criteria	Exclusion criteria
Bays 2004 US + 24 other countries	ACT NR	Eligible patients included men and women aged 18 to 80 years with primary hypercholesterolemia defined as LDL-C concentrations ≥145 mg/dL but ≤250 mg/dL and triglycerides (TG) ≤350 mg/dL at visit 2. In addition, patients were required to have alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations ≤1.5 times the upper limit of normal (ULN) with no active liver disease and creatine kinase (CK) concentrations ≤1.5 times ULN at visit 2. Patients of childbearing age were eligible to participate in the study if they were surgically sterilized or considered highly unlikely to conceive due to use of an acceptable method of birth control (eg, oral contraceptives, intrauterine devices, double-barrier methods, hormone implants).	Individuals were excluded from participating in the study if they met the following criteria: <50% of ideal body weight according to the 1983 Metropolitan Height and Weight tables (or body weight <100 lb), hypersensitivity to statins, or alcohol consumption >14 drinks per week. Pregnant or lactating females were also excluded.

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Fixed dose combination product	Comparator	Run-in/washout period	Allowed other medications/ interventions
Bays 2004 US + 24 other countries	Ezetimibe/simvastatin combination tablet 10/10, 10/20, 10/40, or 10/80 mg	Ezetimibe 10 mg, or simvastatin 10, 20, 40, or 80 mg	Run-in: 4 wk placebo D/C lipid-altering drugs 6 wks, fibrates 8 wks	NR

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Bays 2004 US + 24 other countries	Lab blood measures; wks 0, 2, 4, 8, 12	Mean age 56.4 (SD 10.6) yrs 49% male 89% white	LDL 177.3 (SD 24.6) HDL 51.6 (SD 12.7)	3407/2023/1528

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Bays 2004 US + 24 other countries	133/9/unclear* *modified ITT used including all pts who had at least 1 baseline and 1 post-baseline measurement; results (table 2) present ranges of pts for each intervention group	Mean % change (SE) E/S vs sim vs eze vs placebo: LDL-C -53.0 (0.6)% vs -39.0 (0.6)% vs -18.9(1.2)% vs -2.2(1.2)% TG -24.3(1.1)% vs -20.8(1.2)% vs -10.7(2.6)% vs -1.9(2.6)% TC -37.6(0.5)% vs -27.7(0.5)% vs -13.3(0.9)% vs -1.4(0.9)% HDL-C 7.2(0.5)% vs 6.8(0.5)% vs 5.0(1.1)% vs -0.3(1.1) Pooled E/S vs sim incremental least squares mean change: LDL-C -14.0(0.8)%; p<0.001 TC -9.9(0.6)%; p<0.001 HDL-C 0.4(0.8)%; p=0.607 TG - not calculable (p<0.001)	Lab blood measures AEs; patient reported and investigator assessed other AEs

Evidence Table 7. Vytorin

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Bays 2004 US + 24 other countries	E/S vs sim vs eze vs placebo Tx-related AEs: 92/609 (15.1%) vs 92/622 (14.8%) vs 19/149 (12.8%) vs 12/148 (8.1%) AST or ALT elevation ≥3x ULN 9/604 (1.5%) vs 7/61 (1/1%) vs 1/148 (0.7%) vs 1/146 (0.7%) 1 serious tx-related AE (possible myopathy in simvastatin 40 mg group) NSD in CK elevations	133/66	

Evidence Table 8. Vytorin_Quality

	Internal Validity							
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**
Barrios 2005 Europe (7 countries)	yes	yes	yes	yes	unclear - reported as double blind	unclear - reported as double blind	yes	no
Goldberg 2006 US VYTAL	yes	yes	yes	yes	unclear - reported as double blind	unclear - reported as double blind	yes	no
Ballantyne 2005	yes	yes	yes	yes	unclear - reported as double blind	unclear - reported as double blind	yes	no
Catapano 2006 US	yes	yes	yes	yes	yes	unclear - reported as double blind	yes	no
Bays 2004 US + 24 other countries	method NR	method NR	yes	yes	unclear - reported as double blind	unclear - reported as double blind	yes	no

Evidence Table 8. Vytorin_Quality

					External Validity	
Author, Year Country	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/enrolled**	**Funding**
Barrios 2005 Europe (7 countries)	no	yes	no	good	752/NR/435	Merck/Schering-Plough
Goldberg 2006 US VYTAL	no	no; 231/1229 (19%) patients excluded from efficacy analysis	yes; 3/1229 (0.2%)	fair	2299/1491/1229	Merck/Schering-Plough
Ballantyne 2005	no	no; 70/1902 (4%) patients excluded due to lack of valid baseline or postbaseline measure	NR	good	4343/NR/1902	Merck/Schering-Plough
Catapano 2006 US	no	no; 104/2959 (3.5%) patients excluded due to lack of valid baseline or postbaseline measure	yes; 8/2959 (0.3%)	good	5269/NR/2959	Merck/Schering-Plough
Bays 2004 US + 24 other countries	no	no; varying numbers of patients included in each efficacy analysis although <8% excluded from any particular analysis	no	fair	3401/2023/1528	Merck/Schering-Plough