

Quantify Dyslipidemia Clinical Outcomes Database Release 1.0, September 21, 2010

1. Summary Information

The objective of the database is to extract all relevant changes in lipids, safety parameters, imaging outcomes and cardiovascular outcomes after treatment with statins, fibrates, cholesterol absorption inhibitors, niacin, or combinations thereof. The database is consisted of three groups of studies. The first group includes trials that focus on short term (1 to 6 months) lipid modifying therapy and that report the lipid biomarker outcomes as their primary endpoint (biomarker trials). The second group includes trials that focus on cardiovascular event outcomes as their primary endpoint (event trials). The third group includes trials that focus on measures of progression of atherosclerosis as their primary endpoint (imaging trials).

Table 1. Summary information for part 1 of the dyslipidemia database, which includes trials that focus on lipid biomarker outcomes as their primary endpoint (Biomarker trials).

Parameter	Description
Format	Excel
Indications	Dyslipidemia – biomarker trials
#Trials	360
# Patients	>137,000
# Rows of Data	19,673
Last Updated	September 24, 2009
Compounds	atorvastatin, bezafibrate, cerivastatin, ezetimibe, fenofibrate, fenofibric acid, fluvastatin, gemfibrozil, lovastatin, niacin, pitavastatin, pravastatin, rosuvastatin, simvastatin
Key efficacy end points	Biomarkers: total cholesterol, HDL, LDL, triglyceride, non-HDL, Apo-A1, Apo-B, CRP; progression of atherosclerosis (if available), clinical outcome endpoints (if available)
Key safety end points	Treatment discontinuations, elevated ALT/ AST/CPK, myalgia, myopathy, etc

2. Features and benefits

Key Features:

- **Comprehensiveness:** includes information for marketed drugs as well as drugs in development; data source includes journal publications, conference posters, regulatory reviews, etc.
- **Ease of tracking:** all clinical trial publications are listed in a separated source database and linked to unique clinical trial names
- **Flexibility:** the database design allows for quick updates as well as expansions to include additional indications/drugs/endpoints/trials
- **Model-friendliness:** designed and reviewed by experienced modelers to ensure highest quality and usability for modeling and simulation to support drug development strategies
- **Customizability:** can be augmented with clinical trial data proprietary to the client (this information goes into a separate proprietary database and will be owned by the client)

Potential Applications:

Characterize relative (comparative) clinical safety and efficacy profile:

Example:

- Quantify risk/benefit of statins and fibrates
- Characterize the pharmacodynamic interaction between fibrates and statins across all lipid endpoints

Characterize endpoint-to-endpoint relationships:

Example:

- Quantify relationship between lipid changes and cardiovascular risk reduction
- Explore potential differences or similarities in dose response relationship for a particular drug class

Ultimately, these analysis help drug companies to optimize trial design, improve trial outcomes, and strengthen product differentiation.

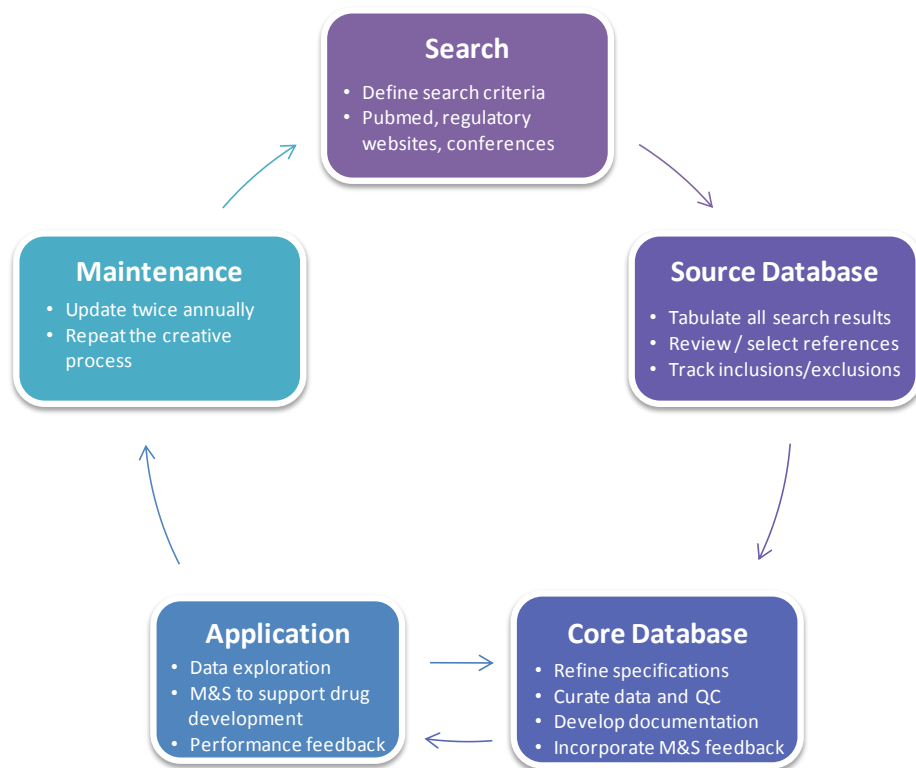
Why use our databases:

- Designed and managed by experienced modelers. There is a strong emphasis to making it easy to extract analysis datasets from the database
- Provide most relevant data to support clients' needs for quantitative decision making
- Contain up-to-date and high quality data so that it is always readily available to provide timely analysis required to support critical clinical trial decisions
- Supported by additional services such as modeling and simulation consulting services (by QS) and custom curation services (by GVK Bio)

3. Organization and Structure

This product consists of two databases, the *source database* and the *clinical outcomes database (core database)*. The *source database* is a database that maintains the sources of information identified by searches and reviewed for inclusion or exclusion from the database. The *clinical outcomes database* contains the information on trial, treatment and patients characteristics and safety and efficacy results of the trials identified for inclusion in the database. In addition, a detailed documentation is provided with these databases.

The following is a flowchart showing the process with which databases are created, optimized and updated.



4. Overview of the Dyslipidemia Source Database

The primary data sources were controlled clinical trials published in the medical literature or available from the FDA. A secondary source of information was published abstracts or presentations of clinical trial data from conferences and corporate websites.

The searches identified 3047 references.

A total of 559 references were selected for inclusion in the database. The inclusion criteria were:

- Randomized controlled trial with a total sample size ≥ 50 for parallel trials or ≥ 25 for cross-over trials
- All trials with the primary objective to modify the lipid or inflammatory biomarker profile, to reduce the progression of atherosclerosis, or to reduce the number of cardiovascular events.
- At least one arm that includes treatment with Atorvastatin, Rosuvastatin, Pravastatin, Lovastatin, Simvastatin, Cerivastatin, Fluvastatin, Pitavastatin, Fenofibrate, Fenofibric Acid (ABT335), Bezafibrate, Gemfibrozil, Ezetimibe, or Niacin (including Niaspan).
- At least one control arm that includes treatment with placebo or active control from treatments mentioned above.
- At least 4 weeks of treatment for biomarker studies and 3 months for event studies

Of the 559 references, 380 belonged to group 1 (biomarker studies); 97 belonged to group 2 (event studies); and 82 belonged to group 3 (progression of atherosclerosis).

5. Overview of the Dyslipidemia Clinical Outcomes Database

The part 1 of the dyslipidemia database (includes the Group 1 trials that focus on lipid biomarker outcomes as their primary endpoint) contains information from 360 trials. There are a total of 19,673 rows (datapoints) in the database. Each row contains the information for an endpoint in one arm of a trial at a specific point in time.

The table below shows the available data for trials in adult patients for which lipid changes are reported. The table shows there is a richness of data across mono therapy as well as combination therapy of statins, fibrates, ezetimibe, and niacin. The data base also contains information from 6 trials in pediatric patients.

Table 3. Overview of available data for adult trials in which lipid changes (HDL, LDL, Triglycerides, etc.) were reported

Treatment	number of trials	number of patients
placebo	174	15859
atorvastatin	117	29971
atorvastatin+ fenofibrate	3	196
atorvastatin+fenofibric acid	1	221
atorvastatin+niacin	1	68
atorvastatin+ezetimibe	3	352
cerivastatin	15	4636
cerivastatin+fenofibrate	1	11
fluvastatin	36	5607
fluvastatin+bezafibrate	1	167

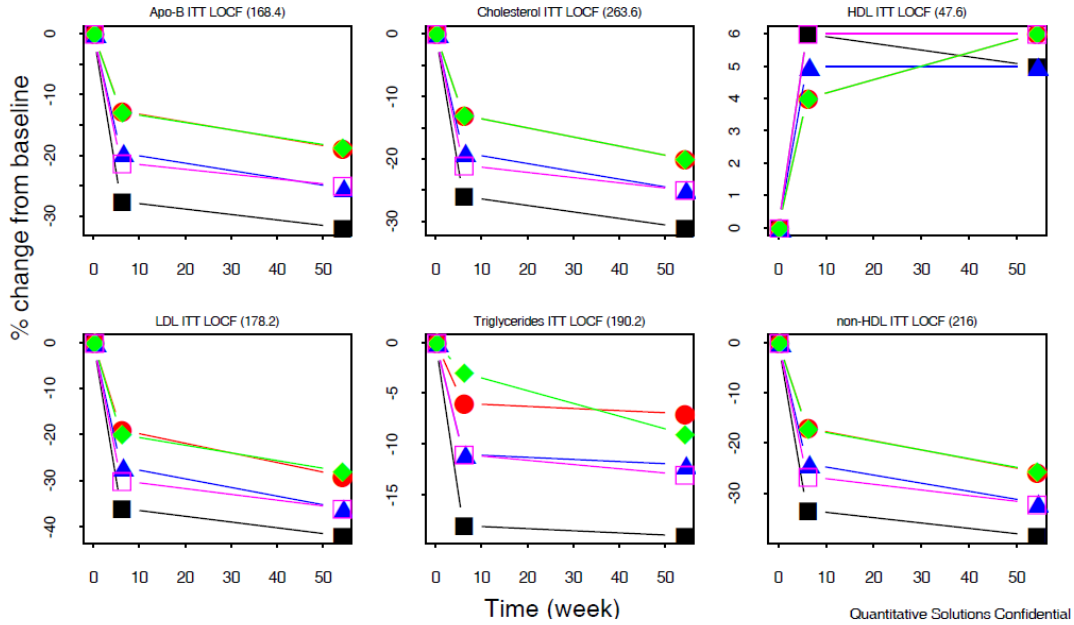
fluvastatin+fenofibrate	1	69
fluvastatin+niacin	1	38
fluvastatin+ezetimibe	1	38
lovastatin	35	11645
lovastatin+niacin	3	371
lovastatin+ezetimibe	1	192
pitavastatin	5	410
pravastatin	76	10436
pravastatin+gemfibrozil	2	210
pravastatin+niacin	2	66
pravastatin+ezetimibe	2	254
rosuvastatin	45	14550
rosuvastatin+fenofibrate	1	114
rosuvastatin+niacin	2	224
rosuvastatin+ezetimibe	1	239
simvastatin	112	20414
simvastatin+fenofibrate	2	511
simvastatin+fenofibric acid	1	238
simvastatin+gemfibrozil	1	136
simvastatin+ezetimibe	17	6885
simvastatin+ezetimibe+fenofibrate	1	183
simvastatin+ezetimibe+niacin	1	676
bezafibrate	14	1043
fenofibrate	40	3033
fenofibric acid	2	232
gemfibrozil	27	3591
niacin	15	1910
ezetimibe	13	2414
ezetimibe+fenofibrate	2	245
Total	353	137,489

6. Example plots of actual trial data

The figures below show example plots of the time course of lipid and other biomarker endpoints for each treatment arm and each trial that has information on these endpoints (double click to open and print).

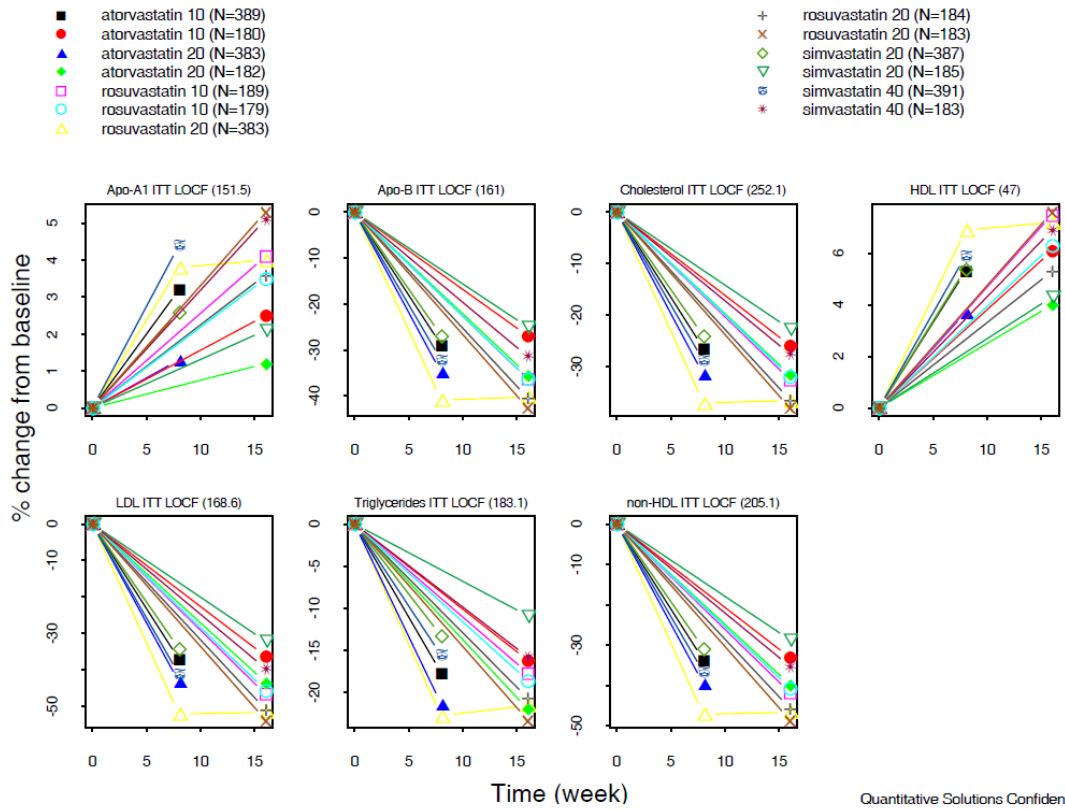
Andrews TC 2001 (ACCESS); hypercholesterolemia; titration if LDL NCEP ATPIII

- atorvastatin 10 80 (N=1834)
- fluvastatin 20 80 (N=467)
- ▲ lovastatin 20 80 (N=461)
- ◆ pravastatin 10 40 (N=450)
- simvastatin 10 40 (N=448)



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Ballantyne CM 2006 (MERCURYII); CHD high risk



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7. Outcome fields

The following endpoints are recorded in the database. For binary outcomes, the number of patients, percent of patients or rate is recorded.

Biomarker outcomes: The following biomarkers were extracted

- LDL; low-density lipoprotein cholesterol
- HDL; high-density lipoprotein cholesterol
- Triglycerides: total triglycerides
- Cholesterol: total Cholesterol
- non-HDL: non high-density lipoprotein cholesterol
- Apo-A1: apolipoprotein A-1
- Apo-B: apolipoprotein B
- CRP: C-reactive protein

Progression endpoints

The progression of atherosclerosis is measured by quantitative coronary angiography (QCA; mean lumen, max lumen diameter and % stenosis), Bmode ultrasonography (mean IMT, max IMT), and IVUS (plaque volume, plaque burden, lumen volume). The progression is often measured at different sites of the vessel. For each of the progression measures the outcomes were extracted for all sites.

The following measures of progression of atherosclerosis were recorded.

- meanLum: Mean lumen diameter () at site
- minLum: Minimum lumen diameter
- Stenosis: % stenosis
- meanIMT: Mean intima-media thickness
- maxIMT: Max IMT

- Plaque volume: The plaque volume is the size of the plaque (atheroma). This is also referred to as the average area of atheroma or total atheroma volume.
- Plaque burden: The plaque burden refers to the % of the vessel that is occluded. This is also referred to as percent atheroma volume
- Lumen volume: The lumen volume refers to the volume of the vessel that is not occluded.
- Plaque progression: number/ percent of patients with progression of plaque/ stenosis (definition with threshold and continuous measure from which it is derived is provided)
- Plaque regression: number/ percent of patients with regression of plaque/ stenosis (definition with threshold and continuous measure from which it is derived is provided)
- Plaque unchanged: number/ percent of patients with no change in plaque/ stenosis (definition with threshold and continuous measure from which it is derived is provided)

Clinical Outcomes: The following clinical event outcomes or certain combinations thereof were extracted

- all cause mortality
- coronary heart disease (CHD) death
- cardiovascular death
- fatal, non-fatal, and total myocardial infarction (MI)
- cardiac arrest with resuscitation
- unstable angina requiring hospitalization
- fatal, non-fatal, and total stroke
- transient ischemic attack (TIA)
- percutaneous coronary intervention (PCI)
- coronary artery bypass grafting (CABG)

Most trials define composite endpoints that include the endpoints listed above. The definition of the composite endpoints varies by trial and for each composite endpoint the events contributing to the composite are listed under the endpoint definition. The list below provides a guide to classifying the composite endpoints

- coronary revascularization (PCI and CABG)
- any revascularization (includes peripheral or others)
- major coronary event (This endpoint mostly includes CHD death or death of any cause, non-fatal MI, or cardiac arrest with resuscitation, however the definition is trial specific and for each trial the exact definition is provided)
- any coronary event (major events + coronary revascularization, or hospitalization for unstable angina)
- major cardiovascular event (major coronary event + fatal or non-fatal stroke)
- any cardiovascular event and/or procedure
- any cerebrovascular event

Adverse events outcome fields: The following adverse events information was extracted:

- Dropout: total dropout (treatment discontinuation). This refers to all patients that did not complete the study.
- Dropout AE: Dropout related to adverse events
- ALT: Number/Percent patients with elevated alanine transaminase
- AST: Number/Percent patients with elevated aspartate transaminase
- ALT/AST: Number/Percent patients with elevated ALT and/or AST
- CPK: Number/Percent patients with elevated creatine phosphokinase
- myalgia: Number/Percent patients with myalgia
- myopathy: Number/Percent patients with myopathy
- rhabdomyolysis: Number/Percent patients with rhabdomyolysis
- proteinuria: Number/Percent patients with proteinuria
- creatinine: Number/Percent patients with increased creatinine.
- flushing: Number of patients with flushing
- additional AE data was extracted if available.