Appendix A:
DARTNet Design Specifications

Note: Prepared by the DARTNet Team, University of Colorado Denver Department of Family Medicine, Contract No. HHSA29020050037I TO2.

Appendix A Contents

Introduction

The Distributed Ambulatory Research in Therapeutics Network (DARTNet) is a prototype federated network of electronic health record (EHR) data from eight organizations representing over 500 clinicians and over 400,000 patients. The prototype system captures, codify and standardize over 150 unique data elements per patient for more than 48 months. DARTNet takes advantage of our team's expertise in analyzing large existing data sets and operating practice-based research networks (PBRN), and is proving to be an asset for the development of a new distributed research network of standardized clinical data from primary care clinicians' EHRs. Four current CO-DEcIDE partners were involved in the development of the first prototype for DARTNet: the University of Colorado Department of Family Medicine (CU-DFM), the University of Colorado School of Pharmacy (CU SOP), the American Academy of Family Physicians National Research Network (AAFP NRN) and the Robert Graham Center (RGC). Two technical partners joined in this effort: the University of Minnesota Center for Excellence in Primary Care (UMN) and Clinical Integration Networks of America, Inc. (CINA).

The process of developing the DARTNet prototype actively explored how we can use existing EHR data to supplement data from large administrative datasets in order to answer questions concerning the safety and effectiveness of medications and medical devices. Furthermore, using our PBRN expertise assisted us to explore the ability to fill gaps in clinical data using point-of-care data collection techniques.

A key requirement for DARTNet is the standardization of data elements across EHR products. We accomplished this using advanced clinical decision support tools already available from CINA. We used tools developed by CINA to access and export standardized data at each clinical organization into a relational data set that we refer to as a Clinical Data Repository (CDR). This standardized data set, which includes patient identifiers, was successfully transferred to a second database (the electronic Primary Care Network Gateway database—Gateway for short), de-identified and presented for query access through a secure Grid enabled web-portal. Both of these databases reside within each participating clinical organization. The movement of data from the CDR to the ePCRN Gateway database is based on the ASTM-standardized Continuity of Care Record (CCR). A full set of patient data never left the clinical sites where they are stored in this effort; however, the DARTNet team has the ability to query the de-identified federated databases in order to answer research questions that cannot be answered from existing administrative datasets. Furthermore, we explored the development of natural language processing (NLP) system to be used to unlock key data elements from EHR text.

The DARTNet system is readily expandable using Grid-based local parallel processing and a two-stage data extraction and de-identification process. The DARTNet architecture will support a final system to accommodate at least two orders per year—of magnitude greater than this prototype with a single central technical support site. By adding additional central support sites (or supernodes) the network is essentially infinitely expandable. Furthermore, the data interfaces are not specific to primary care and can be expanded to include sub-specialty data where they are available electronically. When taken to scale, DARTNet will be able to explore both rare safety events in low usage medications and the safety and efficacy of commonly used ambulatory therapies.

Overall Aims

Aim 1: Develop a federated network of 200+ primary care clinicians who use EHRs, while examining the following issues.

a. Establish a governance system that supports access to federated data while allowing members to maintain control of their data.
b. Create a data extraction approach that will allow virtually any clinicians with EHRs to join the network as desired.
c. Examine the ability of an existing National Institutes of Health (NIH) supported software package to meet the distributed query needs of the network.

Aim 2: Analytically demonstrate how existing large-scale data sets can be enhanced by patient-level data from the federated primary care network to inform and expand knowledge of effective and safe medical therapeutics.

a. Use existing large datasets (e.g., Ingenix) to evaluate medical therapeutics safety and effectiveness from a population based level.
b. Examine what additional information can be obtained from existing patient level data available through DARTNet.
c. Determine what information will only be available through direct data collection from clinicians or patients.

Aim 3: Demonstrate the ability to collect specific data from clinicians or their staff on a clinically defined set of patients to enrich the EHR data set and answer effectiveness and safety questions concerning medical therapeutics.

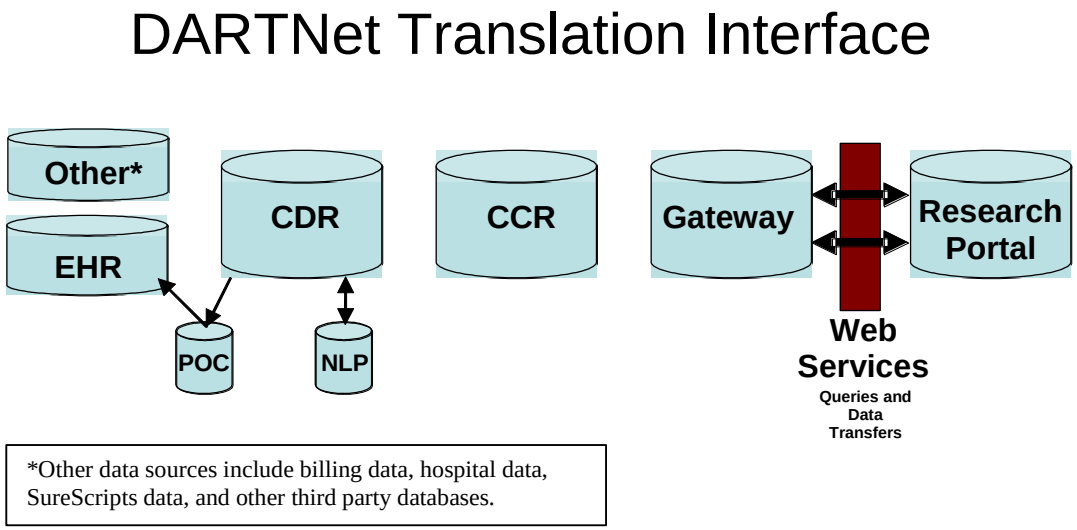
a. Demonstrate the ability of the federated system to use clinical and administrative data to identify patients from whom additional data might be collected.

Technical Overview

The Distributed Ambulatory Research in Therapeutics Network (DARTNet) builds on several best-in-breed technologies to create a true distributed clinical data repository for data acquisition and other activities. The system is currently based in primary care practices. It is not dependent on any particular electronic health record (EHR) for data access. Systems are in place to encourage high quality data collection: improved care processes (which increase the likelihood that selected data elements are captured), multiple data interfaces, data standardization, a data repository, and a GRID presentation for distributed query activities.

Figure A-1 below summarizes the relationships between data sources and data access points. We will highlight elements of this figure throughout this document.

Figure A-1. Relationship of data sources and the DARTNet architecture within a single organization



This document is organized from the point of contact between patient and physician during routine clinical care, moving toward use of the data for research and quality improvement. Beginning with the source of clinical data within the patient-centered medical home, this report will provide a technical description of the following critical data collection and processing components of DARTNet:

- Collecting EHR data from the primary care practice
- Interfaces to secure laboratory, radiology, and medication data
- Interfaces to secure hospital data
- Clinical decision support as the critical linkage between disparate EHR data and a centralized system
- Mapping EHR data
- Grid computing
- DARTNet queries (both local and global)
- Support for local quality improvement and large scale comparative effectiveness studies
- System security
- Natural language processing to obtain information entered as text
- Point-of-care data collection

Clinical Data Sources

The foundation of DARTNet lies in clinical data collected for patient care in the medical home. We rely on clinicians—currently primary care clinicians—who actively use an EHR to document ambulatory patient encounters. The system builds on two important features of practice-based research networks (PBRN) to enhance physician buy-in. First, the entire system is envisioned as a learning community for the member clinicians. The ability to connect to relevant clinical data allows the system to identify top performers so that the rest of the members can learn from them. Second, the system will develop point-of-care data collection processes, the

sine qua non of a true PBRN. These points are also important as we believe both will drive improvements in the overall quality of data in each organization's EHR – thus improving the quality of data available for research from DARTNet.

In this section we outline the data DARTNet will acquire from these ambulatory EHRs and from interfaces with laboratory services, imaging providers, medication fulfillment services, and hospitals. Where possible, data that are not already flowing into the medical home for clinical use will be captured in such a way as to make it available for clinical purposes as well as quality improvement/research purposes.

Electronic Health Record (EHR)

Because DARTNet includes data acquisition as a key component of the system we have elected to work only with EHRs that include coded problem lists, electronic prescribing and laboratory interfaces. The EHR system must also allow read only access to a data extraction/standardization system. It is important to note that we believe virtually all EHRs that meet the minimum requirements above can be supported. EHRs that are known to be compatible with the current data extraction system include Allscripts, A4 Healthmatics, Centricity, EMDs, NextGen, Practice Partners, Soapnotes, and eClinical Works.

DARTNet organizations must commit to using their EHRs in a way that will support the advanced clinical decision support system (CDSS), meaning that the organization uses limited locations for data elements and consistent terminology throughout the EHR. Where use is highly variable by member clinicians, the organization must develop a plan to improve data integrity to support the advanced clinical decision support system. Note that the minimum standards are couched in clinical decision support terms to help solve clinical problems facing DARTNet clinicians with the expectation that this will provide higher quality data for research, while also improving clinical care. See Appendix A-A for DARTNet membership criteria.

Although EHRs are rich sources of data, they do have some limitations. Clinical data cannot be electronically extracted from scanned documents. Likewise it is very difficult to extract data from free text or electronic documents that contain embedded values (such as imaging reports). Thus, EHRs that rely heavily on, or implementations of EHRs that extensively use, free text, scanned text, or electronic interfaces of textual data (such as dictated notes) will be discouraged. A further limitation of using only clinically-derived data is that the frequency and consistency of data collection are likely to be less than ideal when compared to randomized controlled trials. It is important not to think of DARTNet as solely a data acquisition solution, but as a system that also supports randomized and practical clinical prospective trials.

Data interfaces for DARTNet organizations are described below. All are interfaces that operate for clinical purposes. Some are required (and will be noted as such) and some are optional. The development of these interfaces generally occurs at the EHR vendor - data provider level (and occasionally at the CINA - data provider level). These interfaces are not maintained by the DARTNet infrastructure. They are described here for the reader to understand how clinical data are available for use by DARTNet.

Laboratory, Imaging, and Medication Fulfillment Interfaces

An electronic laboratory interface must be in place for the primary laboratory used by each organization, and preferably for all laboratories used by the organization. Electronic interfaces for an organization's secondary labs can be created to store data directly in the CDR if an EHR interface is not available. These labs would then support the CDSS/data extraction

process. CINA creates a clinical data repository (CDR) at each organization (see Figure A-1, above) and the CDR can handle electronic interfaces instead of the EHR if this is more cost effective.

Electronic interfaces with the imaging centers used by the organization are preferred but not required. Even electronically transmitted imaging data arrives as a text file and therefore requires processing for data extraction.

SureScripts-RxHub is a partner in the project and all DARTNet sites are encouraged to install SureScripts-RxHub capabilities as the organization's EHR and region allow. These activities are part of the EHR installation and not within the control of the DARTNet infrastructure development. Once SureScripts-RxHub capabilities are installed, medication fulfillment data can flow either into the organization's EHR (preferred method) or into the CDR until the EHR can support these data. In either case, the medication fulfillment data are available for CDSS/QI/research purposes.

Hospital Inpatient Data Interfaces

Hospital inpatient data interfaces are not included in most ambulatory EHRs. In EHRs where inpatient data are included, the enormous volume of inpatient data has created difficulties in finding useful ways to sort inpatient and outpatient data for efficient review. Selected inpatient data elements can be useful, but the extent of the data required for outpatient clinical care is markedly less than the needs during many inpatient admissions. Therefore, we are exploring specific data interfaces for hospital data that would feed into the clinical data repository (CDR) and be accessed for quality improvement and research. At this time we are focusing on collecting data that will inform us of severe adverse events that originated in the ambulatory arena, rather than developing a robust inpatient related distributed database. Such interfaces require development with each institution in terms of data elements, frequency of data transfers and local data storage. Since DARTNet is also designed to support the patient-centered medical home, data extraction and storage of identified data (such that it can be linked to outpatient data) is HIPAA compliant as it will be available for clinical care.

Demographic and Billing Data

The ability to link to most billing and accounts receivable systems is a feature of the CDR in use for DARTNet. In general, the data contained in these systems are also included in the EHR. Therefore, at this time, interfaces to these data bases are not required of DARTNet participants, though some already have these interfaces in place.

Clinical Decision Support and Data Extraction

Clinical Integration Networks of America, Inc. (CINA) is a small corporation dedicated to providing an advanced clinical decision support system (CDSS) independent of a particular EHR. Practice-level implementation of the CDSS provides an avenue to communicate with clinicians at the point of care. DARTNet capitalizes on the CDSS to facilitate bi-directional communication with clinicians to collect EHR data from their practices, and to provide local clinical decision support services for clinicians to use for their own quality improvement initiatives. This communication can be tailored for each patient visit based on analysis of many different data elements from various sources, including the EHR, the billing system, direct patient data entry, drug fulfillment data and laboratory data that is not linked to the EHR. Additionally, the CDSS can standardize the EHR data elements that DARTNet will aggregate.

Thus, the CINA software will populate the federated database, and provide a method through which DARTNet can manage point-of-care data collection.

Using an Open Database Connectivity (ODBC) connection, CINA connects at the data level to many ambulatory EHRs. At the data level, CINA already has proven interfaces with many of the major ambulatory EHR products in the country as noted above. For this project the primary data sources will be each organization's EHR, augmented where necessary by billing data and medication fulfillment data at some locations, as described above.

CINA completes data extraction and connectivity through a software package called the CINA Protocol Engine (PE). This software system runs locally on each practice's CINA server. The PE is programmed in C#.Net and is a DLL that is compiled through a table driven development process. This approach allows the medical staff at CINA to create the operators necessary to provide the CDSS function without having to be C# programmers. Through connectivity to each organization's EHR and ancillary databases the PE fills the CINA Clinical Data Repository (CDR). After the CDR is filled or appended the PE then performs data standardization and runs a series of CDSS functions (including research specific algorithms) against each patient for which new information has been appended to the CDR since the previous update. All outputs from the CDSS function (such as the need for a particular lab test or the need for additional data collection for a research project) are stored in the CDR and reported to clinicians at the time of the next patient visit and can be exported for batch usage (such as recall letters) and reporting activities. If there is a change in one of the protocols in the protocol engine then the system will run the new protocol against all eligible patients updating their CDSS results. On a timed, automatically triggered basis - typically early each morning—the CINA system within each organization checks with the central CINA server to see if any protocol changes have been made to the organization's PE. If so, the local PE is updated and the new or changed protocols run against the CDR. Thus, we are able to rapidly implement new CDSS and research functions.

The CINA CDR is a normalized and standardized database of relevant clinical information (not an image of the entire EHR database). The CINA CDR can be deployed in a number of ODBC compliant databases, but DARTNet uses a Microsoft Sequel deployment. The CDR stores the raw data format for each data element (in some cases data elements may be represented in the EHR in many different ways) and all outputs related to CDSS protocols are also stored. This allows us to recode any data element in the CDR if we discover a need to present the information in a more granular fashion. For instance, we are initially coding all Hemoglobin A1c values with one SNOMED CT code, though some tests are run in a central laboratory and some are performed using an analyzer at the point of care. If in the future it becomes important to tell the difference between these two circumstances we can look back into the CDR data and recode for each. Finally, within the CDR tags are placed on the data such that it can be appropriately loaded into Qlikview, a reporting structure that is included with the PE. Qlikview reports are used for the quality improvement/learning community activities.

The point-of-care output of the CDSS report can be displayed on a web page, embedded within an EHR, or printed for use. All DARTNet practices have found that printing the output is a superior approach, as the information may be acted upon by the front desk staff, the patient, a nurse and the clinician. Paper is an easy and proven way to move the information between this diverse set of individuals during an office encounter. Also, several practices use the system to highlight patient education and support services on web sites based on diagnoses or other clinical

data. In these practices the paper form is given to patients for educational and personal clinical information tracking purposes.

Data Mapping With Each EHR

Data elements identified as applicable to the CDSS process or for current or future studies are mapped within each EHR and standardized prior to being imported into the onsite CDR. The labor-intensive process of mapping has included identifying the variations on data content and storage locations occurring within each EHR and deciding how to apply standardized nomenclature to each data variant. The EHR mapping process (which uses the *CINA Mapper*) utilizes pattern matching to locate, verify and translate both codes and text into the standardized nomenclature maintained within the CDR. Whether data are stored in constrained fields or not, the CINA Mapper allows likely matches to be viewed by a clinician who then determines whether the "match" is congruent with the concept desired. Once congruence is established, the CDR Mapper will extract these data elements on a regular (typically nightly) basis from the EHR to the CDR.

Data Standardization

The CDR is primarily populated with data elements used for CDSS. All data elements in the CDR are standardized (cross-walked) to one of several coding systems; ICD-9 CM for diagnoses, RxNORM and GCN codes for drugs and SNOMED CT codes for all other data elements. The DARTNet Research Core has identified a robust initial set of data elements for standardization. Most elements have been cross walked to one of the above coding systems, and all data elements required for the pilot research project have been cross-walked (see Appendix A-B). SNOMED CT codes for all data elements including laboratory tests, selected imaging studies and procedures, history, allergies, and family history have been mapped and reviewed by SNOMED SAS, the training and certifying organization for SNOMED CT operated by the College of American Pathologists. We can also cross-walk the SNOMED-CT codes to LOINC for lab results if this is deemed appropriate in the future. Medication cross-walking poses the greatest challenge since information is needed both at the drug classification and the individual medication level and medications come as single entities and combination drugs. We have coded all single agent medications of interest for general CDSS use and for our first research project. We are continuing to explore the best use of SNOMED CT versus commercially available drug codes for group classifications and combination drugs, neither of which is currently included in RxNORM. As there is no single coding system that is comprehensive and without disadvantages, we are currently planning to cross-walk medications to both RxNorm and GCN codes as well as capturing NDC codes when available. We also must incorporate the ability to link both prescription generation data from the EHR to dispensing information from SureScripts-RxHub. As new data elements are added, or if greater detail is required from currently cross-walked codes, new entries will be added to the data dictionary and the CDR will be populated with these codes. All codes are reviewed by in-house physicians, our in-house coding expert, and intermittently by external coding consultants.

Grid Based Computing

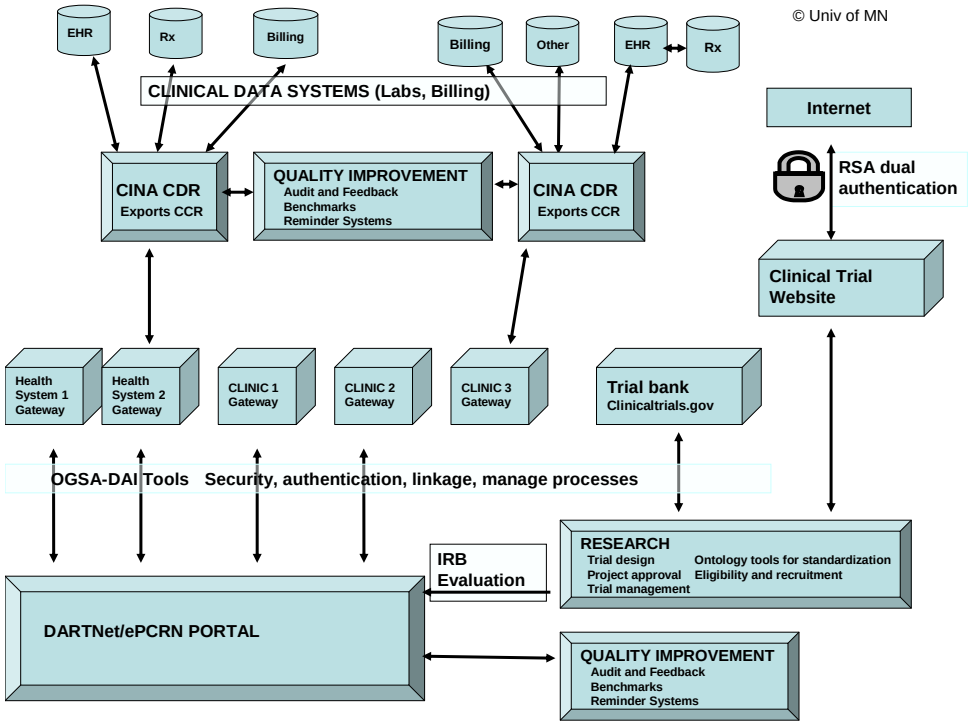
This section of the report describes the computing resources needed to administer and run DARTNet. DARTNet builds upon the work previously carried out by the University of

Minnesota (with funding from NIH) to build the ePCRN Portal. This portal provides the architecture that houses the "Gateway" database for all users (local and centralized), as well as the query capabilities and the security systems. DARTNet uses the connectivity and distributed query capabilities of the ePCRN Portal, which are handled through a specifically designed application of the Globus Toolkit including the X.509 security application, the Open Grid Services Architecture - Data Access and Integration (OGSA-DAI) application, and Globus File Transfer Protocol (FTP) applications.

Grid computing is distinguished from conventional distributed computing by its focus on large-scale resource sharing, innovative applications, and in some cases, high-performance orientation. Grid computing is distinct from Internet access (which is primarily a communication tool) or wide area networks or virtual private networks, which allow access rights behind a fire wall. Grid computing allows functions such as complex queries to be passed to any number of local nodes without crossing an organization's firewall to physically access the data to be acted upon. The query can be executed locally and the output can either be stored on a local computer or, if allowed, returned to the central location. Since the Grid utilizes parallel processing, queries that may take hours to run against a central database can often be completed in minutes across a Grid system. For more details of Globus Toolkit and Grid computing, and their significance for such applications, see Appendix A-C.

The basic structure of the DARTNet system (incorporating the CINA CDSS, ePCRN Gateway Portal, and linkages to local EHRs) is displayed in Figure A-2. Each DARTNet organization has (1) an EHR database that is designed for clinical transactions and under the control of the local organization and EHR vendor, (2) a CDR database that is controlled by CINA (a HIPAA business associate of each organization) and the local organization and (3) a Grid-enabled database, called the ePCRN Gateway database, that is controlled locally but accessed by the Technical Core of DARTNet. Figure A-2 displays the potential data feeds and the relationship of the various components of the system to each other. This model does not show all potential connecting arrows or copies of each database to simplify the diagram, but highlights multiple clinical organizations within the network.

Figure A-2. Basic structure of the DARTNet system (incorporating the CINA CDSS, ePCRN Gateway Portal, and linkages to local EHRs)



Data Export and Presentation to the Grid

The movement of data from the CDR to the ePCRN Gateway database is based on the ASTM standardized Continuity of Care Record (CCR). The CINA tools access data in the EHR, standardize the data, and then create CCRs locally for each eligible patient at each of the clinical organizations. CCR files consist of an XML string, which is passed to the ePCRN Gateway database (created in MySQL), and the file is parsed into fields that are selectively available to outside Grid enabled queries, effectively de-identifying the dataset. The use of the CCR and XML allows all potential data elements to be exposed to a Grid query to be accounted for within the XML schema. Thus, the OGSA-DAI query engine does not have to be modified as new data elements are added to the Gateway database.

Security Overview/ Authentication

The overall DARTNet security model adopts a "defense-in-depth" strategy developed by the University of Minnesota for the ePCRN Portal. We describe each piece in turn. The term "clinic" represents any holder of patient data that will be securely exposed to the DARTNet infrastructure. The DARTNet security framework is based on a X.509 Public Key Infrastruture-based (PKI) security scheme. The system supports mutual authentication between clients and services, Transport Level Security (TLS) based secure communication, and authorization (access control). For secured communication, both the server and the client must have a certificate and key and a proxy for TLS based communication. During the handshaking process, proxy certificates are exchanged as well as a client/server's public key to test each party's authenticity.

If the handshake succeeds, a TLS-based secure session is set up and all Simple Object Access Protocol (SOAP)[A-1] messages are encrypted and transferred securely.

For access control to services, data resources, and database activities, each user is associated with a specific and identifiable DARTNet role (e.g. Admin, Research staff, Physician, Nurse, etc.) who is allocated a set of privileges that are controlled by the local clinic site. There are three different tiers for authorization and access control: (1) user-role mapping after authentication, (2) access control on resources and activities, and (3) access control on the database layer, as shown in Figure A-3 and Figure A-4. The current DARTNet implementation focuses on access control on the database layer.

Figure A-3. Access control at the server side

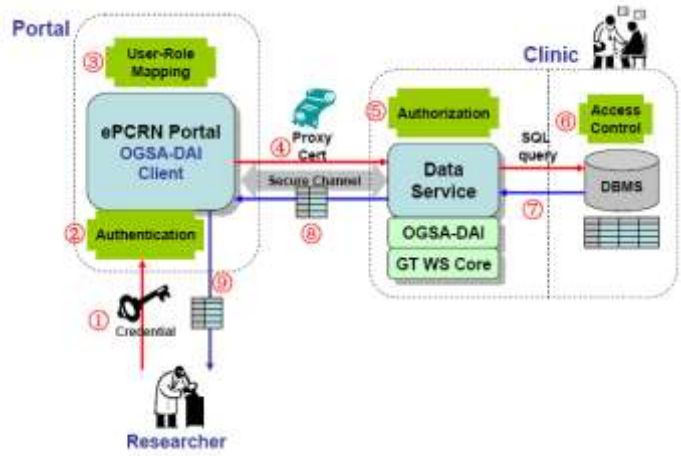
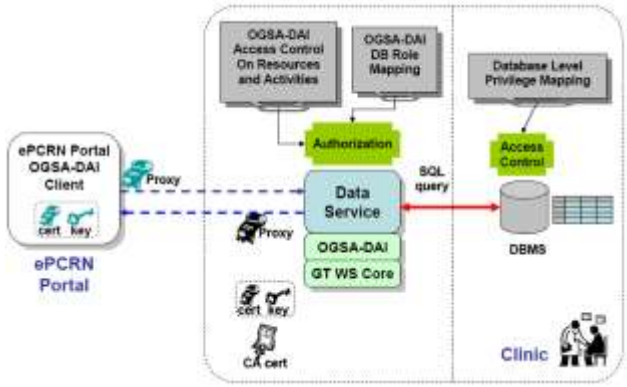


Figure A-4. ePCRN security infrastructure



Each clinical site is an independent research domain and is primarily responsible for local data security. The security requirements for the clinic sites consist of two types of controls: physical access control and technical security control.

1) Physical access control
   a. Physical access to computers and software systems (OGSA-DAI server and Database) is restricted.
   b. All monitors have a pre-defined time-out feature.
   c. Passwords for the database and the computers are properly and securely managed, including hard password requirements.
2) Technical security control
   a. Firewall setting for access control
      i. Only the Internet Protocol (IP) address of the DARTNet portal through the correct port number is allowed to access the OGSA-DAI server system.
      ii. Access to the MySQL database is only allowed over local connections.
      iii. All communication between the DARTNet portal and OGSA-DAI server are encryption based.
   b. SQL Query restriction

[A-1] www.w3.org/TR/soap

i. Only SQL query (SELECT) is allowed from the Web Portal to the local Gateway database.
ii. Any other SQL statements that might modify the database are deleted before being sent to the database.
iii. SELECT statements that include a locally restricted column, such as patient identification information, are blocked by the OGSA-DAI server.

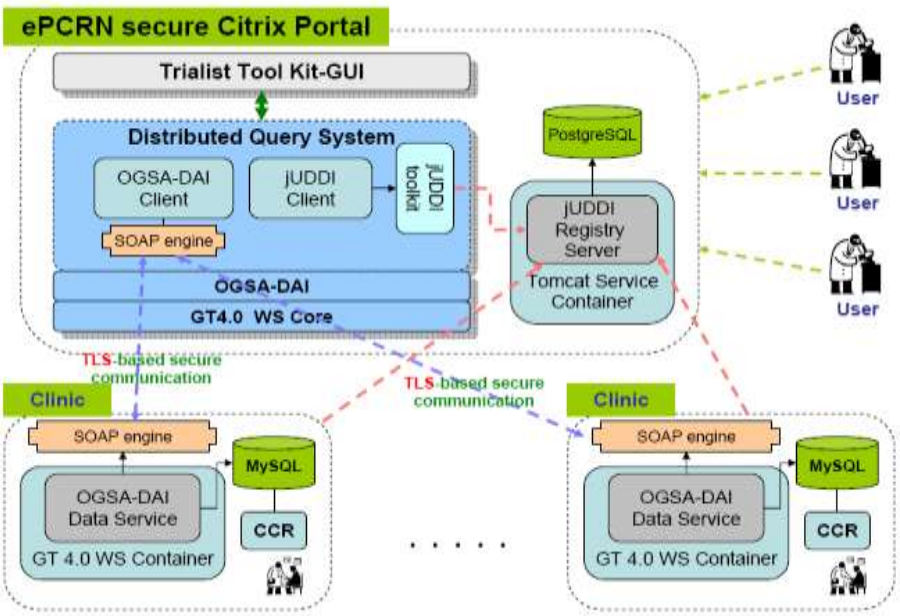
c. Client/Server verification: Client/server verification (authentication) is performed based on x.509 based PKI infrastructure.
   i. Only the clients that have certificates legitimately signed by the DARTNet certificate authority are able to access the OGSA-DAI server.
   ii. Certificates are generated based on the RSA public-key authentication algorithm (a user held system that changes the authentication code between user and the OGSA-DAI server every 60 seconds.)

d. Universal Description Discovery and Integration (UDDI) Server protection
   i. HTTPS protocols are used for all connections to the UDDI server in the DARTNet portal. The connection to the database (PostgreSQL) is restricted to local access only. Finally, where possible the entire system operates over Internet 2, thus further limiting potential data snooping.

Data Query

The DARTNet query architecture is shown in Figure A-5. The figure depicts the interactions such as registering, discovering, and querying databases in the clinics, which can be accessed via Grid services interfaces. A middleware, OGSA-DAI (Open Grid Service Architecture – Data Access & Integration[A-2]), is used to allow data resources, such as relational or XML databases, to be exposed as Grid services. This OGSA-DAI data service is deployed in

Figure A5. DARTNet query architecture



[A-2] www.ogsadai.org.uk

the default Globus Toolkit Web Services Resource Framework (WSRF)-compliant Web Services Core java container.[A-3] In order to support a Web-based distributed directory service (publishing/discovering Web services) for the OGSA-DAI services, we adopt Apache jUDDI,[A-4] an open source Java implementation of UDDI specification. We have developed client Application Interfaces (APIs) supporting jUDDI publish/query, concurrent distributed queries, and error/exception handling.

Query Development

Queries are dynamically created by the ePCRN Research Portal application. This is a web based interface that allows complex queries to be developed through an intuitive interface. The interface performs several functions:

a. References the National Cancer Institute Enterprise Vocabulary Services (EVS)
b. Allows queries to be generated with different code types
c. Generates the executable query in the form of an XPath Query

DARTNet will employ this interface in carrying out the research project designed to test the prototype system. The first study will be a comparative effectiveness study of oral hypoglycemic drugs.

Query Execution

Once a query has been developed the ePCRN Research Portal application submits the query to the OGSA-DAI APIs, which pass them to each node within DARTNet to be run against the Gateway database through a Java application on the local server. All queries run locally and simultaneously. If the query is designed to return only aggregate data the results are returned in the same session to the OGSA-DAI server. If the results return de-identified patient level data the query can only be passed into the local server and must be activated by someone behind the local firewall. Results of these queries are returned locally and then, after local permission is given, transferred to the research team. These two additional steps guarantee local control over any patient-level data used for research purposes.

Data Transfer

Aggregate practice-level data are currently being transferred using two different mechanisms, with the expectation that eventually the Globus system will handle all data transfers. While the full Globus installation at each organization is being finalized and fine-tuned, we will use a secure FTP transfer from each location to a University of Colorado Department of Family Medicine secure server. We will use standard secure FTP software for this transfer and will set up the receiving server to transfer received files every 5 minutes to a data server, which is not visible to the Internet.

As the system matures, we will be able to use the OGSA-DAI queries to return aggregate data directly from the organizational-level Gateway databases to the University of Minnesota (UMN). We can then aggregate further and move the data between the UMN and other research sites using either the Globus transfer capabilities or secure FTP.

[A-3] www.globus.org
[A-4] ws.apache.org/juddi

Patient level data will always be extracted to a local directory within each organization. If the select statement is passed over the Globus system it must be activated by clinic personnel or a business partner. Clinic personnel must also manually move the data to a location that is accessible to the Globus secure transport functions. If the data extraction occurs directly against the CDR (as it does currently) it must be physically run by CINA personnel or a practice representative (these queries would be written by CINA using a stored procedure to create the data set). This data set can then be transferred through secure FTP. This redundant approach is more labor intensive but provides a backup data extraction system as we fine-tune the Globus environment.

Quality Improvement

For member organizations, one of the key DARTNet functions is the creation of an effective learning community. To this end, DARTNet's Board of Directors has directed the Technical Core to develop mechanisms to report both process and intermediate outcome quality measures at the practice level. The indicators must include both individual measures and combination measurements (such as an overall score for diabetes care in addition to presenting each measure independently). Finally, the Board instructed the Technical Core to explore appropriate mechanisms to control for variability in practice populations.

Eventually, many of these quality improvement reports will be created by running a series of queries using the Gateway database. By varying the inclusion and exclusion criteria we should be able to explore the effects on quality indicators of a number of variables, such as the number of visits in a year, insurance status and other variables.

While we are finalizing and testing the Gateway database and Grid services we will rely on existing quality reports within each organization to create these system-wide reports. The CINA system tags data as it populates the CDR and these tags allow the building of a sophisticated reporting system using the Business Intelligence software package Qlikview. This report allows an organization to move from the full organization level to individual patient level data in a few clicks. We truncate these data at the practice level and provide tags for additional population-level variables of interest so that the quality reports can take these variables into account.

Paper copies of these reports are available as part of the Qlikview package at each organization and on a secure SharePoint web site. The SharePoint site uses Microsoft Sequel Reporting Services to create dynamic reports that DARTNet members can manipulate. Reports only identify a single practice or an organization's full set of practices, depending on an individual's level of permission on the SharePoint site. The three top-performing practices for each final report product (the report that best controls for population variability) will be identified so that other organizations may learn from them.

Data Additions Through Natural Language Processing

Even in EHRs that offer extensive data templates for coding history and physical exam items, these areas are frequently entered using free text because of the clinical nuances involved. Therefore, by using natural language processing (NLP), DARTNet data will be significantly enhanced for quality improvement and research purposes.

The free text of EHRs has significant benefits for clinical research and care, as has been shown for heart failure (Pakhomov et al., 2007a) and chronic angina (Pakhomov et al., 2007b). EHR text constitutes a more complete source of information than billing records for identifying

patients' clinically relevant data. Even relatively simple NLP methods can be used to "unlock" the valuable patient- and disease-specific information from an EHR. This methodology may be used to gather data from clinical reports to improve the quality and safety of care and for research. For example, when searching for evidence of foot exams in patients with diabetes, the sensitivity of the NLP approach was 91% (95% CI 85-96), the specificity was 76% (95% CI 58-94), while the overall accuracy was 88% (95% CI 82-94). The reliability of manual review was 91% (95% CI: 85-97), which is not significantly different than using NLP.

The DARTNet Natural Language Processing system will be designed initially for processing the text of physical examination, procedural or history of present illness data. The system will be constructed by adapting existing basic components to the task at hand and will rely on the publicly available software platform – Unstructured Information Management Architecture (UIMA).[A-5] UIMA was developed by IBM, Inc. and represents a powerful Java-based software platform for development and implementation of modularized applications for processing unstructured data including text, video, audio and genomic data. The UIMA Working Group was sponsored in 2005 by the US government. This working group facilitated the integration of several similar platforms including the Generalized Architecture for Text Engineering[A-6] (GATE) and Stanford's OpenNLP toolkit.[A-7] All of these platforms are publicly distributed as open source.

For this project, we propose to use UIMA to implement the NLP system because it is emerging as a powerful, versatile, and well-documented technology that is widely accepted in the bio-NLP community. One of the unique advantages of UIMA is that it supports distributed grid-enabled applications, which is critical for the interface with the ePCRN system. Furthermore, our group has prior experience with implementation of NLP technology using UIMA. The NLP system will consist of the components described below and illustrated in Figure A-6.

Common Annotation Structure (CAS) Initializer: This is a pre-processor component specific to the UIMA platform. Its purpose is to provide an interface to the clinical report on ePCRN servers and to generate a Common Annotation Structure. The latter is a Java data structure in object form that will be subsequently manipulated by the NLP components.

Tokenizer: The function of the tokenizer is to break up the continuous stream of text into its basic segments including word tokens, digit tokens and punctuation tokens that are compatible with subsequent NLP components.

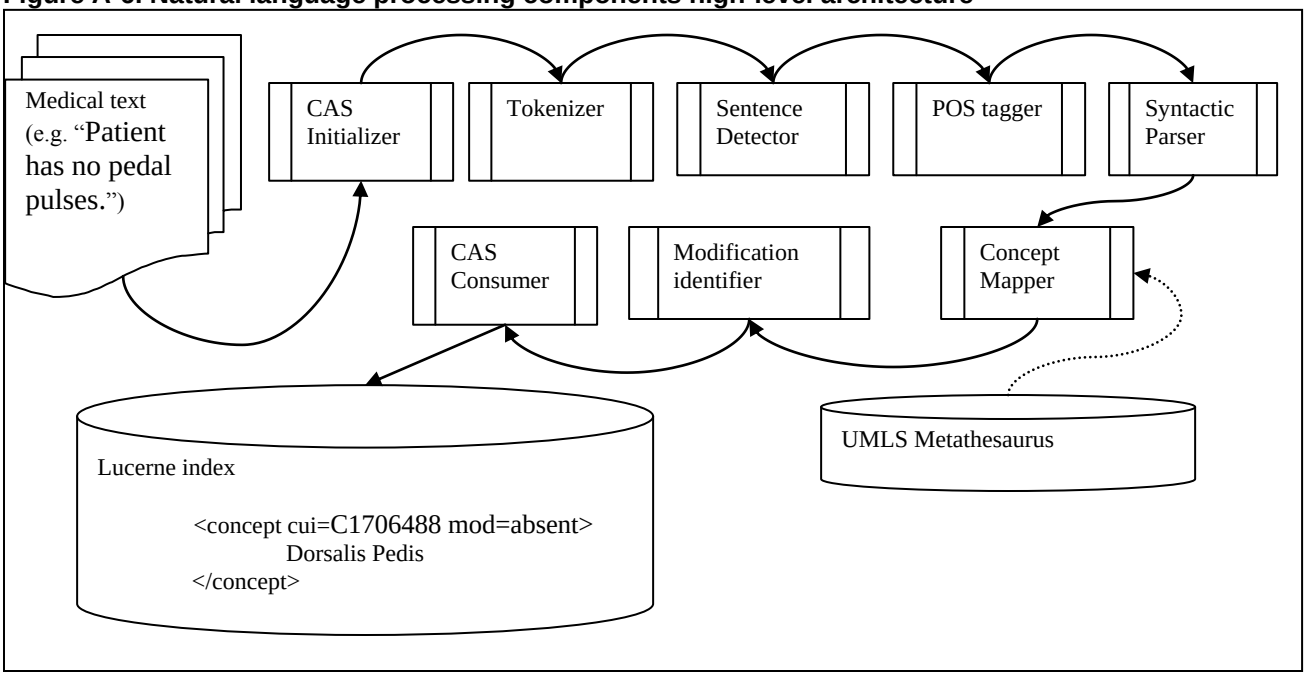
Sentence Detector: The function of the sentence detector is to identify sentence boundaries in the tokenized stream of text to support subsequent processing. The sentence detector is based on an open-source Maximum Entropy[A-8] classifier that categorizes punctuation tokens as either constituting a sentence boundary or not. For example, the period in "Dr. Smith" would be categorized as a non-boundary token, while the period in "No skin lesions." will be classified as a sentence boundary.

Part-of-speech (POS) Tagger: The function of the POS Tagger is to identify the appropriate lexical category (noun, verb, preposition, conjunction, etc.) from a list of 45 Penn

[A-5] http://www.alphaworks.ibm.com/tech/uima
[A-6] http://gate.ac.uk/
[A-7] http://opennlp.sourceforge.net/
[A-8] http://maxent.sourceforge.net/

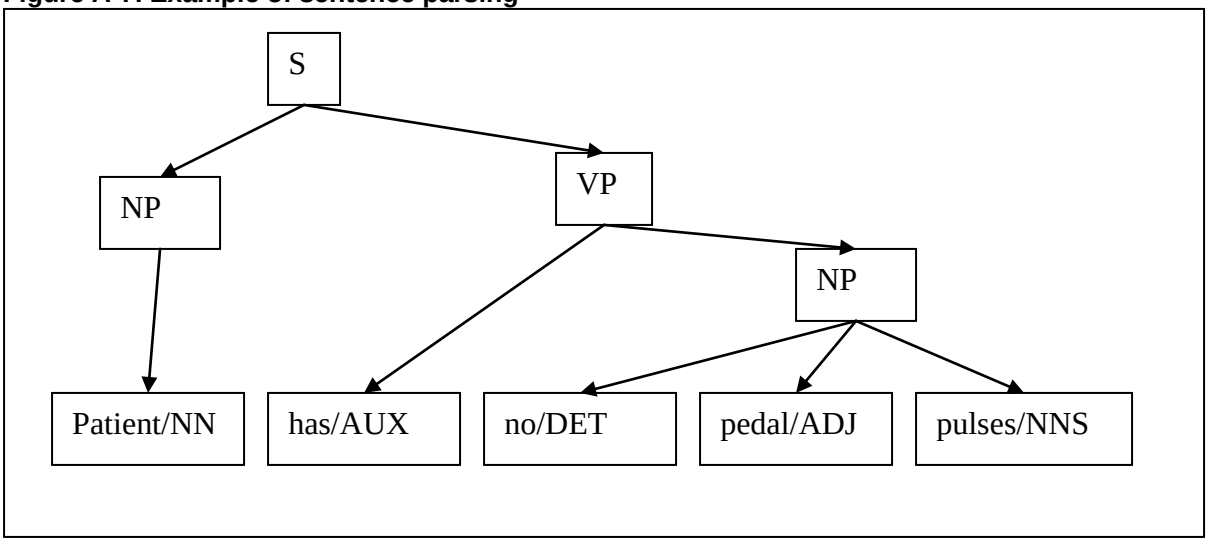
Treebank part-of-speech categories. We propose to use a publicly available Hidden Markoff Model (HMM) based POS tagger Medpost. For example, the words in the sentence "Patient has no pedal pulses" will be tagged as "Patient/NN has/AUX no/DET pedal/ADJ pulses/NNS." The part-of-speech information is necessary for the subsequent step of syntactic parsing.

Figure A-6. Natural language processing components high-level architecture



Stanford Syntactic Parser: The function of the syntactic parser is to identify the syntactic structure and composition of phrases within sentences identified by the Sentence Detector component. For example, the sentence "Patient/NN has/AUX no/DET pedal/ADJ pulses/NNS." will be parsed as shown in Figure A-7.

Figure A-7. Example of sentence parsing



This simple parse tree represents two noun phrases ("patient" and "no pedal pulses") and one verb phrase ("has no pedal pulses."). This structured representation of the sentence will enable subsequent mapping of the sentence to the UMLS metathesaurus and identification of modifications such as negation.

Concept Mapper: The purpose of the concept mapper is to assign unique identifiers to medical concepts identified within the phrases parsed in the previous step. The mapping proceeds by permuting the words within each phrase and then looking up each permutation in the UMLS Metathesaurus. The UMLS Metathesaurus is the largest collection of medical vocabularies maintained by the National Library of Medicine. The Metathesaurus contains over 100 medical vocabularies and encompasses over 1 million medical concepts. One of the valuable characteristics of the Metathesaurus is that it maintains a set of orthographic, lexical and semantic variants for each concept identifier (e.g. "Babinski's Reflex" = "Babinski's Sign" = "Extensor Plantar Reflex" aggregated under the Concept Unique Identifier C0034935). In addition to the richness of the Metathesaurus, the National Library of Medicine makes available a Lexical Variant Generator (LVG) tool specifically designed to identify orthographic and lexical variants of medical terms. We will use LVG as part of the mapping process.

Modification Identifier: The function of this component is to look for modification of the concepts identified in the previous steps. Identifying modification of concepts is critical for information retrieval from clinical documents. In particular, identification of negated concepts (e.g. "denies chest pain," "absent pulses") is crucial to constructing the correct representation of a physical examination from the text of the clinical report. We will use a publicly available tool, NegEx, specifically designed to identify negation in clinical discourse. NegEx is a regular expression mechanism with a set of rules that designate keywords indicating negation in the vicinity of the index term. Despite its simplicity, it has been shown to perform with 78% sensitivity and 94.5% specificity on terms identified in hospital discharge summaries. In addition to negation, we will generalize NegEx to determine other statuses of the findings including history and family history. This will be done by manual examination of a random sample of 500 finding mentions occurring in the electronic medical records to identify the adjustments and extensions necessary to adapt NegEx to the task at hand.

Common Annotation Structure (CAS) Consumer: This UIMA platform component is responsible for converting the internal representation of the elements identified by the NLP components to XML format for input to the indexing engine.

Lucene Index: Lucene[A-9] is a high-quality open-source indexing engine specifically designed to enable fast indexing and search of textual documents. The engine is also capable of indexing non-textual fields including numerical values, thus making Lucene equivalent to a database for most common applications. One of Lucene's features that is not commonly available in commercial databases is the ability to restrict searches by proximity of elements found in the text. This feature makes Lucene particularly attractive for indexing medical records as it allows greater flexibility in constructing ad-hoc queries and will serve as a mechanism to overcome possible limitations of the NLP methods and the UMLS Metathesaurus. The medical records will be indexed both on the concepts identified by NLP and the standard single keywords normalized with LVG.

[A-9] http://lucene.apache.org/

The process illustrated in Figure A-7 will run in batch mode to process relevant records from the participating centers. While the UMLS is a rich ontology comprising a large number of different sources of medical terminology, the vocabularies that are part of the UMLS are not fully curated by the UMLS staff and are accepted "as is" leading to potential problems with granularity and possible inconsistencies. In order to alleviate this concern we will use a subset of the UMLS consisting of the following sources: Systematized Nomenclature of Medicine, Clinical Terminology (SNOMED-CT), International Classification of Disease (ICD-9, 10), Medical Subject Headings (MeSH) and the National Cancer Institute Thesaurus (NCI Thesaurus).

Directed Point-of-Care Data Collection

Even in a highly coded EHR there will be data elements that are essential to understanding the effectiveness or safety issues related to a therapeutic agent that are not likely to be included in a clinical note. Examples include a PHQ-9 score for all depressed patients or a standardized assessment of bipolar symptoms in patients starting to take an antidepressant. In these situations the ability to direct data collection during an office visit will enable the collection of additional critical data to supplement routine clinical data for selected patients. This ability will allow DARTNet to essentially create a controlled trial environment within the routine care process.

The CINA PE creates a clinical decision support report for every patient visiting DARTNet practices. This report can also direct specific data collection at the level of a patient or data element, based on existing data within the CDR. This ability to fill in missing data and supplement clinical data is one of the reasons the DARTNet Board demanded that any CDSS system be able to support point-of-care recommendations. There are two possible scenarios to be dealt with: (1) the data are frequently collected during routine care but the results are missing on a large portion of the population of interest or (2) the data are not typically collected to the degree of standardization that is needed for the study in question.

For the first scenario, where the data are often collected during routine care, the CINA PE would be programmed to look for these data within the specified period of time when a patient eligible for the study is being seen. If the data element is present and timely then no prompt would be included on the point-of-care report. If the data element is lacking, a request to collect the information would be generated.

In the second scenario, where data standardization needs to be improved (such as a standardized assessment of depression severity) the CINA PE would be programmed to print the full data collection form for patients meeting study criteria. Depending on the questions to be asked and other factors this could be done only with patients who have provided their consent to participate, or could be done as an extension of clinical care. The results of this standardized assessment would then be entered into the EHR for extraction to the CDR and eventually to the study team.

Summary

The DARTNet data collection, standardization, presentation, query and reporting system is a state of the art implementation of a series of public and private software systems that have been linked to provide data acquisition, data standardization and quality improvement activities. The system is independent of most EHRs, can extract data from multiple data sources and

supports centralized research activities as well as local and system-wide quality improvement and learning.

References

Pakhomov S, Weston SA, Jacobsen SJ, et al (2007a). Electronic medical records for clinical research: application to the identification of heart failure. *American Journal of Managed Care* 13(6 Part 1), 281-8.

Pakhomov SS, Hemingway H, Weston SA, et al (2007b). Epidemiology of angina pectoris: role of natural language processing of the medical record. *American Heart Journal* 153(4), 666-73.

Appendix A-A: Criteria for Adding New Member Organizations to DARTNet

1. Data extraction from electronic health record to DARTNet specifications
    a. Minimum data types must be included
2. Use advanced clinical decision support at point of care
    a. implementation process
    b. provider level
3. Organizational commitment to the process
4. Organizational key leaders engaged
5. Share de-identified aggregate data (with appropriate safeguards/approvals)
6. Willingness to be identified if top performer
7. Adds to research/learning needs of DARTNet

Appendix A-B: Coding Dictionaries for DARTNet Data

Procedures

Full Specified Name	Master Concept ID	Concept ID
Lymphocyte count (procedure)	74765001	74765001
Neutrophil count (procedure)	30630007	30630007
Alanine aminotransferase measurement (procedure)	34608000	34608000
Albumin measurement (procedure)	26758005	26758005
Alkaline phosphatase measurement (procedure)	88810008	88810008
Aspartate aminotransferase measurement (procedure)	45896001	45896001
Urine bacteria test (procedure)	167575008	167575008
Bilirubin measurement (procedure)	302787001	302787001
Bilirubin, direct measurement (procedure)	302787001	39748002
Bilirubin, total measurement (procedure)	302787001	359986008
Blood urea nitrogen measurement (procedure)	105011006	105011006
C-reactive protein measurement (procedure)	55235003	55235003
Calcium measurement (procedure)	71878006	71878006
Carbon dioxide measurement (procedure)	38007001	38007001
Urine microscopy for casts (procedure)	167335004	167335004
Creatinine measurement (procedure)	70901006	70901006
Erythrocyte sedimentation rate measurement (procedure)	416838001	416838001
T4 free measurement (procedure)	5113004	5113004
Glucose measurement, fasting (procedure)	33747003	52302001
Glucose measurement, random (procedure)	33747003	73128004
High density lipoprotein measurement (procedure)	28036006	28036006
Hemoglobin determination (procedure)	35170002	35170002
Hemoglobin A1c measurement (procedure)	43396009	43396009
Hepatitis B core antibody level (procedure)	62889000	315133002
Hepatitis B e antibody level (procedure)	62889000	315134008
Hepatitis B e antigen test (procedure)	62889000	313476009
Hepatitis B surface antibody measurement (procedure)	62889000	65911000
Hepatitis B surface antigen measurement (procedure)	62889000	47758006
Hepatitis C antibody measurement (procedure)	187033005	64411004
Hepatitis C antigen measurement (procedure)	187033005	58589004
Low density lipoprotein cholesterol measurement (procedure)	113079009	113079009
Mean corpuscular hemoglobin determination (procedure)	54706004	54706004
Mean corpuscular volume - (procedure)	104133003	104133003
Microalbumin measurement, urine, quantitative (procedure)	46716003	104819000
Platelet count (procedure)	61928009	61928009
Potassium measurement (procedure)	59573005	59573005

Glucose measurement, blood (procedure)	33747003	33747003
Blood sodium measurement (procedure)	312469006	312469006
Urine dipstick for specific gravity (procedure)	252386004	252386004
Total cholesterol measurement (procedure)	121868005	121868005
Total protein measurement (procedure)	304383000	304383000
Triglycerides measurement (procedure)	14740000	14740000
Thyroid stimulating hormone measurement (procedure)	61167004	61167004
Urine dipstick for glucose (procedure)	269879003	269879003
Urine dipstick for hemoglobin (procedure)	275714003	275714003
Hemoglobin determination, urine (procedure)	104143000	104143000
Urine dipstick for protein (procedure)	271346009	271346009
White blood cell count (procedure)	767002	767002
Urine dipstick for urobilinogen (procedure)	167321001	167321001
Urine dipstick for ketones (procedure)	271347000	271347000
Urine dipstick for nitrite (procedure)	302791006	302791006
Urine dipstick for leukocyte esterase (procedure)	252385000	252385000
Tri-iodothyronine measurement, total (procedure)	89793009	89793009
Urobilinogen measurement, urine (procedure)	67410005	67410005
Urine ketone test (procedure)	167285005	167285005
Nitrite measurement (procedure)	104831003	104831003
Leukocyte esterase measurement (procedure)	104779000	104779000
Protein measurement, urine (procedure)	57378007	57378007
Hemoglobin determination, urine (procedure)	104143000	104143000
Urinalysis, specific gravity measurement (procedure)	20501000	20501000
Platelet mean volume determination (procedure)	75672003	75672003
Chlamydia trachomatis DNA assay (procedure)	122321005	122321005
Urine protein/creatinine ratio measurement (procedure)	46716003	313500004
Microalbuminuria measurement (procedure)	46716003	46716003
Urine microalbumin/creatinine ratio measurement (procedure)	271076007	271076007
Prostate specific antigen measurement (procedure)	63476009	63476009
Influenza vaccination (procedure)	49083007	86198006
Pneumococcal vaccination (procedure)	312871001	12866006
Tetanus vaccination (procedure)	312871001	127786006
Vaccination for diphtheria, pertussis, and tetanus (procedure)	312871001	399014008
International normalized ratio (observable entity)	396451008	165581004

Measurements

Full Specified Name	Master Concept ID	Concept ID
Body height measure	50373000	50373000
Body mass index (observable entity)	60621009	60621009
Systolic blood pressure (observable entity)	271649006	271649006

Diastolic blood pressure (observable entity)	271650006	271650006
Standing systolic blood pressure (observable entity)	271649006	400974009
Standing diastolic blood pressure (observable entity)	271650006	400975005
Sitting systolic blood pressure (observable entity)	271649006	407554009
Sitting diastolic blood pressure (observable entity)	271650006	407555005
Lying systolic blood pressure (observable entity)	271649006	407556006
Lying diastolic blood pressure (observable entity)	271650006	407557002
Body weight measure (observable entity)	363808001	363808001
Body temperature	386725007	386725007
Pulse	8499008	8499008

Functional Tests

Full Specified Name	Master Concept ID	Concept ID
Forced expired volume in 1 second (observable entity)	106053004	59328004
Total vital capacity measurement (procedure)	106053004	3862003
Forced expired volume in one second/vital capacity ratio (observable entity)	106053004	251943006
Maximum breathing capacity, function (observable entity)	106053004	3309000
Peak expiratory flow rate (observable entity)	106053004	18491006
Total vital capacity measurement (procedure)	106053004	3862003
Electrocardiographic procedure (procedure)	29303009	29303009
Holter extended electrocardiographic recording (regime/therapy)	427047002	427047002
24 Hour ECG (procedure)	252417001	252417001
Cardiovascular stress testing (procedure)	76746007	76746007
Transesophageal echocardiographic monitoring features (observable entity)	398153005	398153005
Exercise stress echocardiography (procedure)	252424000	252424000
Transthoracic echocardiography (procedure)	252418006	252418006
Echocardiography (procedure)	40701008	40701008
Forced expiratory flow rate between 25+75% of vital capacity (observable entity)	106053004	251932003

Family and Personal Medical History

Full Specified Name	Master Concept ID	Concept ID
Family history of malignant neoplasm of breast	429740004	429740004
Family history of cancer of colon (situation)	312824007	312824007
Family history: premature coronary heart disease (situation)	134439009	134439009
Family history: Diabetes mellitus (situation)	160303001	160303001
[D]Nonspecific abnormal Papanicolaou cervical smear NOS (situation)	119252009	207484000
H/O splenectomy	38096003	161626009

Functional asplenia	38096003	38096003
Family history: Asthma (situation)	160377001	160377001
History of - asthma (situation)	161527007	161527007
History of - atrial fibrillation (situation)	312442005	312442005
Personal history of primary malignant neoplasm of breast (situation)	415076002	415076002
History of - cardiovascular disease (situation)	266995000	266995000
Family history: Cardiovascular disease (situation)	266894000	266894000
History of malignant neoplasm of cervix (situation)	429484003	429484003
Family history: neoplasm of cervix (situation)	160298003	160298003
History of - renal failure (situation)	414417004	414417004
History of malignant neoplasm of colon	429699009	429699009
Family history of cancer of colon (situation)	312824007	312824007
Family history of chronic obstructive lung disease (situation)	297241004	297241004
History of - chronic obstructive airway disease (situation)	270473001	270473001
History of - diabetes mellitus (situation)	161445009	161445009
History of - liver disease (situation)	161535005	161535005
Family history: Liver disease (situation)	266902008	266902008
History of - hypercholesterolemia (situation)	414416008	414416008
Family history: Hypercholesterolemia (situation)	160314003	160314003
History of - hypertension (situation)	161501007	161501007
Family history: Hypertension (situation)	160357008	160357008
Premature menopause (finding)	373717006	373717006
Metabolic syndrome X (disorder)	237602007	237602007
History of - myocardial infarction (situation)	399211009	399211009
Family history: Myocardial infarction (situation)	266897007	266897007
History of - kidney disease (situation)	275552000	275552000
Family history of kidney disease (situation)	289916006	289916006
History of - obesity (situation)	161453001	161453001
Family history: Obesity (situation)	160311006	160311006
Osteopenia (disorder)	312894000	312894000
History of - pregnancy (situation)	271903000	271903000
History of malignant neoplasm of prostate (situation)	428262008	428262008
Family history of prostate cancer (situation)	414205003	414205003
Family history: Sickle cell anemia (situation)	160320002	160320002
Sickle cell anemia NOS (disorder)	191199004	191199004
History of - hormone replacement (HRT) (situation)	161652003	161652003
Osteoporosis (disorder)	64859006	64859006
Family history: Osteoporosis (situation)	160313009	160313009
Ex-smoker (finding)	8517006	8517006
Non-smoker (finding)	8392000	8392000

Smoker (finding)	77176002	77176002

Procedure History

Full Specified Name	Master Concept ID	Concept ID
History of colectomy (situation)	427816007	427816007
History of - renal dialysis (situation)	161693006	161693006
History of - hysterectomy (situation)	161800001	161800001
History of - lower limb amputation (situation)	161622006	161622006
History of bilateral mastectomy (situation)	428529004	428529004
Bone density scan (procedure)	312681000	312681000
Colonoscopy (procedure)	275978004	73761001
Seen in diabetic eye clinic (finding)	313340009	313340009
Diabetic foot examination (regime/therapy)	401191002	401191002
Double contrast barium enema (procedure)	275978004	241164003
Fecal occult blood test (procedure)	275978004	167665003
Flexible fiberoptic sigmoidoscopy (procedure)	275978004	44441009
Date of last mammogram	429736008	429736008
Papanicolaou smear test (procedure)	119252009	119252009

Medication Allergies

Full Specified Name	Master Concept ID	Concept ID
History of - angiotensin II receptor antagonist allergy	407579007	407579007
Angiotensin-converting-enzyme inhibitor allergy	295036000	295036000
Adrenergic neurone blocking drug allergy	295032003	295032003
Acarbose allergy	294742003	294742003
Insulin allergy	294714000	294714000
Sulfonylurea allergy	294728006	294728006
Adrenergic neurone blocking drug allergy	293962009	293962009
Beta-adrenoceptor blocking drug allergy	293962009	293962009
Calcium-channel blocker allergy	293994004	293994004
Digoxin allergy	295054001	295054001
Diuretic allergy	294990004	294990004
HMG COA reductase inhibitor allergy	294954006	294970008
Lipid-lowering drug allergy	294954006	294954006
Nicotinic acid allergy	294954006	294929006
Omega 3-marine triglycerides allergy	294954006	294969007
Biphosphonates allergy	294833000	294833000
Anticoagulant allergy	294869008	294869008
Salicylate allergy	293585002	293585002
Warfarin allergy (disorder)	294869008	294881007
Biguanide allergy	294739009	294739009

Influenza vaccine allergy	294640001	294647003
Pneumococcal vaccine allergy (disorder)	294640001	294652008
Tetanus vaccine allergy (disorder)	294640001	294658007

Medications

Medication Name	RxNorm Code	GCN Code
Abacavir	190521	007687
Acarbose	16681	004299
Acarbose	16681	004299
Aceclofenac	16689	005957
Acemetacin	16695	003916
Acetaminophen	161	001605
Acetazolamide	167	002286
Acetohexamide	173	000907
Allopurinol	519	001084
Amiodarone	703	004484
Amitriptyline	704	004600
Amoxapine	722	001506
Clavulanate	48203	
Amoxicillin	723	003675
Apazone	1029	003712
Aspirin	1191	001587
Atorvastatin	83367	006321
Azathioprine	1256	003419
Benazepril	18867	003597
Benorilate	1372	003933
Black Cohosh Extract	236665	006560
Black Cohosh Root Extract	259511	008256
Bosentan	75207	009514
Bromfenac	19737	006757
Bumetanide	1808	002312
Butriptyline	19895	003938
Candesartan	214354	007275
Captopril	1998	000656
Carbamazepine	2002	001634
Carprofen	20343	005102
Celecoxib	140587	007731
Celecoxib	140587	007731
Cerivastatin Sodium	221072	006489
Chlorpromazine	2403	004587
Chlorpropamide	2404	000910

Chlorthalidone	2409	002309
Citalopram	2556	005106
Clomipramine	2597	004614
Clopamide	2603	003711
Comfrey Preparation	285150	003837
Cyclophosphamide	3002	002631
Cyclosporine	3008	003420
Desipramine	3247	004602
Dibenzepin	3332	006897
Dichlorphenamide	3353	002288
Diclofenac	3355	004409
Didanosine	3364	003604
Diflunisal	3393	001599
Diltiazem	3443	004514
Disulfiram	3554	000752
Dothiepin Hydrochloride	142133	003961
Doxepin	3638	004607
Emtricitabine	276237	001321
Enalapril	3827	004500
Eprosartan	83515	007065
Erythromycin	4053	002755
Erythromycin Estolate	4055	002756
Erythromycin Ethylsuccinate	4056	002757
Erythromycin Gluceptate	24346	002758
Erythromycin Lactobionate	24347	002759
Erythromycin Stearate	24351	002760
Erythromycin Stinoprate	236847	006993
Escitalopram Oxalate	353108	009710
Estrogens	4100	
Etodolac	24605	003587
Etoricoxib	307296	009633
Exenatide	60548	010772
Ezetimibe	341248	009817
Fatty Acids, Omega-3	4301	002053
Felbamate	24812	004277
Fenbufen	24830	004090
Fenofibrate	8703	003789
Fenoprofen	4331	004810
Fluoxetine	4493	004613
Flurbiprofen	4502	002382
Fluvastatin	41127	004439

Fluvoxamine Maleate	203143	003634
Fosinopril	50166	004501
Garlic Preparation	265647	002585
Gemfibrozil	4719	002050
Glimepiride	25789	005624
Glipizide	4821	000913
Glyburide	4815	000912
Glyburide, Micronized	217364	006286
Greater Celandine	236982	007347
Ibuprofen	5640	002377
Imipramine	5691	001498
Indapamide	5764	002313
Indomethacin	5781	002373
Iprindole	5979	003982
Irbesartan	83818	006921
Isoniazid	6038	002844
Kava Root	259421	008009
Kava Preparation	285228	009426
Ketoconazole	6135	002903
Ketoprofen	6142	002394
Ketorolac	35827	004812
Lamivudine	68244	005079
Lisinopril	29046	000658
Lofepramine	6465	004095
Lornoxicam	20890	007785
Losartan	52175	004991
Lovastatin	6472	002063
Loxoprofen	28908	008162
Mafenide	6572	004960
Magnesium Salicylate	52364	001593
Meclofenamic Acid	6678	002387
Mefenamic Acid	6693	001578
Mefruside	6696	004000
Meloxicam	41493	006272
Dipyrone	3523	001609
Metformin	6809	004534
Methimazole	6835	002139
Methotrexate	6851	002644
Methyl Salicylate	29787	001990
Methyldopa	6876	000646
Metolazone	6916	002310

Miglitol	30009	007635
Minocycline	6980	004864
Nabumetone	31448	003622
Naproxen	7258	002380
Nateglinide	274332	009028
Niacin	7393	001052
Nimesulide	53694	004182
Nitrofurantoin	7454	002852
Nortriptyline	7531	004601
Olmesartan Medoxomil	118463	009635
Opipramol	7674	004149
Oxaprozin	32613	004113
Oxyphenbutazone	7816	002376
Parecoxib	279950	009631
Paroxetine	32937	004016
Pemoline	7966	001384
Perindopril	54552	004018
Phenobarbital	8134	001406
Phenylbutazone	8160	002375
Phenytoin	8183	001617
Pioglitazone	33738	007823
Piroxicam	8356	002389
Pramlintide	139953	010717
Pravastatin	42463	003606
Probenecid	8698	002321
Procainamide	8700	004481
Propylthiouracil	8794	002137
Protriptyline	8886	004603
Pyrazinamide	8987	002849
Quinapril	35208	003612
Quinidine	9068	000618
Ramipril	35296	003585
Ranitidine	9143	004444
Repaglinide	73044	007421
Rifampin	9384	002789
Rofecoxib	232158	007787
Rosiglitazone	84108	007789
Rosuvastatin	301542	009902
Salsalate	36108	001596
Sertraline	36437	004615
Simvastatin	36567	003621

Sitagliptin	593411	011790
Skullcap Preparation	262263	007910
St. John’s Wort Extract	258326	006442
Stavudine	59763	004502
Sulfacetamide	10169	004890
Sulfadimethoxine	10172	002825
Sulfamethoxazole	10180	002827
Sulfanilamide	10184	002833
Sulfasalazine	9524	002832
Sulfinpyrazone	10205	002322
Sulindac	10237	002386
Sulthiame	10240	007045
Sumatriptan	37418	004044
Suprofen	10255	002393
Tacrine	10318	004378
Tamoxifen	10324	004826
Telmisartan	73494	007683
Tenoxicam	37790	003632
Terbinafine	37801	004051
Tiaprofenic acid	38253	003468
Tolazamide	10633	000911
Tolbutamide	10635	000908
Tolcapone	72937	007040
Tolmetin	10636	004811
Trazodone	10737	004610
Trimipramine	10834	004605
Troglitazone	72610	006355
Troglitazone	72610	006356
Trovafloxacin	115552	007320
Valdecoxib	278567	009503
Valerian Root	253206	007932
Valproic Acid	11118	001622
Valsartan	69749	006279
Vitamin A	11246	001000
Xipamide	11371	004068
Zafirlukast	114970	006206
Zalcitabine	3363	003661
Zidovudine	11413	003019
Zileuton	40575	006297
Zofenopril	39990	008183

Appendix A-C: About the Globus Toolkit

The Globus toolkit is an enabling technology that has become the *de-facto* standard for technology solutions that enable secure sharing of databases across organizational boundaries. The federal government has recognized the significance of the Globus Framework, and has adopted it for several key applications. This includes the use of use of the Globus framework for caBIG, which is NCI's Cancer Bioinformatics Grid. Globus is made universally available to qualified groups, which also makes it ideally suited for use in large-scale applications where replicability is critically important.

The ePCRN Portal makes use of the Globus technology for these reasons. The information in Appendix A-C provides a detailed overview of Globus as background for why this technology was chosen for the development of the ePCRN Portal (developed by the University if Minnesota), and the relative importance of this technology to the University of Colorado in selecting the ePCRN Portal as a key component of the DARTNet system.

Grid Technologies

"Grid" computing is distinguished from conventional distributed computing by its focus on large-scale resource sharing, innovative applications, and, in some cases, high-performance orientation. Grid computing facilitates flexible, secure, coordinated resource sharing among dynamic collections of individuals, institutions, and resources. In such settings, one encounters unique authentication, authorization, resource access, resource discovery, and other challenges. It is this class of problem that is addressed by Grid technologies.

The real and specific problem that underlies the Grid concept is coordinated resource sharing and problem solving in dynamic, multi-institutional virtual organizations. This sharing is not primarily file exchange but rather direct access to computers, software, data, and other resources, as is required by a range of collaborative problem-solving and resource brokering strategies emerging in industry, science, and engineering. This sharing is, necessarily, highly controlled, with resource providers and consumers defining clearly and carefully just what is shared, who is allowed to share, and the conditions under which sharing occurs. A set of individuals and/or institutions defined by such sharing rules form what we call a virtual organization.

Current distributed computing technologies do not address the concerns and requirements just listed. For example, current Internet technologies address communication and information exchange among computers but do not provide integrated approaches to the coordinated use of resources at multiple sites for computation. Business-to-business exchanges focus on information sharing (often via centralized servers). So do virtual enterprise technologies, although here sharing may eventually extend to applications and physical devices.

Enterprise distributed computing technologies such as CORBA and Enterprise Java enable resource sharing within a single organization. The Open Group's Distributed Computing Environment supports secure resource sharing across sites, but most virtual organizations would find it too burdensome and inflexible. Storage service providers and

application service providers allow organizations to outsource storage and computing requirements to other parties, but only in constrained ways; for example, storage service providers' resources are typically linked to a customer via a virtual private network (VPN). Emerging "Distributed computing" companies seek to harness idle computers on an international scale but, to date support only highly centralized access to those resources. In summary, current technology either does not accommodate the range of resource types or does not provide the flexibility and control on sharing relationships needed to establish virtual organizations.

Because of their focus on dynamic, cross-organizational sharing, Grid technologies complement rather than compete with existing distributed computing technologies. For example, enterprise distributed computing systems can use Grid technologies to achieve resource sharing across institutional boundaries; in the storage service providers and application service providers space, Grid technologies can be used to establish dynamic markets for computing and storage resources, hence overcoming the limitations of current static configurations.

Effective virtual organization operation requires that we be able to establish sharing relationships among any potential participants. Interoperability is thus the central issue to be addressed. In a networked environment, interoperability means common protocols. Hence, Grid architecture is first and foremost a protocol architecture, with protocols defining the basic mechanisms by which virtual organization users and resources negotiate, establish, manage, and exploit sharing relationships. A standards-based open architecture facilitates extensibility, interoperability, portability, and code sharing; standard protocols make it easy to define standard services that provide enhanced capabilities. We can also construct Application Programming Interfaces and Software Development Kits to provide the programming abstractions required to create a usable Grid. Together, this technology and architecture constitute what is often termed middleware ("the services needed to support a common set of applications in a distributed network environment"). The following brief and partial list provides a resource specific characterization of capabilities.

- *Computational resources*: Mechanisms are required for starting programs and for monitoring and controlling the execution of the resulting processes. Management mechanisms that allow control over the resources allocated to processes are useful, as are advance reservation mechanisms. Inquiry functions are needed for determining hardware and software characteristics as well as relevant state information such as current load and queue state in the case of scheduler-managed resources.
- *Storage resources*: Mechanisms are required for putting and getting files. Third-party and high-performance (e.g., striped) transfers are useful, as are mechanisms for reading and writing subsets of a file or executing remote data selection or reduction functions. Management mechanisms that allow control over the resources allocated to data transfers (space, disk bandwidth, network bandwidth, CPU) are useful, as are advance reservation mechanisms. Inquiry functions are needed for determining hardware and software characteristics as well as relevant load information such as available space and bandwidth utilization.
- *Network resources*: Management mechanisms that provide control over the resources allocated to network transfers (e.g., prioritization, reservation) can be

useful. Inquiry functions should be provided to determine network characteristics and load.

- *Code repositories*: This specialized form of storage resource requires mechanisms for managing versioned source and object code; for example, a control system such as CVS.
- *Catalogs*: This specialized form of storage resource requires mechanisms for implementing catalog query and update operations: for example, a relational database.

The Globus Toolkit® has emerged as the dominant middleware for Grid deployments worldwide.

Globus Toolkit

The open source Globus® Toolkit is a fundamental enabling technology for the "Grid," letting people share computing power, databases, and other tools securely online across corporate, institutional, and geographic boundaries without sacrificing local autonomy. The toolkit includes software services and libraries for resource monitoring, discovery, and management, plus security and file management. In addition to being a central part of science and engineering projects that total nearly a half-billion dollars internationally, the Globus Toolkit is a substrate on which leading IT companies are building significant commercial Grid products.

The toolkit includes software for security, information infrastructure, resource management, data management, communication, fault detection, and portability. It is packaged as a set of components that can be used either independently or together to develop applications. Every organization has unique modes of operation, and collaboration between multiple organizations is hindered by incompatibility of resources such as data archives, computers, and networks. The Globus Toolkit was conceived to remove obstacles that prevent seamless collaboration. Its core services, interfaces and protocols allow users to access remote resources as if they were located within their own machine room while simultaneously preserving local control over who can use resources and when.

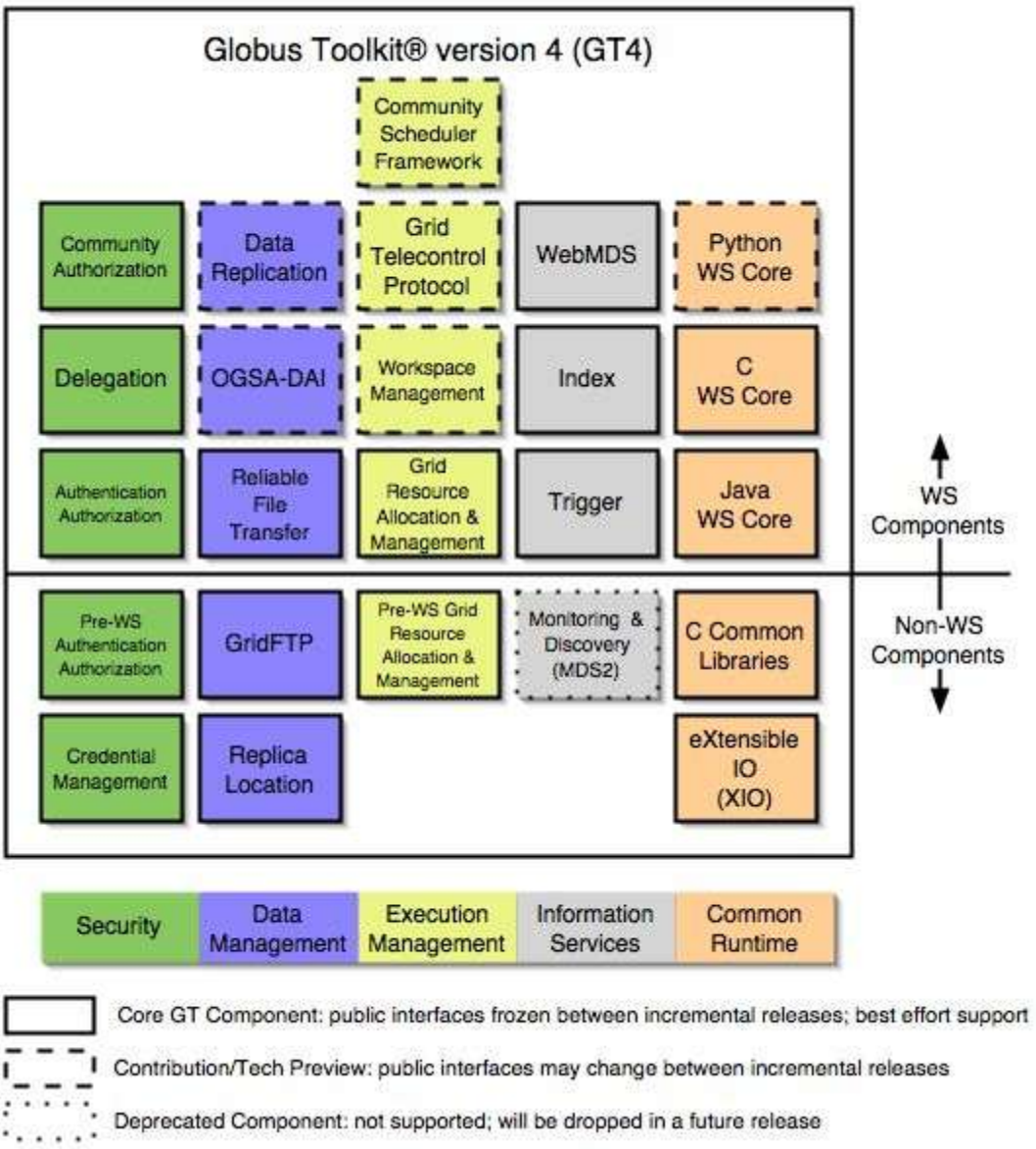
The Globus Toolkit has grown through an open-source strategy similar to the Linux operating system, and distinct from proprietary attempts at resource-sharing software. This encourages broader, more rapid adoption and leads to greater technical innovation, as the open-source community provides continual enhancements to the product.

The Globus Toolkit has been designed to use (primarily) existing fabric components, including vendor-supplied protocols and interfaces. However, if a vendor does not provide the necessary Fabric-level behavior, the Globus Toolkit includes the missing functionality. For example, inquiry software is provided for discovering structure and state information for various common resource types, such as computers (e.g., operating system version, hardware configuration, load scheduler queue status), storage systems (e.g., available space), and networks (e.g., current and predicted future load) and for packaging this information in a form that facilitates the implementation of higher-level protocols, specifically at the Resource layer. Resource management, on the other hand, is generally assumed to be the domain of local resource managers.

Essential background is contained in the papers "Anatomy of the Grid" and "Physiology of the Grid":

- The Anatomy of the Grid: Enabling Scalable Virtual Organizations. I. Foster, C. Kesselman, S. Tuecke. International J. Supercomputer Applications, 15(3), 2001.
- The Physiology of the Grid: An Open Grid Services Architecture for Distributed Systems Integration. I. Foster, C. Kesselman, J. Nick, S. Tuecke, Open Grid Service Infrastructure WG, Global Grid Forum, June 22, 2002.

Figure A-8. Elements of the Globus Toolkit



X.509 Security

Proxy credentials are commonly used in security systems when one entity wishes to grant to another entity some set of its privileges. The Globus Toolkit uses standardized X.509 security for authentication between servers. X.509 Proxy Certificates provide restricted proxy access and delegation within a public key infrastructure-based authentication system.

The Grid Security Infrastructure is the portion of the Globus Toolkit that provides the fundamental security services needed to support Grids. Grid Security Infrastructure provides libraries and tools for authentication and message protection that use standard X.509 public key certificates, public key infrastructure, the SSL/TLS protocol, and X.509 Proxy Certificates, an extension defined for Grid Security Infrastructure to meet the delegation requirements of Grid communities.

Proxy Certificates allow an entity holding a standard X.509 public key certificate to delegate some or all of its privileges to another entity which may not hold X.509 credentials at the time of delegation. This delegation can be performed dynamically, without the assistance of a third party, and can be limited to arbitrary subsets of the delegating entity's privileges. Once acquired, a Proxy Certificate is used by its bearer to authenticate and establish secured connections with other parties in the same manner as a normal X.509 end-entity certificate.

Open Grid Services Architecture – Data Access and Integration (OGSA-DAI)

The Open Grid Services Architecture—Data Access and Integration (OGSA-DAI) is a middleware product that allows data resources, such as relational or XML databases, to be accessed via web services. An OGSA-DAI web service allows data to be queried, updated, transformed and delivered. OGSA-DAI web services can be used to provide web services that offer data integration services to clients. OGSA-DAI web services can be deployed within a Grid environment. OGSA-DAI thereby provides a means for users to Grid-enable their data resources.

OGSA-DAI is motivated by the need to:

- Allow different types of data resources—including relational, XML and files—to be exposed onto Grids.
- Provide a way of querying, updating, transforming and delivering data via web services.
- Provide access to data in a consistent, data resource-independent way.
- Allow metadata about data, and the data resources in which these data are stored, to be accessed.
- Support the integration of data from various data resources.
- Provide web services that can be combined to provide higher-level web services that support data federation and distributed query processing.
- To contribute to a future in which scientists move away from technical issues such as handling data location, data structure, data transfer and integration and instead focus on application-specific data analysis and processing.

What Does OGSA-DAI Do?

OGSA-DAI can support the following:

- Different types of data resources—including relational, XML and files—can be exposed via web services. A number of popular data resource products are supported.
- Data within each of these types of resource can be queried and updated.
- Data can be transformed (using XSLT).
- Data can be delivered to clients, other OGSA-DAI web services, URLs, FTP servers, GridFTP servers, or files.
- Requests to OGSA-DAI web services have a uniform format irrespective of the data resource exposed by the service (though the actions specified within each request may be data resource-specific).
- Information on the data resources exposed by an OGSA-DAI web service and the functionality supported by the service can be accessed by clients.
- OGSA-DAI users can extend OGSA-DAI web services to expose their own data resources and to support application-specific functionality, in addition to that provided by OGSA-DAI.

OGSA-DAI provides web services compliant with the Web Services Resource Framework (WSRF)

OGSA-DAI and DAIS

The Database Access and Integration Services (DAIS) Working Group of the Open Grid Forum (OGF) is formulating standards for database access and integration services. The development of OGSA-DAI has been occurring in parallel to the development of these specifications: OGSA-DAI influences, and is influenced by, this work. OGSA-DAI is currently based upon the DAIS specifications of March 2003. It is intended that OGSA-DAI will eventually provide a reference implementation of the final version of these standards.

The OGSA-DAI middleware facilitates data access and integration of data resources, such as relational and XML databases, within a Grid context.

The OGSA-DAI project started in February 2002. It received £3.3 million funding for two years from the UK Core e-Science funding program to develop Grid enabled middleware to facilitate data access and integration capabilities for UK based e-Science projects. The project was tasked with producing software based on the Globus Toolkit 3 which, in turn, was based on the then emerging Global Grid Forum's Open Grid Services Infrastructure specification.

Appendix B:
Pilot Research Project: DARTNet Phase I—
Patterns of Use, Comparative Effectiveness, and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes: A Retrospective Cohort Study

Prepared by the DARTNet Team, University of Colorado Denver Departments of Family Medicine and Clinical Pharmacy, Contract No. HHSA29020050037I TO2

Appendix B Contents

I. Abstract

Objective: To compare patterns of use, comparative effectiveness, and safety of oral diabetes medications (ODM) in the treatment of type 2 diabetes.

Design: A retrospective, new-user, open cohort design using claims data from 2002-2007 from the Ingenix Impact National Managed Care Database. Three cohorts of subjects were identified: diabetic subjects treated with ODM (N=48,477); untreated diabetic subjects (N=36,614); and a matched comparison cohort of subjects with a diagnosis of either CAD or dyslipidemia (N=37,412).

Methods: Patterns of use were compared by identifying the most commonly used ODM for initial treatment of diabetes, either alone or in combination. Persistence with therapy (time to first regimen change) was compared for the most commonly used monotherapy and combination therapy groups. Comparative effectiveness, defined as reduction in H-A1C from baseline to lowest or baseline to last value, was evaluated among ODM users using 2-stage, propensity adjusted, multivariable GLM models. Safety outcomes (hypoglycemia, liver injury, and liver failure) were evaluated among ODM users, untreated diabetic subjects, and CAD/Dyslipidemia subjects through crude event counts, and using 2-stage, propensity adjusted Cox Proportional Hazard models.

Results: Among diabetics receiving ODM, nearly 80% were initiated on monotherapy while 20% were initiated on combination therapy regimens. Persistence with initial ODM therapies differed across specific monotherapy and combination therapy groups. In terms of comparative effectiveness, only slight differences across ODM drugs and combinations were observed, in comparison to metformin monotherapy (statistically significant findings were numerous, but many were of questionable clinical significance).

In terms of safety, crude rates of hypoglycemia, liver injury, and liver failure were relatively low (ranging from 0.007 to 0.015 events per person-year of therapy/follow-up in the entire study cohort). Unadjusted rates of all three safety outcomes were similar among diabetic subjects, whether treated with ODM or not. Adjusted safety results showed that compared to those receiving metformin monotherapy, users of sulfonylureas (SUs), either alone or in combination with other ODM, were at greater risk of hypoglycemic events and liver injury, but not liver failure. No such increases in risk (relative to metformin monotherapy) were observed for patients receiving thiazolidinediones (TZDs), or for those receiving statins concurrently. Neither stratification of effectiveness and safety model results by propensity score quintiles, nor use of multiple propensity score methods instead of base case methods resulted in significant changes to the principal findings or conclusions.

Conclusions: The findings of our analysis suggest there are no substantial, clinically significant differences in adjusted effectiveness of any of the most commonly used ODM monotherapies. Furthermore, the adjusted differences in initial monotherapy versus combination therapy are minimal and, suggest there is little reason to consider starting patients on combination therapy. While all ODM monotherapies appear to be equally effective, sulfonylureas appear to be associated with increased risk of hypoglycemia and liver injury, which may indicate that these agents may not be ideal initial therapy.

II. Background

In 2003, the Medicare Prescription Drug, Improvement, and Modernization Act (MMA, Section 1013) authorized the Agency for Healthcare Research and Quality (AHRQ) to conduct and support research with a focus on outcomes, comparative clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services. In 2005, AHRQ created the the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network to help achieve this goal.

The DEcIDE Network conducts accelerated practical studies about the outcomes, comparative clinical effectiveness, safety, and appropriateness of health care items and services. The network is comprised of research-based health organizations with access to electronic health information databases and the capacity to conduct rapid turnaround research. Initial research within the DEcIDE Network focuses on the outcomes of prescription drug use and other interventions for which randomized controlled trials would not be feasible or timely, or would raise ethical concerns that are difficult to address. Other DEcIDE Network projects focus on electronic registries, methods for analyzing health databases, and observational or interventional studies.

The Colorado DEcIDE (CO-DEcIDE) Center, led by David R. West, Ph.D., has conducted research pursuant to Task Orders from the AHRQ Effective Healthcare Program, and under contract #HHSA29020050037I-TO2, tested the Distributed Ambulatory Research in Therapeutics Network (DARTNet). DARTNet, led by Wilson Pace, M.D. (Task Order Leader), is a working prototype federated network of electronic health record (EHR) data from eight organizations representing over 500 clinicians and over 400,000 patients. The prototype system will capture, codify and standardize a subset of unique data elements per patient for 48 months or more. The original aims of the DARTNet pilot project were to: (1) develop a federated network of 200+ primary care clinicians, all using electronic health records (EHR); (2) analytically demonstrate how existing large-scale data sets can be enhanced by patient-level data from the federated primary care network to inform and expand knowledge of effective and safe medical therapeutics; and (3) demonstrate the ability to collect specific data from clinicians or their staff on a clinically defined set of patients to enrich the EHR data set and answer effectiveness and safety questions concerning medical therapeutics.

As part of the development and testing of DARTNet, a pilot research study was proposed in the area of diabetes—a priority condition under Section 1013 of the MMA, and one for which an AHRQ-funded Comparative Effectiveness Review (CER) was recently published. The CER, Number 8 in a series of such reports, described and summarized the available evidence to date on the "Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes." (AHRQ, 2007) The CER on comparative effectiveness and safety of oral diabetes medications served as the framework for identification of specific aims and hypotheses for the DARTNet pilot research project. The results of both Phase 1 (claims data analysis) and Phase 2 (DARTNet EHR data replication) of the pilot research project are presented in Appendix B.

III. Specific Aims and Hypotheses

In Phase 1 of the DARTNet diabetes pilot research project, a retrospective, claims-based study was proposed with the dual goals of: (1) determining the extent to which readily

(commercially) available, integrated medical claims databases could be used to answer key research questions related to comparative effectiveness and safety of oral diabetes medications for adults with Type 2 diabetes; and (2) identifying areas where such databases are limited, and for which DARTNet (through access to EHR and/or POC data) may be useful for augmenting and improving upon the results that can be obtained from claims-database studies.

As described above, the CER for oral diabetes medications for adults with Type 2 diabetes was used to generate several specific aims and testable research hypotheses for the DARTNet pilot research project. The specific aims and research hypotheses are:

A.	Specific Aim #1:	Patterns of Use of Oral Diabetes Medications
	Hypothesis PU-1:	The pattern of use of various drug classes individually and in combination will not be significantly different over a five-year period or by age or gender over that period.
	Hypothesis PU-2:	Persistence of use will not be significantly different between any two-drug combinations.
B.	Specific Aim #2:	Comparative Effectiveness of Oral Diabetes Medications
	Hypothesis CE-1:	Glycemic control will be significantly better for all combinations of oral agents compared to single agents.
	Hypothesis CE-2:	Glycemic control will not be significantly different between any two drug class combinations.
C.	Specific Aim #3:	Comparative Safety of Oral Diabetes Medications
	Hypothesis CS-1:	All combinations of medications will have significantly higher rates of hypoglycemic events compared to single agents.
	Hypothesis CS-2:	Liver toxicity, as defined by elevated liver enzymes greater than 3 times normal, will not be significantly different among users of any single drug class.
	Hypothesis CS-3:	Liver toxicity, as defined in CS-2 above, will not be significantly different among users of any two drug combinations.
	Hypothesis CS-4:	Liver toxicity, as defined in CS-2 above, will not be significantly different among any combination of oral hypoglycemic agents, either singly or in two-drug combinations, with the addition of a statin agent.

Hypothesis CS-5: There will be no significant differences in rates of liver failure, as defined by elevations in liver function enzymes along with an elevation in prothrombin time (for patients not on warfarin), or a drop in platelet counts, or a diagnosis of liver failure.

These three specific aims, and their associated nine research hypotheses (two in the area of patterns of use, two in the area of comparative effectiveness, and five in the area of comparative safety), were researched using methods consistent with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP), and with the recently published Effective Healthcare Report Number 6: Improving Patient Safety and Pharmacovigilance: Methods Using Observational Data and Cohort Studies (ISPE 2007; AHRQ 2008).

IV. Methods

A. Overview of Study Design

This study was a retrospective, new-user, open cohort design that compared patterns of use, effectiveness and safety of individual and combination regimens of oral diabetes medications (ODM). The terminology used to describe the study design means that: all data was collected (or already existed) prior to the start of the study; users of ODM were new users (aka incident or first users) of these drugs after an initial diagnosis of diabetes; and exposure times and observation periods for each individual varied during the observation window. Such study designs are considered both optimal and essential for the quantification of drug benefit and risk assessment. (AHRQ 2008; Ray 2003)

Because of the nature of comparative effectiveness and safety research, which often involves the study of rare outcomes (in this case, liver injury or failure) or those which may be underreported or underdetected in medical claims data (in this case, hypoglycemia), studies with very large cohort sizes are required to provide adequate statistical power for detecting events and making comparisons with a reasonable degree of scientific certainty. Further, depending upon the study question, certain databases may be better suited than others for addressing specific hypotheses. For this study, a number of commercially and publicly available databases were considered and explored for feasibility: Ingenix/Impact, i3/innovus, the PHARMetrics Patient Centric Database, MEDSTAT databases, and state level Medicaid data. While no single claims data source is ideally suited for all purposes, for the proposed pilot study we determined that several key attributes were most desirable, including: large sample sizes; inclusion of integrated medical, pharmacy, facility, and eligibility data; inclusion of laboratory data with results (including at least two HA1C results per subject to enable the analysis of drug effectiveness); and availability of data for at least 5 years to enable longitudinal analysis of usage patterns and accrual of larger sample sizes and spans of person-time (to enable the analyses of drug safety).

B. Data Source

Data for the pilot study were obtained from the Ingenix Impact National Managed Care Database. The Impact database is a high-quality data resource with the combined claims of approximately 45 health plans representing approximately 30 million covered lives in 2006. The

database is robust from 1999 to 2007, and has a 6-9 month lag. The Impact database includes data for individuals in all U.S. census regions, predominantly in the North, North Central and Atlantic regions. Data include medical claims (physician and facility), pharmacy claims, and enrollment records. Inpatient claims are summarized at the stay level. Financial fields are standardized. All patients aged 65+ are in standard commercial or managed care plans.

An initial extract of data from the Impact database was obtained according to the following criteria:

Patient Selection Criteria:

- Both medical and drug benefits
- Eligibility data available
- Exclude Medigap members
- Laboratory results available
- Time period: 7/2002 – 6/2007
- ICD-9-CM (primary or nonprimary) = 250xx OR
- Drug (brand and generics) = any oral antidiabetic agent

Specific study cohorts, used for each aim of the analysis, were identified and drawn from the above extract. Cohorts used for each aim varied slightly, depending upon the aim, the required data elements, the desired time windows for variable construction and followup, etc., as detailed in subsection H below.

C. Data Control and Management

Prior to data extraction, contracts and data use agreements were executed between Ingenix and the University of Colorado to assure compliance with all laws relating to data privacy, security, and patient confidentiality (e.g., HIPAA). Data from the Impact database were extracted by personnel at Ingenix and shipped to the Colorado DEcIDE Center at the University of Colorado Denver on a secure, password protected, portable hard drive (with the password sent under separate cover). Data were loaded onto a secure, password and firewall protected analytic server computer at the Information Technology Server Farm of the University of Colorado Denver. Access to the study data was limited to essential study personnel only. A primary data analyst (Dr. Heather Orton) was appointed for the study, to coordinate all activities related to data management, cohort and variable creation, and statistical analysis, under the direction of the DARTNet Research Core Director (Dr. Robert Valuck).

D. Human Subjects Review

Prior to the receipt of the study data, human subjects reviews and approvals were obtained from two independent boards: the Colorado Multiple Institutional Review Board (COMIRB, Aurora, CO) and the American Academy of Family Physicians (AAFP) Institutional Review Board (Kansas City, MO). Data and analyses for Phase 1 of the DARTNet pilot study (i.e., those involving the claims database research questions and analyses) were considered exempt from full IRB review and were approved as proposed.

E. Study and Comparison Cohort Construction

Three main cohorts of subjects were defined and constructed to complete the proposed analyses:

1. A cohort of subjects diagnosed with diabetes (according to one or more claims with an ICD-9 code of 250.xx), and receiving an oral diabetes medication at some point after diagnosis; this was the primary study cohort, and was called the ODM Cohort.
2. A cohort of subjects diagnosed with diabetes (as above), but who did not receive any diabetes medications (either ODM or insulin); this was a comparison cohort for the safety aim and was called the Nontreated Diabetic Comparison Cohort.
3. A cohort of subjects without any recorded diagnosis of diabetes or use of diabetes medications, but with a diagnosis of either coronary heart disease or hyperlipidemia; this was a second comparison cohort for the safety aim and was called the CHD/Hyperlipidemia Comparison Cohort.

F. Definitions of Index Dates and Spans for Analyses

Several key definitions were made and used to anchor the subsequent analytic steps of variable creation, subject matching, specification of pre/post periods (follow up windows), identification of outcomes, and statistical analyses. These included:

1. *Date of First Diabetes Diagnosis:* The date of the first occurrence of a claim record with an ICD-9 code of 250.xx, without any other diagnoses of diabetes or any prescriptions for diabetes medications (oral or insulin) in the prior 90 days (and a minimum 90 day pre-period of continuous eligibility) was considered the date of first diabetes diagnosis for the analyses.
2. *Date of Oral Diabetes Medication Initiation:* For those subjects with a diagnosis of diabetes as defined in F-1 above, the date of the first prescription claim for an oral diabetes medication (ODM) was considered to be the date of ODM therapy initiation. This date was the "Index Date" for the patterns of use, comparative effectiveness, and safety aims of the study.
3. *Time from First Diagnosis to First Medication Dispensing:* As a proxy for duration of diabetes, the time from first diabetes diagnosis to first ODM dispensing was determined and used as a covariate in the patterns of use and comparative effectiveness aims.
4. *Time to First Medication Change:* Consistent with the "new user" design of the study, and to keep the number of study groups and statistical comparisons reasonable and feasible, subjects in the ODM Cohort were followed until the first change to their initial regimen occurred (i.e., discontinuation, loss to follow up, switching to another ODM, augmentation with another ODM, etc, as defined below in subsection H-1). This follow up period was used as the ODM exposure period for all three aims of the study.
5. *Time to First Occurrence of Outcome:* Consistent with the "open cohort" design of the study and the variability in timing of study outcomes (e.g., time to hypoglycemic or liver injury event), subjects in the ODM Cohort and the two Comparison Cohorts were followed until the first occurrence of an outcome event

meeting study criteria. This allowed for varied "cohort enrollment" dates/spans, and varied amounts of person-time followup, primarily for the comparative effectiveness and safety aims of the study.

G. Propensity Analysis Methods

One of the major problems in the use of claims data for conducting comparative effectiveness and safety studies is the issue of nonrandom allocation of subjects to treatments, which may manifest in terms of confounding by indication and require appropriate design and/or analytic approaches to assure more valid results. In this pilot study, we used propensity analysis, two-stage multivariate modeling, and stratification of results to adjust for this phenomenon to the extent possible (given the available data).

First, based on the work of Kahler et al. (2007), and on treatment guidelines promulgated by the American Diabetes Association (2003), multivariable unconditional logistic regression models with "initial ODM treatment with metformin monotherapy" as the dependent variable and specified baseline patient and physician characteristics as independent variables were used to estimate each subject's likelihood (propensity) for receiving treatment with metformin (vs. another ODM drug or combination). The sets of patient and physician variables we used was based on prior research (starting with the Kahler et al. measures), with extensions based on input from the DARTNet Research Team.

For the comparative effectiveness and safety aims of the study, each subject's propensity score was then used as an adjustment variable in either General Linear Models or Cox Proportional Hazard regression models of the study outcomes (based on the scale of measurement, rarity, and functional form of the outcome measure specified in each hypothesis). Model results were computed and reported for both the full study cohorts, with the propensity score as a covariate; and by propensity score quintile, excluding the propensity score variable from the models. The robustness of model results across propensity score quintiles was evaluated using the Chow test.

H. Measures and Analyses

The specific subcohort definitions, measures, and analytic techniques used for each aim of the pilot study are described here sequentially, as proposed and performed. See Figure B-1 (CONSORT Chart) for a visual depiction of the construction and composition of the study cohorts for each aim of the analysis. Figure B-1 also describes subjects excluded (numbers of subjects excluded, by reason for exclusion).

1. Aim 1 – Patterns of Use

Cohort Definition

Of the 303,241 members of the Ingenix Impact Database who had at least one diagnosis of diabetes, 98,992 were continuously eligible during the 90 days prior to and 90 days following their index diagnosis date and had not received any diabetes drugs during the 90 days prior to their index diabetes diagnosis date. Of this diabetic cohort, 46,464 received no diabetes drugs following their diagnosis, 4,051 received insulin as their first line therapy following diagnosis,

and the remaining 48,477 received an oral diabetes medication (ODM) as their first line therapy following diagnosis.

The initial cohort for Aim 1 included the 98,992 subjects with at least one diagnosis of diabetes, no diabetes drugs during the 90 days prior to their first diabetes diagnosis date, and 90 days of continuous eligibility prior to and following their first diabetes diagnosis date. From this diabetic cohort, the primary study cohort of ODM Users (n=48,477) was identified and used for Patterns of Use analyses.

Drug Exposure

Among those receiving an ODM, the top ten monotherapy and combination therapies were identified, and subjects were classified into one of the following groups: biguanide (metformin) monotherapy, sulfonylurea (SU) monotherapy, thiazolidinedione (TZD) monotherapy, meglitinide monotherapy, GLP-1 Mimetic monotherapy, DPP-IV Inhibitor monotherapy, SU-Biguanide combination therapy, Biguanide-TZD combination therapy, Biguanide-TZD combination therapy, and SU-Biguanide-TZD combination therapy. These initial ODM therapy groups were used as a primary analytic grouping variable throughout all research aims.

For all subjects who received ODM (either monotherapy or combination therapy), algorithms were used to identify their first regimen change following the date of their first ODM dispensing. These changes were defined as follows:

- No change: stayed on the initial ODM(s) throughout the duration of their follow-up (i.e., eligibility) period
- Discontinuation: stopped the initial ODM(s) with no other ODM prescribed within 90 days of the end of their last prescription and with continuous eligibility for at least an additional 91 days past the end date of their last prescription
- Lost to follow-up: discontinuation (as above), with non-continuous eligibility during the 91 days following the end date of their last prescription
- Switch: stopped initial ODM therapy and started a new regimen of ODM therapy
- Reduction: started on combination ODM therapy and stopped one or more (but not all) of the initial ODM drugs
- Augmentation: remained on original ODM(s) with one or more ODMs added

Outcome Measures

The primary outcome measure for Aim 1 was the identification of the *most frequently used first line monotherapies and combination therapies*: Biguanide (metformin) monotherapy, SU monotherapy, TZD monotherapy, Meglitinide monotherapy, GLP1 Mimetic monotherapy, DPP-4 Inhibitor monotherapy, SU-Biguanide combination, Biguanide-TZD combination, Biguanide-TZD combination, and SU-Biguanide-TZD combination.

The *type of first therapy change* (no change, discontinuation, loss to follow-up, switch, reduction or augmentation) and *persistence*, defined as days from first ODM dispensing to first therapy change, were also used as outcome measures for this aim.

Covariates

In addition to baseline demographic characteristics (age in years at time of first diabetes diagnosis, gender, U.S. Census region), the diabetes-diagnosing provider type (endocrinologist,

PCP, other–known, other–unknown) was described for subjects in the diabetic cohort. The initial ODM therapy drug groups described above were used as the main effect in the analysis of time to first regimen change.

Statistical Analyses

Most frequently prescribed Initial Oral Diabetes Medications. The frequencies and percentages of each type of most commonly prescribed initial ODM therapy (single and combination) were reported for each study year (2002 – 2007) for the overall cohort, stratified by gender, and stratified by age group (< 45 years, 45 – 64 years, and 65 + years).

Persistence Analysis (time to first regimen change). Kaplan-Meier curves and the life table survival analysis method (with the log-rank tests) were used to compare the time to first regimen change (any type of change vs. no change) across the eight monotherapy groups and across the four combination therapy groups. Non-parametric Wilcoxon tests were used to test for pairwise differences, if any, in the median time to first regimen change between the eight monotherapy ODM groups and between the four combination therapy ODM groups. Due to the large number of comparisons being made, the standard alpha value of 0.05 was adjusted downward by dividing by the number of comparisons being made (28 comparisons among the eight monotherapy groups, 6 comparisons among the four combination therapy groups).

As an additional form of analysis (not specified according to an a priori hypothesis), Kaplan-Meier curves and the life table survival analysis method (along with the log-rank test) were used to compare the time to each specific type of regimen change among each of the individual ODM groups. Plot figures only are presented for these additional analyses (no statistical tests were performed, as these analyses were not specified a priori).

2. Aim 2 – Comparative Effectiveness

Cohort Definition

For the Comparative Effectiveness aim, diabetes medication users were required to have at least two Hemoglobin A1C (H-A1c) tests: the last occurring H-A1c test within the date range of 90 days prior to or 7 days following the date of their initial ODM drug dispensing was identified as their *baseline* H-A1c test; the latest H-A1c test that occurred at least 60 days after their first ODM dispensing but before the first change in ODM medication regimen was identified as the *last* H-A1c test. During this same time period, the H-A1c test with the *lowest* result value was also identified. As defined, the *last* and *lowest* H-A1C test results could be the same. After implementing these restrictions on the cohort of ODM users and excluding those who did not receive one of the top ten ODMs (per Aim 1), the resulting cohort for Aim 2 included 14,361 subjects who had valid results for their first, lowest and last H-A1c tests and had complete drug claims data for their exposure time period.

Outcome Measures

The main outcome measure for Aim 2 was effectiveness, which was measured by Hemoglobin A1C (H-A1c) levels according to laboratory result claims records. Baseline H-A1c levels were known and used to calculate two specific measures of effectiveness:

- the absolute change in H-A1c level from each subject's baseline H-A1c test (the earliest H-A1c test within 90 days prior to or 7 days following the date of their first ODM

dispensing) to the H-A1c test that occurred at least 60 days following their first ODM dispensing but prior to their first change in medication regimen with the *lowest* level (aka "Baseline to Lowest" H-A1C reduction)
- the absolute change in H-A1c level from each subject's baseline H-A1c test to the *last* H-A1c test that occurred at least 60 days following their first ODM dispensing but prior to their first change in ODM medication regimen (aka "Baseline to Last" H-A1C reduction)

Covariates

To make valid estimates and comparisons of ODM exposure-outcome associations, and to account for differential patterns of ODM consumption by subjects (and therefore different degrees of exposure), drug treatment for each study subject receiving ODM therapy was quantified using measures of *persistence* and *compliance* to characterize intensity of drug exposure. These measures were included as covariates in subsequent analytic models and were defined as follows:

- *Persistence* was defined as days from first ODM dispensing to first ODM therapy change (time to first ODM regimen change, as described above)
- *Compliance* during each subject's "period of persistence" was measured using a modification of the medication possession ratio (MPR), equal to the total days supplied of medication dispensed divided by the time elapsed between the first prescription fill and the last prescription fill, plus the days supply of the last fill. The resulting value represents the percentage of days that a given subject had an ODM available for consumption (and is assumed to have taken the medication).

A number of other variables were used in the outcome models of comparative effectiveness (unless specified as baseline, these covariates were measured from the date of first ODM dispensing to date of first regimen change): initial ODM therapy group, propensity score, age, gender, persistence, compliance, diabetes duration proxy (time from date of first diabetes diagnosis to first ODM dispensing), baseline H-A1c, renal dysfunction (yes/no indicator), hepatic dysfunction (yes/no indicator), number of diabetes-related physician visits, and number of diabetes education visits.

Statistical Analyses

Baseline Hemoglobin A1c Levels and Crude Changes. Crude baseline H-A1c levels and both absolute change outcome measures (baseline to lowest and baseline to last) were described for each ODM medication group by reporting the mean, median and range of values for each outcome.

Adjusted Hemoglobin A1c Change. As a first step in estimating the effect of type of first line ODM therapy on the effectiveness outcomes (change from baseline to lowest and change from baseline to last), an estimate of each subject's propensity to receive Metformin monotherapy was calculated using a propensity model with a dichotomous outcome (Metformin vs. other ODM therapy). This propensity score was included as a covariate in each comparative effectiveness model in order to adjust for each subject's likelihood of receiving Metformin monotherapy.

For each effectiveness outcome, a generalized linear model (GLM) was run and included the propensity score, variables to indicate the ODM medication groups (Metformin monotherapy

was the referent group), and other covariates as listed above. Using the parameter estimates obtained from each GLM model and the cohort mean values for each covariate included in the models, the adjusted mean levels of H-A1c change were calculated. In addition, the cohort was stratified based on propensity score quintiles and the effectiveness models were run for each quintile, excluding the propensity score variable from each quintile-based model.

3. Aim 3 – Comparative Safety

Cohort Definitions

Of the primary analytic cohort of ODM Users, 38,892 received one of the top ten mono/combination therapies, had at least 180 days of continuous enrollment prior to the first date of ODM dispensing and did not meet any other exclusion criteria based on pre-existing diagnoses during the 6 months prior to starting ODM therapy (see Appendix B-C for list of exclusions). These 38,892 diabetic subjects were matched 1:1 on age, gender, and region to subjects in the CAD/Dyslipidemia Comparison Cohort to provide a balanced external reference group of subjects for comparison. After applying the same inclusion and exclusion criteria to this matched cohort, 37,412 comparison subjects were retained for analysis. The third and final cohort was the Untreated Diabetic Cohort, which consisted of 36,614 diabetic subjects who received no diabetes medications following their index diagnosis and met the same inclusion and exclusion criteria as the first two cohorts.

Subjects from the CAD/Dyslipidemia Comparison Cohort that were matched to ODM Users were assigned their corresponding match's values for the following: index date of diabetes diagnosis, first date of ODM dispensing, and first date of regimen change. For members of the Untreated Diabetic Cohort, subjects' time to first regimen change was replaced by their follow-up time, calculated as the time from their index diabetes diagnosis date to the end of their current span of continuous enrollment. As such, subjects from each of the three cohorts in the comparative safety aim could enter the cohort at any time during their continuous enrollment in the database, and could contribute differing amounts of person-time (of either ODM drug exposure or follow up time for non-ODM-exposed subjects) to the subsequent statistical analyses.

Outcome Measures

Safety was measured by the occurrence of *hypoglycemia* (any, either major or minor), *liver injury*, and *liver failure*, according to medical, facility, and laboratory result claims records. Specific ICD-9, CPT-4 and LOINC codes and lab results were used to identify each outcome. Rates of safety outcome events, and time to first occurrence of each such event, were recorded as well.

Covariates

As in Aim 2, a propensity model was used to obtain a propensity score for each subject. The covariates included in the propensity model for Aim 3 were the same as those listed and used for Aim 2. Additional covariates were used in each safety model, including the following (grouped according to safety outcome parameter):

Hypoglycemia safety outcome model covariates included (unless specified as baseline, these covariates were measured from the date of first ODM dispensing to date of first regimen change): initial ODM therapy group, propensity score, age, gender, persistence, compliance,

renal dysfunction (yes/no indicator), hepatic dysfunction, number of diabetes-related physician visits, and number of diabetes education visits, number of other medications received, and receipt of specific drugs that have been associated with increased risk of hypoglycemic events (aspirin products, ACE inhibitors, angiotensin receptor blockers, antidepressants, beta blockers, or fluoroquinolones).

Liver injury and *liver failure* safety outcome model covariates included (unless specified as baseline, these covariates were measured from the date of first ODM dispensing to date of first regimen change): initial ODM therapy group, propensity score, age, gender, persistence, compliance, renal dysfunction (yes/no indicator), hepatic dysfunction (according to specific diagnoses, number of diabetes-related physician visits, number of diabetes education visits, and other diagnoses and receipt of specific drugs that have been associated with increased risk of liver injury or failure.

Statistical Analyses

Crude incidence rates of Hypoglycemic Events, Liver Injury and Liver Failure. For each of the three cohorts described above for the comparative safety aim (the ODM User cohort and the two comparison cohorts), crude incidence rates were calculated for each of the safety outcomes (hypoglycemia, liver injury, and liver failure). Incidence rates were calculated per 1,000 subjects (i.e., per subject/course of therapy) and per person-year of therapy or follow-up (to account for differential exposure or follow-up time).

Relative Risks of Hypoglycemic Events, Liver Injury and Liver Failure. Three Cox Proportional Hazards models were fitted to estimate relative risks (i.e., hazard ratios) of each outcome event, estimating the effect of initial ODM therapy group membership and adjusting for propensity score and other covariates. The propensity score for this aim was created using the same type of propensity as described above for Aim. In addition to estimating the propensity-adjusted hazard ratios for each outcome, each model was also re-run, stratified by propensity score quintile (with propensity score excluded from each model).

I. Sensitivity Analyses

A number of sensitivity analyses were run, to evaluate the robustness of the methodologic and analytic decisions and assumptions that were made in the course of this pilot work. First, a series of sensitivity analyses were performed to evaluate the possible effect of varied definitions of several key measures:

Continuous Eligibility Requirements

The primary diabetic cohort (n=98,992) from which the cohorts for each aim were drawn was based on the requirement of having at least 90 days of continuous eligibility prior to and following the subject's index diabetes diagnosis date, with no record of any diabetes medication having been dispensed during the prior 90-day period. As a sensitivity analysis, this requirement was changed to at least 180 days of continuous eligibility prior to and following the subject's index diabetes diagnosis date and no diabetes medications dispensed during the prior 180-day period. As a result, the diabetic cohort decreased in size to 68,013 subjects; and the ODM User cohort decreased in size to 33,414. The observed patterns of initial ODM therapy use, persistence with therapy, time to first regimen change, baseline H-A1C value, etc. were not different for this "more restricted" set of subjects, so the original 90 day pre/post continuous

eligibility requirement was retained for the analyses.

Time to First Medication Change Measure

In determining the first type of medication regimen change, subjects were given a window of 90 days in which they could stop and re-start the same medication or start a new medication before being classified as discontinued or lost to follow-up. In a sensitivity analysis, this time window was shortened to 31 days, but was deemed to be too restrictive to allow for real-world patterns of use (including later than expected refilling of prescriptions; varied days supply patterns of 30, 60 or 90 days depending on insurance benefit design and use of mail order pharmacies; etc.). For example, many subjects did not refill an ODM within 31 days after the end date of a particular prescription, but did receive a refill between 32 and 90 days; in the 31-day window for defining discontinuation, such subjects were being misclassified as discontinued or lost to follow-up. A more conservative window of 90 days allowed subjects who did not in fact discontinue their therapy to be followed for a longer (and still valid) period of observation in which to determine rates of effectiveness and safety outcomes.

Covariates Included in Propensity Models

The propensity models used in Aims 2 and 3 (comparative effectiveness and safety) were based on those used by Kahler, et al. (2007) in a similar study of ODM effectiveness. Based on the model used by Kahler, three scenarios for propensity models were created. The first matched Kahler's list of covariates as closely as possible with respect to covariates included and the measurement scales of those covariates. The second scenario matched Kahler's model and included additional covariates considered relevant by the DARTNet Research Team. The third model scenario included Kahler's list of covariates with more specific levels of measurement (e.g., continuous variables rather than categorical) as well as the additional covariates per the DARTNet Research Team. After review, the second model was chosen for estimating the propensity scores for Aims 2 and 3. The sample size resulting from the first and second scenarios was the same but there was more variation (discriminatory power) in the range of propensity scores resulting from the second scenario than the first. The third scenario also resulted in a much smaller sample size (i.e., reduced by nearly 80%) because for many variables, subjects were coded as missing and were therefore dropped from the model; the first and second scenarios considered such subjects to have valid data because "missing/unknown" was defined as a valid category. See Appendix B-A for the list of covariates included in the final propensity models.

Pre-Period for Safety Aim

The cohorts for Aim 3 (comparative safety) were required to have at least 180 days of continuous eligibility prior to the date of their first ODM dispensing in order to have a look-back period for assessing pre-existing conditions (exclusion criteria) based on evidence of pre-existing liver injury. Longer look-back periods of 270 days and 365 days were considered but resulted in much smaller sample sizes (the ODM User cohort decreased from 38,892 to 25,865 if 270 days of look-back was required and to 20,685 if a year of look-back was required). As such, the 180 day look-back period was retained.

Propensity Analysis Methods

An additional sensitivity analysis was performed to compare the base-case propensity analysis approach (which created a single propensity score for each subject's likelihood of receiving metformin monotherapy vs. any other ODM therapy), versus a multiple propensity score approach which created propensity scores for each subject for receiving each of the ODM therapies in the study (i.e., each monotherapy group and each of the combination therapy groups), with the sum of the multiple propensity scores being equal to 1.0 for each subject. This analysis employed polytomous (multinomial) logistic regression to estimate propensity scores, using the method described by Imbens (Imbens 2000), and was applied to all of the base case comparative effectiveness and safety models that used propensity score adjustment.

The results of the sensitivity analysis using the multiple propensity score approach are included in the report (presented in Tables B18 through B-23). These results, when compared and contrasted to their base-case counterparts (found in Tables B-10 through B-12 and B-15 through B-17), showed no appreciable differences versus the results of the primary analyses. Only extremely slight changes in the magnitude of certain outcome model parameters were noted, and none of these altered the findings or conclusions drawn at the end of the study. As such, for this study the results based on the single propensity score adjustment approach were retained and presented as the primary findings.

V. Results

The results of the pilot study are presented here, first in overview (bulleted) form, then grouped by phase and aim (as arranged and presented in the Methods section). It should be noted that the detailed findings include both primary findings (i.e., specifically oriented to answer the nine research hypotheses that were tested), and secondary findings that were not essential to the testing of the research hypotheses but were viewed as being of potential interest to readers and of value for hypothesis generation for future research. As such, the primary findings are discussed in greater detail and secondary findings in lesser detail. Phase 2 results are discussed separately.

To provide orientation to the reader to the Tables and Figures:

- Figure B-1 provides a CONSORT chart, describing the composition of the various study cohorts for each aim of the analysis
- Tables B-1 – B-8 and Figures B-2 - B-15 pertain to Phase 1, Aim 1 – Patterns of Use
- Tables B-9 – B-12 pertain to Phase 1, Aim 2 – Comparative Effectiveness
- Tables B-13 – B-17 pertain to Phase 1, Aim 3 – Comparative Safety
- Tables B-18 – B-23 pertain to Phase 1, Aims 2 and 3 - Sensitivity Analysis (i.e., multiple propensity score-adjusted versions of Tables B-10 – B-12 and B-15 – B-17)
- Tables B-24 – B-27 pertain to Phase 2 – DARTNet Replication Analyses (i.e., replications of Tables B-1, B-7, B-10, and B-14a using EHR data)

A. Overview of Principal Findings

Summary findings from the pilot study of ODM patterns of use, comparative effectiveness, and safety include the following:

- The diabetic cohort from the Ingenix Impact Database is sufficient in size and scope to enable the study of several important aspects of patterns of use, comparative effectiveness, and safety of ODM. Approximately 100,000 diabetic subjects comprised the utilization and safety aims of the study, and a subset of approximately 14,000 subjects comprised the effectiveness aim.
- Among diabetics prescribed ODM, nearly 80% were initiated on monotherapy while 20% were initiated on combination therapy regimens.
- Persistence with initial ODM therapies differed across specific monotherapy and combination therapy groups. Subjects initiated on biguanides or TZDs had greater persistence than those initiated on other monotherapies; subjects initiated on SU+Biguanides or Biguanides+TZDs had greater persistence than those initiated on other combinations.
- In terms of comparative effectiveness, unadjusted reductions in Hemoglobin A1C from baseline to lowest value were similar to previous findings reported in the literature, for both monotherapy and combination therapy subjects. Use of any single ODM resulted in unadjusted reductions in H-A1C of approximately 1%; use of 2-drug ODM combinations resulted in unadjusted reductions in H-A1C of about 2%; and use of 3-drug combinations resulted in unadjusted reductions in H-A1C of about 2.6%. Adjusted reductions in H-A1C (either baseline to lowest or baseline to last) attenuated some of the crude differences observed by number of ODM received, and resulted in the various drug groups becoming more similar in terms of observed, real-world effectiveness. Changes from baseline to last H-A1C were somewhat lower for all agents, either alone or in combination.
- Multivariate modeling results on the primary effectiveness outcome showed only slight differences across individual ODM drugs or combinations, in comparison to metformin monotherapy (statistically significant findings were numerous, but many were of questionable clinical significance). Other factors associated with achievement of greater H-A1C reduction included: propensity score, persistence and compliance with therapy, baseline H-A1C, and number of diabetes-related MD and diabetes education visits.
- In terms of safety, crude rates of hypoglycemia, liver injury, and liver failure were relatively low (ranging from 0.007 to 0.015 events per person-year of therapy or followup in the entire study cohort). Unadjusted rates of all three safety outcomes were similar among diabetic subjects, whether treated with ODM or not.
- Multivariate modeling results on the safety outcomes showed that as compared to those receiving metformin monotherapy, users of sulfonylureas (either alone or in combination with other ODM) were at greater risk of hypoglycemic events and liver injury, but not liver failure. No such increases in risk (relative to metformin monotherapy) were observed for patients receiving TZDs, or for those receiving statins concurrently. Other factors associated with adverse safety outcomes included renal dysfunction and certain specific other diagnoses and medications associated with these outcomes.

- Propensity adjustment was used in all comparative effectiveness and safety models; neither stratification of effectiveness and safety model results by propensity score quintiles, nor alternative specification of the propensity modeling approach using multiple (vs. base-case, single) propensity scores, resulted in any significant changes to the principal findings or conclusions of the study.

B. Detailed Results: Study Cohort Compositions

From the initial extraction of 303,241 subjects from the Ingenix Impact database, 98,992 met criteria for inclusion in Aim 1; 14,361 met criteria for inclusion in Aim 2; and 112,918 (38,892 ODM users and 74,026 comparison subjects) met criteria for inclusion in Aim 3. Figure B-1 displays the steps used to identify subjects for each Aim.

C. Detailed Results: Patterns of Use of Oral Diabetes Medications

As described above, 98,992 subjects with a first diagnosis of diabetes according to study criteria were included in the analyses for Aim 1. Table B-1 displays the demographic characteristics of these subjects (overall and by study year, 2002-2007).

Approximately 53% of the subjects were male, most resided in the Mid Atlantic (41.0%) and South Atlantic (31.8%) census regions, most (61.6%) were diagnosed with diabetes by a primary care provider as opposed to an endocrinologist (3.3%) or other type of provider (35.1%). The average number of chronic conditions for each study subject was 4.0 (including their diabetes diagnosis; or, 3.0 other chronic conditions), while the average Charlson score for each subject was considerably lower (0.27). Table B-2 reports the top 10 concurrent and past diagnoses for members of the diabetic cohort. The most common conditions observed were dyslipidemia, hypertension, and other/general symptoms.

Following initial diabetes diagnosis, 49% of subjects received therapy with ODM (either as monotherapy, 39%, or combination therapy, 10%). Nearly 47% of subjects did not receive any type of diabetes medication at any time during their continuous followup/eligibility span. Over the course of the study period (from mid-2002 to mid-2007), the percentage of subjects that received no diabetes medications during followup increased from 34% in 2002 to 69% in 2007. Overall, approximately 4% of subjects received treatment with insulin (decreasing from 14% in 2002 to only 1.6% in 2007).

In terms of specific ODM therapies, Table B-3a displays the patterns of use of specific monotherapies overall, and by study year, according to drug class and individual agent. Among subjects initiated on a single ODM, metformin (60.6%) was the most commonly used agent, followed by sulfonylureas (20.7%) and TZDs (15.6%). Other and newer agents were used in only about 3.4% of new users. Tables B-3b and B-3c display patterns of use by gender; and Tables B-3d through B-3f display patterns of use by age group over the same time period overall, and by study year. A number of statistically significant differences were observed in terms of patterns of use, both by year, by gender, and by age (see Tables B-3a – B-3f); given large sample sizes and the number of comparisons made, it is left to the reader to determine which, if any, of these differences is clinically meaningful.

Table B-4a displays the patterns of use of specific fixed-dose combination ODM therapies overall, and by study year, according to drug classes/combinations. Among subjects initiated on a fixed-dose combination, the combinations of Metformin+TZD (48.9%) and Metformin+SU (46.3%) were by far the most commonly used. SU+TZD (4.6%) and DPP-4+Metformin (0.4%) fixed-dose combinations were only rarely used in this period of time. Tables B-4b – B-4f display patterns of use of fixed-dose ODM combintations by age group and

by gender over the entire study period, and by year. Again, a number of statistically significant differences were observed, but these may or may not have clinical relevance.

Table B-5 displays the 25 most commonly used non-fixed-dose combinations of ODM drugs in the DARTNet diabetic cohort, by individual agent(s) prescribed, and clustered by 2-drug and 3-drug combinations. Table B-6 displays similar results, grouped this time by drug class, to enable identification of the most commonly used 2-drug and 3-drug combinations of ODM drugs (for further study in Aims 2 and 3). The most commonly used 2-drug combinations were: Metformin+SU (46.4%), Metformin+TZD (32.9%), and SU+TZD (14.2%). The most commonly used 3-drug combination was: Metformin+SU+TZD (87.9%). As such, these three 2-drug combinations and one 3-drug combination of ODM were used as the comparison groups in Aims 2 and 3 when comparing the effectiveness and safety of selected combinations of drugs (from among all of the possible combinations that may have been in use).

Table B-7 displays the time to first regimen change (persistence) for the twelve initial ODM therapy groups that had sufficient sample size for study (8 monotherapy groups, and the three 2-drug and one 3-drug combinations identified above in Table B-6). Among monotherapy groups, the median time to therapy change ranged from a high of 182 days with Biguanides to a low of 32 days with Amylin Analogues. Mean values were higher (285 days for Biguanides to 51 days for Amylin Analogues). Ranges were very broad (as low as 2 days, reflective of subjects who entered the open cohort design during the last few days of the study period; and as high as 1755 days, reflective of subjects who entered the open cohort design in 2002 and had both continuous eligibility and no regimen changes from their initial ODM drug(s) during that entire span of time). Statistical tests revealed a number of differences between individual ODM monotherapy groups in terms of persistence (these are footnoted in Table B-7). Among the four ODM combination therapy groups, the median time to regimen change ranged from 153.5 days for Biguanide+TZD subjects to 96 days for SU+TZD+Biguanide subjects (again, mean values were higher for each combination therapy group). Statistical tests revealed that subjects initially receiving either SU+Biguanide or Biguanide+TZD therapy had higher persistence than those initially receiving either SU+TZD or SU+TZD+Biguanide therapy ($p<0.0083$, adjusted for multiple comparisons). This last statistical test was the primary persistence analysis according to the study protocol.

Kaplan-Meier plots of time to first regimen change are presented as Figures B-2 – B-15. Figure B-2 displays time (days) to first regimen change (of any type) for subjects initiated on combination therapy; Figure B-3 displays the same information for subjects initiated on ODM monotherapy. Figures B-4 – B-15 display the time to first regimen change, by type of regimen change (e.g., discontinuation, LTFU, switch, reduction or augmentation), for each of the 12 specific combination therapy or monotherapy groups that were studied. Table B-8 presents the results of Log Rank tests for the 14 Kaplan-Meier plots. These plots and their associated statistical tests were considered secondary analyses, and did not correspond to any of the specific research hypotheses.

To conclude the detailed results for Aim 1, the research hypotheses for this aim are restated here, with a statement for each hypothesis that it was either rejected or not rejected, based on the results obtained in this study:

Hypothesis PU-1: The pattern of use of various drug classes individually and in combination will not be significantly different over a five-year period or by age or gender over that period. **[Hypothesis rejected; differences observed]**

Hypothesis PU-2: Persistence of use will not be significantly different between any two-drug combinations. **[Hypothesis rejected; differences observed]**

D. Detailed Results: Comparative Effectiveness of Oral Diabetes Medications

As described previously, the cohort for Aim 2 included 14,361 subjects from the diabetic cohort who received ODM, were in one of the 12 most commonly used drug groups, had valid results for their first, lowest and last H-A1c tests and had complete drug claims data for their exposure time period. Table B-9 displays the demographic characteristics of these subjects (overall and by initial ODM therapy group). Subjects in the cohort for Aim 2 were similar to those in the Aim 1 cohort in terms of age, gender, region, provider type, and chronic disease burden.

Table B-10 displays the Hemoglobin A1C (H-A1C) results for each of the 12 initial ODM therapy groups, arranged by baseline H-A1C, change from baseline to lowest, and change from baseline to last. Unadjusted H-A1C values (mean, median and range) are presented for all columns; adjusted values are also presented for the two "reduction" measures (i.e., the primary effectiveness endpoints). As seen in Table B-10, baseline mean H-A1C values varied across the 12 initial ODM therapy groups, from a high of 9.65 for the SU+TZD+Biguanide and SU+TZD combinations to a low of 7.01 for the GLP1 Mimetic monotherapy group. Median baseline H-A1C values were slightly lower across the board, and values ranged from a low of 4.3 to a high of 20.0. As the differences in baseline H-A1C became apparent, they also reinforced our decision to include this variable in subsequent outcome models of comparative effectiveness, to adjust for possible confounding by severity of illness and/or regression to the mean.

In terms of H-A1C reduction from baseline to lowest, unadjusted mean values ranged from -0.63 for GLP1 Mimetic therapy to -2.71 for SU+TZD combination therapy. Our "base case" therapy (Metformin monotherapy) had an unadjusted mean reduction of -1.14; this reduction was greater than that observed for meglitinides, TZDs, or GLP1 Mimetics, but less than that observed for SUs, DPP-4 Inhibitors, or any combination therapy groups. In general, the monotherapy groups achieved approximate unadjusted reductions in H-A1C from baseline to lowest of about 1.0-1.5%; 2-drug combinations achieved approximate unadjusted reductions of about 2.0-2.7%; and the 3-drug combination achieved an approximate unadjusted reduction of about 2.7%.

In terms of H-A1C reduction from baseline to last, unadjusted mean values ranged from -0.54 for GLP1 Mimetic therapy to -2.58 for SU+TZD combination therapy. Our "base case" therapy (Metformin monotherapy) had an unadjusted mean reduction (from baseline to last) of -0.95; this reduction was, again, greater than that observed for meglitinides, TZDs, or GLP1 Mimetics, but less than that observed for SUs, DPP-4 Inhibitors, or any combination therapy groups. In general, the monotherapy groups achieved approximate unadjusted reductions in H-A1C from baseline to last of about 0.7-1.2%; 2-drug combinations achieved approximate unadjusted reductions of about 2.0-2.6%; and the 3-drug combination achieved an approximate unadjusted reduction of about 2.5%. Thus, slightly less reduction was observed from unadjusted baseline to last, as opposed to unadjusted baseline to lowest, H-A1C value in the comparative effectiveness study cohort.

Table B-10, in the columns labeled "Adjusted Mean" (i.e., the far right hand columns in the second and third groupings of results), also displays the adjusted reductions in H-A1C from

baseline to lowest and baseline to last for the comparative effectiveness cohort, by initial ODM therapy group. These reductions in H-A1C are adjusted for all variables specified for inclusion in the effectiveness models (see footnote to Table B-10, Methods section, and Appendix B-B). Adjusted mean reductions in H-A1C from *baseline to lowest* ranged from -1.36 for subjects initially receiving Metformin monotherapy to -1.71 for subjects initially receiving GLP1 Mimetic therapy. Adjusted mean reductions from baseline to lowest were similar for both monotherapy and combination therapy groups. Adjusted mean reductions in H-A1C from *baseline to last* ranged from -1.09 for subjects initially receiving SU monotherapy to -1.52 for subjects initially receiving DPP-IV Inhibitor therapy. Adjusted mean reductions from baseline to last were also similar for both monotherapy and combination therapy groups.

Table B-11 displays the results of multivariable generalized linear models (GLM models) of the effect of initial ODM therapy group and other covariates on H-A1C change from *baseline to lowest*. Results are presented for the entire effectiveness aim cohort, and by propensity score quintile. Metformin monotherapy was the referent group for the comparative effectiveness aim (just as it had served as the anchor for the propensity analysis models); as such, in this table, the results for the other ODM therapy groups are in comparison to those observed for subjects initallly receiving Metformin. Among the initial ODM therapy groups, all groups other than SU show a statistically greater reduction in H-A1C from baseline to lowest than Metformin monotherapy, though numerically these differences are in the range of an additional -0.15 to -0.35 of reduction in H-A1C, which may or may not be of clinical significance.

In terms of specific 2-drug combinations of ODM drugs (a study hypothesis), it was observed that the combinations of Biguanide+TZD, SU+TZD, and SU+TZD+Biguanide all were associated with statistically greater reductions in H-A1C than the combination of SU+Biguanide (with additional marginal reductions in H-A1C of about -0.20), which may or may not be of clinical significance. All covariates in the effectiveness model other than age and hepatic dysfunction were statistically significantly associated with H-A1C reduction, though again, the clinical significance of these associations is a matter for discussion. The comparative effectiveness results for H-A1C reduction (baseline to lowest) differed slightly by propensity score quintile, but not to the extent that they substantively changed the findings of the study, so the overall (entire cohort) results are believed to be reasonably stable and robust.

Table B-12 displays the results of multivariable generalized linear models (GLM models) of the effect of initial ODM therapy group and other covariates on H-A1C change from *baseline to last*. Results are presented for the entire effectiveness aim cohort, and by propensity score quintile. Metformin monotherapy was the referent group (as above). Among the initial ODM therapy groups, all groups other than SU show a statistically greater reduction in H-A1C from baseline to last than Metformin monotherapy, though numerically these differences are in the range of an additional -0.16 to -0.36 of reduction in H-A1C, which may or may not be of clinical significance.

In terms of specific 2-drug combinations of ODM drugs (a study hypothesis), it was observed that the combinations of Biguanide+TZD, SU+TZD, and SU+TZD+Biguanide all were associated with statistically greater reductions in H-A1C than the combination of SU+Biguanide (with additional marginal reductions in H-A1C of about -0.25 or so), which again may or may not be of clinical significance. All other covariates in the effectiveness model besides age and gender were statistically significantly associated with H-A1C reduction, though again, the clinical significance of these associations is a matter for discussion. As above, the comparative effectiveness results for H-A1C reduction (but in this case, from baseline to last) differed slightly

by propensity score quintile, but not to the extent that they substantively changed the findings of the study, so the overall (entire cohort) results are believed to be reasonably stable and robust.

To conclude the detailed results for Aim 2, the research hypotheses for this aim are restated here, with a statement for each hypothesis that it was either rejected or not rejected, based on the results obtained in this study:

Hypothesis CE-1: Glycemic control will be significantly better for all combinations of oral agents compared to single agents. **[Hypothesis not rejected; differences observed (though subject to interpretation as to clinical significance)]**

Hypothesis CE-2: Glycemic control will not be significantly different between any two drug class combinations. **[Hypothesis rejected; differences observed (though subject to interpretation as to clinical significance]**

E. Detailed Results: Comparative Safety of Oral Diabetes Medications

As described previously, the cohort for Aim 3 included 112,918 subjects (38,892 in the ODM Cohort; 36,614 in the Untreated Diabetic Cohort; and 37,412 in the CAD/Dyslipidemia Comparison Cohort). These subjects were required to have at least 180 days of continuous eligibility prior to their index date of ODM dispensing (or index date of diabetes diagnosis, or matched index date, respectively). Table B-9 displays the demographic characteristics of these subjects (overall, by cohort, and by initial ODM therapy group). Subjects in the cohorts for Aim 3 were generally similar to those in the Aim 1 cohort in terms of age, gender, region, provider type, and chronic disease burden.

Table B-14a displays crude incidence rates of the three safety outcomes (hypoglycemia, liver injury, and liver failure) overall, and by study cohort (initial ODM therapy group or one of the two comparison cohorts). Results are presented in terms of number of events observed, number of events per 1,000 subjects, number of person years of observation (ODM exposure or follow-up time, depending upon cohort membership), and number of events per person-year of therapy (or follow up, for those not exposed to ODM). Across the three study cohorts (overall), 1842 hypoglycemic events, 1083 liver injury events, and 888 liver failure events were detected.

The first safety outcome, hypoglycemia (expressed in terms of crude rates of the event per person-year of exposure to ODM, or follow-up time for subjects not exposed to ODM), occurred at a rate of 0.015 per person-year across the three study cohorts. The rate was 0.006 hypoglycemic events per person-year in the CAD/Dyslipidemia comparison cohort, and 0.019 events per person-year in the Untreated Diabetic comparison cohort. Among the initial ODM therapy groups, crude rates of hypoglycemic events ranged from 0.010 events per person-year of exposure in the TZD monotherapy group to 0.070 in the SU+TZD+BG combination therapy group. Rates of hypoglycemia were in the range of 0.010 to 0.016 events per person-year for all monotherapy groups, with the exception of SUs (0.035) and Meglitinides (0.032). Among the combination therapy groups, rates of hypoglycemia were lowest (0.046 per person-year of exposure) for Biguanide+TZD subjects, somewhat higher for SU+TZD (0.035) and SU+Biguanide (0.046) subjects, and somewhat higher still for subjects in the SU+TZD+Biguanide (0.070) group.

The second safety outcome, liver injury (expressed in terms of crude rates of enzyme elevation events per person-year of exposure to ODM, or follow-up time for subjects not

exposed to ODM), occurred at a rate of 0.009 per person-year across the three study cohorts. The rate was 0.004 liver injury events per person-year in the CAD/Dyslipidemia comparison cohort, and 0.009 events per person-year in the Untreated Diabetic comparison cohort. Among the initial ODM therapy groups, crude rates of liver injury ranged from 0.000 events per person-year of exposure in the DPP-4 Inhibitor monotherapy group to 0.026 in the SU+Biguanide combination therapy group. Rates of liver injury were in the range of 0.000 to 0.012 events per person-year for all monotherapy groups, with the exception of SUs (0.019) and Meglitinides (0.022). Among the combination therapy groups, rates of liver injury were lowest (0.010 per person-year of exposure) for Biguanide+TZD and SU+TZD+Biguanide subjects, and somewhat higher for SU+TZD (0.019) and SU+Biguanide (0.026) subjects.

The third and final safety outcome, liver failure (expressed similarly as above, but for liver failure according to diagnoses or lab results), occurred at a rate of 0.007 per person-year across the three study cohorts. The rate was 0.004 liver failure events per person-year in the CAD/Dyslipidemia comparison cohort, and 0.009 events per person-year in the Untreated Diabetic comparison cohort. Among the initial ODM therapy groups, crude rates of liver failure ranged from 0.000 events per person-year of exposure in the DPP-4 Inhibitor monotherapy and SU+TZD+Biguanide combination therapy groups, to 0.016 in the GLP1 Mimetic monotherapy group. Rates of liver failure were in the range of 0.000 to 0.006 events per person-year for all monotherapy groups, with the exception of SUs (0.009) and GLP1 Mimetics (0.016). Among the combination therapy groups, rates of liver injury were lowest (no events detected, or 0.000 per person-year) for the SU+TZD+Biguanide group, and ranging from 0.006 to 0.009 events per person-year for all three of the 2-drug combination therapy groups.

Tables B-14b and 14c present similar results to those in Table B-14a (crude rates of safety outcome events (overall, and by study cohort), stratified further according to concurrent statin use during the period of ODM exposure (Table B-14b presents results for concurrent statin users; Table B-14c presents results for non-statin users). It should be noted that approximately one-third of the subjects in each cohort were concurrent statin users in this population. Rates of all safety outcomes were similar to those presented from the overall cohort (Table B-14a), when presented for either statin users or non-users alone. Similar ranges of crude rates, patterns of drugs with slightly increased crude rates, etc., were observed for the three safety outcomes in these stratified resuts.

Table B-15 displays the results of a multivariable Cox Proportional Hazard model of the effect of initial ODM therapy group and other covariates on the relative hazard (RR) of hypoglycemic events among subjects in the ODM User cohort. Results are presented for the entire ODM User cohort, and by propensity score quintile. Biguanide (metformin) monotherapy was the referent group (as in Aim 2). Among the initial ODM therapy groups, all groups (and only those groups) containing a SU showed a statistically increased risk of hypoglycemia. For SU monotherapy, the risk of hypoglycemia was 3.23 times greater (HR=3.23, CI=2.58-4.05) than for metformin monotherapy; for SU+Biguanide combination therapy, the risk was 4.43 times greater (HR=4.43, CI=3.41-5.76); for SU+TZD combination therapy, the risk was 2.87 times greater (HR=2.87, CI=1.52-5.41); and for SU+TZD+Biguanide combination therapy, the risk was nearly 6 times greater (HR=5.97, CI=3.31-10.77). No other monotherapy groups showed any evidence of increased risk of hypoglycemia compared to metformin monotherapy. Other covariates that were associated with risk of hypoglycemia in the model were: male gender (lower risk, HR=0.80, CI=0.67-0.96), renal dysfunction (higher risk, HR=3.09, CI=2.34-4.07), the numbers of diabetes physician visits (HR=1.007, CI=1.001-1.014) and diabetes education

visits (HR=1.131, CI=1.06-1.21), and the number of unique drugs taken by subjects (HR=1.057, CI=1.04-1.07). The results for the hypoglycemia outcome models differed slightly by propensity score quintile, but not to the extent that they substantively changed the findings of the study, so the overall (entire cohort) results are believed to be reasonably stable and robust.

Table B-16 displays the results of a multivariable Cox Proportional Hazard model of the effect of initial ODM therapy group and other covariates on the relative hazard (RR) of liver injury among subjects in the ODM User cohort (presented as above). Among the initial ODM therapy groups, two specific therapy groups containing a SU showed a statistically increased risk of liver injury (SU monotherapy, HR=1.51, CI=1.15-1.98; and SU+Biguanide combination therapy, HR=1.66, CI=1.20-2.29) than the metformin monotherapy group. No other initial ODM therapy group was associated with increased risk of liver injury. Of specific (*a priori*) interest in this analysis, concurrent statin use was found to be associated with lower risk of liver injury (HR=0.52, CI=0.41-0.67) in this cohort of subjects. Other covariates that were associated with risk of liver injury in the model were: propensity score (lower risk, HR=0.44, CI=0.24-0.80), age (lower risk, HR=0.97, CI=0.96-0.97), male gender (higher risk, HR=1.34, CI=1.07-1.69), renal dysfunction (HR=1.99, CI=1.31-3.02), the number of diabetes related physician visits (HR=1.01, CI=1.01-1.20), and a number of other drugs (acetaminophen, allopurinol, amiodarone, quinidine) and diagnoses (hepatitis C or D infection, EBV infection, jaundice, chronic liver disease, primary/metastatic neoplasia, sclerosing cholangitis, or hypercholesterolemia) that have previously been associated with liver injury. The results for the liver injury outcome models differed slightly by propensity score quintile, but not to the extent that they substantively changed the findings of the study, so the overall (entire cohort) results are believed to be reasonably stable and robust.

Table B-17 displays the results of a multivariable Cox Proportional Hazard model of the effect of initial ODM therapy group and other covariates on the relative hazard (RR) of liver failure among subjects in the ODM User cohort (presented as above). In this model, none of the initial ODM therapy groups demonstrated any higher or lower risk of liver failure than metformin monotherapy (the referent group). Of specific (*a priori*) interest in this analysis, neither TZD use (HR=1.01, CI=0.59-1.70) nor concurrent statin use (HR=0.83, CI=0.60-1.13) was found to be associated with any higher or lower risk of liver failure than metformin monotherapy, either. Other covariates that were associated with risk of liver failure in the model were: renal dysfunction (HR=1.90, CI=1.08-3.37), and a number of other drugs (isoniazid, methotrexate) and diagnoses (hepatitis B, C or D infection, EBV infection, chronic liver disease, biliary tract problems, or hypercholesterolemia) that have previously been associated with liver failure. As above, the results for the liver failure outcome models differed slightly by propensity score quintile, but not to the extent that they substantively changed the findings of the study, so the overall (entire cohort) results are believed to be reasonably stable and robust.

To conclude the detailed results for Aim 3, the research hypotheses for this aim are restated here, with a statement for each hypothesis that it was either rejected or not rejected, based on the results obtained in this study:

Hypothesis CS-1: All combinations of medications will have significantly higher rates of hypoglycemic events compared to single agents. **[Rejected; not all combinations had statistically higher rates]**

Hypothesis CS-2: Liver toxicity, as defined by elevated liver enzymes greater than 3 times

normal, will not be significantly different among users of any single drug class. **[Rejected; SU group had statistically higher rate]**

Hypothesis CS-3: Liver toxicity, as defined in CS-2 above, will not be significantly different among users of any two drug combinations. **[Rejected; SU+Biguanide group had statistically higher rate]**

Hypothesis CS-4: Liver toxicity, as defined in CS-2 above, will not be significantly different among any combination of oral hypoglycemic agents, either singly or in two-drug combinations, with the addition of a statin agent. **[Rejected; statin users had statistically lower risk of liver injury]**

Hypothesis CS-5: There will be no significant differences in rates of liver failure, as defined by elevations in liver function enzymes along with an elevation in prothrombin time (for patients not on warfarin), or a drop in platelet counts, or a diagnosis of liver failure. **[Not rejected; no differences observed]**

F. Sensitivity Analysis Results: Comparing Propensity Score Approaches

As noted previously, an additional sensitivity analysis was performed to compare the base-case, propensity analysis approach (using single propensity scores), versus a multiple propensity score approach which created propensity scores for each subject for receiving each of the ODM therapies in the study, using polytomous (multinomial) logistic regression. Each of the base case comparative effectiveness and safety models that used propensity score adjustment was re-run adjusting for the multiple propensity scores generated by this alternative approach.

Tables B-18 through B-23 present the results of the sensitivity analysis using the multiple propensity score approach. These results, when compared and contrasted to their base-case, single propensity score counterparts (found in Tables B-10 through B-12 and B-15 through B-17), showed no appreciable differences versus the results of the primary analyses. Only extremely slight changes in the magnitude of certain outcome model parameters were noted, and none of these altered the findings or conclusions drawn at the end of the study. As such, for this study the results based on the single propensity score adjustment approach were retained and presented as the primary findings.

VI. Discussion

A. Conclusions

The findings of our analysis suggest there are no substantial, clinically significant differences in adjusted effectiveness of any of the common ODM monotherapies. Furthermore, the adjusted differences in initial monotherapy versus combination therapy are minimal and, suggest there is little reason to consider starting a patient on combination therapy. But while all monotherapies appear to be equally effective, sulfonylureas (SU) appear to have several characteristics that would indicate they may not be ideal initial therapy. For instance, SU do not appear to maintain glycemic control as well as all other mono therapies. SU are associated with

hypoglycemic events and liver injury events. Contrary to FDA guidelines, which recommend liver monitoring for TZD, this class of drugs does not appear to be associated with increases in liver injury or liver failure. Interestingly, neither are statins, which also carry recommendations for liver monitoring, while SU do not. Even in combination, biguanides and TZD do not appear to increase the risk of hypoglycemia or liver injury events. Usage trends indicate there has been a significant decrease in the usage of TZD since the concerns of potential increases in cardiac events from one of the drugs in this class. If a clinician believes that this finding (whether valid or not) is not a class effect but a unique concern with that single drug, then it would appear that metformin and TZD are the drugs of choice for type 2 diabetes mellitus as long a potential clinical contraindications are observed.

B. Limitations

1. General Limitations of Administrative Claims Data

There are a number of limitations when using administrative claims data to conduct retrospective, observational studies of comparative drug effectiveness and safety. Most of these are well known, and are not generally considered to be "fatal flaws", as long as they are addressed appropriately and with the best available research designs and analytic methods. (AHRQ 2008).

In this analysis, our reliance on administrative claims data could result in a number of biases. Subjects may be misclassified if their diagnoses (based on ICD-9 codes) were not accurate; estimates of drug exposure may be biased if prescriptions are not paid for by subjects' insurance plans, or if over the counter drugs such as aspirin or acetaminophen (each associated with some of the study outcomes) were widely used by subjects, as OTC drug use is not captured in the database. Censoring of data (i.e., having data for subjects for only limited, isolated periods of time; or "in and out" of coverage) may lead to biases if exposures, outcomes, or important covariate conditions occurred during periods for which subjects were not continuously eligible for such coverage. And importantly, many variables of interest in our analysis (including weight, BMI, family history of diabetes, duration of diabetes, smoking history, alcohol use, OTC medication use, herbal drug use, exercise, diet, and other factors which may impact the onset or course of Type 2 diabetes) are typically not captured in administrative claims data of this type. And while the dataset used for this analysis had laboratory test results available, these results are limited to those paid for by the subject's health plan, and thus may not reflect all such results, or those for which patients typically perform tests on themselves (e.g., blood glucose readings, which are the primary indicator of hypoglycemic events).

2. Specific Limitations of Methodologic Assumptions and Definitions

In addition to the known, general limitations of claims data and observational methods, a number of methodologic assumptions and definitions were made that could potentially affect the results of the study. First, the design is observational in nature, and thus is subject to confounding by indication, severity, and other potential sources of bias. It is known that prescribing choice (which translates to initial ODM therapy group assignment) is not random, and is probably related to a number of unmeasured or unknown characteristics. We used

propensity score models, multivariable adjustment, and stratification of results to address this problem, but such methods are not perfect and can only reduce confounding due to measured factors. Our propensity models are believed to be reasonable and robust for the purposes of our analysis, though other alternative methods could have been used (in addition to, or instead of, our chosen approach).

A number of definitions and assumptions may also have affected the results that were obtained in our study. First, we identified diabetic subjects according to a single occurrence of an ICD-9 code of 250.xx, which could result in high sensitivity but low specificity for this condition. We considered a "two-diagnosis" rule, but did not believe it to be necessary for the primary, comparative ODM aims of the study, as subjects with BOTH a diagnosis of diabetes AND use of an ODM are, in the opinion of our Research Team, very likely to in fact be Type 2 diabetics. Second, our use of the time from initial diabetes diagnosis to time of first ODM drug dispensing may not be an accurate proxy for the duration of a subject's diabetes. A subject's initial diagnosis may have come months or even years earlier, before the subject had records in the database; or, if the initial diagnosis, as we defined it, was inaccurate (e.g., reflective of screening for the condition rather than actual diagnosis of the condition), the time from diagnosis to ODM prescribing may also be inaccurate. Third, we studied incident users ("new users") of ODM in our analysis, and focused on patterns of initial ODM use, up until the time of first therapy/regimen change. While this is believed to be an appropriate group to study when comparing drugs on effectiveness or safety parameters, this group certainly does not reflect all users of ODM drugs (many may have been taking these drugs for some time, and been excluded from our analysis). As such, our results should not be generalized from incident to prevalent (or all) users of ODM medications. Fourth, the impact of our inclusion and exclusion criteria may result in a population that is different from those used in other studies, making cross-study comparisons difficult. Fifth, the impact of time window specification (pre/post continuous eligibility requirements) may have impacted our study findings, although our sensitivity analyses suggested that this impact is likely to be minimal. Sixth, we did not attempt to study ODM dose, or changes in dose, as a determinant of comparative effectiveness or safety. It is possible that higher dosages are associated with both higher effectiveness and higher rates of the safety-related outcomes. Last, many of our variable specifications (scales of measurement, use of indicators as opposed to scales in some cases, use of MPR as a proxy for compliance/consumption of medication, use of the CDI as a proxy for chronic disease burden, etc.) have unique limitations of their own, and these in turn may have affected our findings.

C. Comparisons of Present Findings With Existing Literature

The results of our study should be viewed in context with existing literature, regulatory actions, market developments, and changes in medical practice and patient care over time. We offer comments here, by study aim, to place our findings into a broader context.

As seen in the results from Aim 1 of our analysis, increased rates of prescribing were observed with metformin during the study period. This appears to directly correspond to decreases in SU and TZD utilization during the same time period. TZD use significantly decreased beginning in 2006 after reports linking TZDs with increased risk of congestive heart failure and in 2007 after publication of a meta-analysis by Lincoff et al. demonstrating a statistically significant increase in CAD events with rosiglitazone. (Lincoff et al. 2007) The increase in metformin use may have also been influenced to some extent by the publication of

treatment guidelines for management of type 2 diabetes recommending that metformin be used as first line therapy.

We observed a significant increase in the use of both GLP-1 mimetics (i.e., exenatide) and DPP-IV inhibitors (i.e., sitagliptin), as both agents were FDA approved during the study period. As one might expect, sitagliptin use exceeded that of exenatide in our study as sitaglipitin is approved for monotherapy while exenatide is approved only for use in combination with other oral hypoglycemic drugs.

We also observed that SU use was greater in patients over the age of 65, as compared to those less than 45 years. This finding was also observed by Karter et al in 2007 when evaluating glycemic response in over 15,000 patients newly started on diabetes therapies in the Northern California Kaiser system (Karter et al., 2007).

As seen in the results of Aim 2 of our analysis, clinically significant differences existed between mean baseline H-A1c values among those initially prescribed various ODM monotherapies and combination therapies. Patients initially prescribed combination therapies had H-A1c values 1-2% greater than those patients prescribed monotherapy. Patients initially prescribed SU monotherapy had an A1c value 0.6 to 1% higher than patients prescribed other monotherapies. This may be explained in part by the quick onset of action of SU compared to other monotherapies, and due to the fact that selection of SUs may be biased to those individuals presenting with more diabetes-related symptoms at the time of diagnosis. This finding is different than that observed by Karter et al., who observed a greater number of patients being prescribed non-SU therapies when presenting with worse glycemic control (H-A1C > 9%). This difference may be a result of the study design by Karter et al., who evaluated new therapies in patients with long-standing diabetes, many of which were on 1 or more oral diabetes medications at baseline, while our study was a new-user design.

Unadjusted reductions in H-A1C values of approximately 1% were observed in this study and are similar to what has been reported in the literature (Karter et al. 2007, Bolen et al., 2007) with metformin, TZD and SU therapies. Combination therapies reduced H-A1C values from 2.1 to 2.7% which is also consistent with published data from other effectiveness studies. GLP-1 Mimetic use reduced H-A1C values by 0.63% which is somewhat lower than what has been published in the literature (0.8-1.2%), but the mean baseline H-A1C in this group of our study was 7%, which may in part explain the small change in H-A1C that we observed. Interestingly, half of the patients who were initially prescribed meglitinides, TZDs or GLP-1 mimetics had less than 0.5% reduction, suggesting that a subset of patients prescribed these drugs do not respond to these medications as well as others. One possible explanation could be that patients with prolonged diabetes and decreased beta cell mass (decreased insulin production) may not receive as much benefit from these drugs because of significant reductions in endogenous insulin levels.

As seen in the results of Aim 3 of our analysis, hypoglycemia was more likely to be reported in patients with diabetes and on no drug therapy compared to the non-diabetic (CAD/Dyslipidemia) cohort. As previously reported in the literature, hypoglycemia has been more commonly associated with sulfonylurea and meglitinide therapy, as these drugs are responsible for stimulating insulin release from the beta-cells. Our findings suggest SU and meglitinides are associated with an approximate 3-fold increase in hypoglycemia compared to metformin alone, which is consistent with other reports. Combination therapy with SU also appears to increase the risk of hypoglycemia in an additive fashion, however, combination therapy with metformin + TZD does not increase the risk of hypoglycemia compared to either class alone. In terms of liver injury, patients with diabetes were at two times greater risk than

patients with CAD/dyslipidemia (without diabetes). This may due to increased rates of NASH in this diabetic population. Liver injury associated with SU use (alone or in combination with either TZD or metformin) was 1.5-2.0 times greater compared to meformin alone. Interestingly, there appears to be no increased risk of liver toxicity with TZD alone or in combination with metformin. This is of importance because periodic liver monitoring is still recommended with TZD therapy, but currently is not recommended with SU or meglitinide therapy. Further evaluation of SU and meglitinide related liver injury is warranted to confirm these findings.

D. Implications for Patient Care

The findings of our study suggest there are no substantial, clinically significant differences in the adjusted effectiveness of any of the common ODM monotherapies. Furthermore, the adjusted differences in initial monotherapy versus combination therapy are minimal and suggest there is little reason to consider starting a patient on combination therapy. After adjusting for multiple covariates, mean H-A1C reductions across all monotherapy and combination therapy groups were similar (range -1.36 to -1.71), suggesting similar real-world effectiveness. Baseline H-A1C values were a strong predictor of effectiveness as H-A1C was reduced an additional 0.76% for each additional 1% increase in baseline H-A1C. Our findings also suggest that the longer the period between diagnosis and beginning ODM therapy the less effectiveness is observed with such therapy. This may have implications in the future as earlier and more aggressive therapy may have long term benefits such as beta-cell preservation. Patients who received diabetes-specific education had a significantly greater reduction in H-A1C values with an additional 0.07% drop with each additional visit, so on average, those individuals who had 5 diabetes education visits had an additional 0.35% reduction in H-A1C values. Taken together, these findings suggest that unadjusted reductions in H-A1C values are similar to that reported in the literature, but when evaluating multiple covariates there is little difference in H-A1C reduction between ODM monotherapy and combination therapy groups. Because of the potential for increased risk of adverse drug events with combination therapy, it may be wise to start patients with single drug therapies and then progress to combination therapy as needed, in patients with new onset type 2 diabetes.

But while all monotherapies appear essentially equally effective, sulfonylureas (SU) appear to have several characteristics that would indicate they may not be ideal initial therapy. For instance, SU do not appear to maintain glycemic control as well as all other monotherapies. SU are associated with higher risk of hypoglycemic events and liver injury events. Contrary to FDA guidelines, which recommend liver monitoring for TZD, this class of drugs does not appear to be associated with increases in liver injury or liver failure. Interestingly, neither are statins, for which liver monitoring are also recommended, while SU do not have such a recommendation. Even in combination with other ODM therapies, biguanides and TZD do not appear to increase the risk of hypoglycemia or liver injury events. Usage trends indicate there has been a significant decrease in the usage of TZD since the concerns of potential increases in cardiac events from one of the drugs in this class. If a clinician believes that this finding (whether valid or not) is not a class effect but a unique concern with that single drug, then it would appear that metformin and TZD are the drugs of choice for type 2 diabetes mellitus as long a potential clinical contraindications are observed.

E. Implications for Further Research

The implications of our findings for further research are many. Replication of our findings in other databases would be extremely useful, to determine the impact of different study populations, data sources, etc., on the observed findings. Testing of other design, methodologic, definitional, measurement, and statistical analysis choices would also be useful in the same regard.

Further refinement of our measures and methods using DARTNet could also yield more reliable, valid, and precise estimates of safety outcomes. For example, in our study, hypoglycemia detection was not very sensitive (i.e., it was only identified via diagnoses or lab test results; and we had no access to charts or POC/patient-generated clinical data), though it was probably reasonably specific. Our detection of liver injury and failure events was probably just the opposite—reasonably sensitive, but not very specific, based on previous literature on the topic. We would need chart data and or POC data collection to validate cases, particularly for the more severe outcome of liver failure. These are examples of how DARTNet could be used to improve upon current, state-of-the-art observational studies using observational data and cohort designs (AHRQ 2008).

Finally, as noted in AHRQ Effective Health Care Report, Number 8: Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes, a large number of remaining issues exist with respect to our understanding of these medications, and could be studied using DARTNet. Our knowledge of the comparative effectiveness and safety of ODM on proximal clinical outcomes, distal diabetes-related complications, quality of life, adverse effects, and differences across specific clinical and demographic populations is still limited, and literally dozens of studies could be proposed and conducted with the combination of available claims data and DARTNet. Examples include, but are not limited to the following:

1. Evaluation of ODM monotherapy drug effects on macrovascular (CVD events) and microvascular disease in newly diagnosed patients with type 2 diabetes over a 5-10 year period.
2. Determination of the impact of variables such as hypoglycemia (SMBG records), BMI and blood pressure on effectiveness and safety of oral diabetes medications.
3. Continued evaluation of prescribing trends, effectiveness and safety of new agents such as GLP-1 mimetics (exenatide) and DPP-IV inhibitors (sitagliptin), especially in regards to increased pancreatitis reports by the FDA with exenatide.
4. Evaluation of TZD therapy on safety issues such as CVD and bone fractures.
5. Further evaluation of combination therapy, including insulin regimens used with oral diabetes medications on effectiveness and safety such as minor and severe hypoglycemic events and weight gain.
6. Evaluation of effectiveness and safety of combinations such as DPP-4 or GLP-1 drugs used in combination with oral diabetes therapies or with basal and/or basal/bolus insulin regimens.

VII. Phase II: DARTNet Replication

A. Summary of Results of Phase 1

The findings of Phase 1 of our analysis suggest that there are no substantial, clinically significant differences in the adjusted effectiveness of any of the common ODM monotherapies. Furthermore, the adjusted differences in initial monotherapy versus combination therapy are minimal and, suggest there is little reason to consider starting patients on combination therapy regimens. But while all monotherapies appear to be equally effective, sulfonylureas (SU) appear to have several characteristics that would indicate they may not be ideal initial therapy. The findings of our safety analyses suggest that SU may put patients at increased risk of hypoglycemia and liver injury, when compared to other ODM agents used as initial therapy for type 2 diabetes.

The limitations of our study, some inherent to claims data in general and to the data source that was used in this particular study, and some due to the methods and measures that were employed in the analyses, could potentially be overcome to some extent (and in some cases, perhaps to a large extent or entirely) through the use of DARTNet and its relatively large sample (panel) size, access EHR data, and potential for POC data collection, provider surveys, and/or gathering of patient-generated clinical data.

B. Confirmation/Verification of Phase 1 Results

Our primary objective in Phase 2 was to run confirmatory analyses of selected, illustrative aims from Phase 1, using data available from the DARTNet system and subject panel. The same criteria for subject identification, inclusion/exclusion, cohort membership, measurement, and analysis were be used, and the results from Phase 2 (presented in Tables B-24 through B-27, and described below) were compared with those from Phase 1 to determine the extent to which DARTNet can be used to replicate and improve upon the findings of large, database oriented, observational studies of comparative drug effectiveness and safety to yield more informative answers to important clinical and policy questions. Our confirmatory analyses focused on replicating the following specific analytic areas: subject demographics and clinical characteristics; patterns of ODM use (and time to first regimen change); crude effectiveness analyses (HA1C at baseline and reductions from baseline to lowest and baseline to last); and crude safety analyses (rates of hypoglycemia, liver injury, and liver failure), all performed initially without multivariate or propensity adjustment. Subsequent work will refine these results further using those more complex methods.

Table B-24 describes demographic and clinical characteristics of the DARTNet Diabetes Replication Cohort (i.e., an equivalent cohort of subjects to those used in the Phase 1, claims-based analyses, but coming in this case from DARTNet EHR-enabled practices; inclusion/exclusion criteria, variable definitions, and analysis specifications were applied similarly to provide a consistent approach and enable comparisons of subjects identified from the two data sources). As displayed in Table B-24, a large panel of subjects (N=35,215) meeting study criteria was identified, and these subjects have similar age and gender distributions, CDI scores, and patterns of initial ODM prescribing (e.g., approximately 80% of those receiving an ODM were initiated on a monotherapy regimen). Two notable differences are that a larger

fraction of subjects in the DARTNet Replication Cohort (77.7%) received ODM during the study period (versus 53.06% of subjects in the claims dataset); and that subjects in the DARTNet Replication Cohort had a longer median time from diagnosis to first ODM prescription (though this may be due to the fact that data are available for DARTNet subjects for much greater time spans of continuous "eligibility" or followup). Notably, even in its "proof of concept" stages, the DARTNet system was able to identify similarly sized panels of diabetic subjects, and subjects receiving various ODM drugs/groups, to enable analyses of similar power to the claims based studies performed in Phase 1.

Table B-25 displays the time to first regimen change for monotherapy and combination therapy groups in the DARTNet Diabetes Replication Cohort. Of note, for this particular analysis, prescribing information from subjects' electronic health records was used to identify ODM regimens and changes (on specific dates), without the presence of the pharmacy (prescription fulfillment) data that was used in the claims-based analyses in Phase 1. Thus, the results were expected to be somewhat different on that basis alone. In general, though, the results in Table B-25 are similar to those that were seen in Table B-7 with respect to which drugs were most frequently used, and in terms of mean time to regimen change. Median time to regimen change was shorter in the DARTNet Diabetes Replication Cohort, most likely owing to the fact that a different data source (EHR data) was used, and this likely reflected intended therapeutic changes more quickly than did the pharmacy claims (i.e., due to zero lag between the change in the medical record vs. a subsequent pharmacy claim reflecting the change). When pharmacy (prescription fulfillment) data are available in DARTNet (currently being pilot tested), replication of the Phase 1 results in this area will be undertaken and the results will be more directly comparable. Importantly, when the DARTNet EHR data and the pharmacy (prescription fulfillment) data are both available, additional analyses comparing what the prescriber wrote (intended) versus what was actually dispensed (carried out) will also be possible. Traditionally, only one of the two (an "either/or" situation) was possible.

Table B-26 presents the results of replication of crude effectiveness outcomes from Phase 1, now using the DARTNet Diabetes Replication Cohort. Baseline HA1C values, change from baseline to lowest HA1C, and change from baseline to last HA1C are presented. Sufficient laboratory result information (two HA1C values, within specific time windows) was available for 9,229 (~26%) of the DARTNet subjects to enable this analysis, a similar proportion as was found using the claims data in Phase 1. Baseline HA1C values were very similar in the DARTNet Diabetes Replication Cohort as in the claims cohort, as were crude changes in HA1C from baseline to lowest and baseline to last. Slightly smaller reductions were observed in the crude DARTNet results, but the patterns were similar (e.g., greater reduction from baseline to lowest than from baseline to last; substantial variation in reduction; and slightly greater reduction for combination regimens versus monotherapy regimens). With additional clinical variables and multivariable (adjusted) analyses, the models from the Phase 1 will be refined further in subsequent work.

Lastly, Table B-27 presents the results of replication of crude safety outcomes from Phase 1, now using the DARTNet Diabetes Replication Cohort. Rates of hypoglycemia, liver injury, and liver failure—using specific laboratory test result ranges and/or ICD-9 diagnosis codes—were determined from subjects' electronic health records. In this analysis, 27,158 (77%) of the subjects in the replication cohort met criteria for inclusion; this fraction is similar to the proportion observed in the claims based studies in Phase 1. As was the case in Phase 1, rates of hypoglycemia (0.000 – 0.0625 events per person year of exposure to ODM); liver injury (0.0115

– 0.0363 events per person year of exposure to ODM); and liver failure (0.000 – 0.0091 events per person year of exposure to ODM) were rare, and did not differ substantially across major ODM drugs or classes. Some slight differences in crude rates of these outcomes was noted, but as these are crude (unadjusted) rates, no firm or definitive conclusions can or should be drawn at this time regarding the comparative safety outcomes in the Phase 2 replication cohort. A few findings do bear mentioning, however: total numbers of events (event counts) are high enough in the replication cohort (numbering in the hundreds) to suggest that subsequent safety studies are indeed possible in the DARTNet system; liver injury and liver failure events could be further explored in greater detail in the DARTNet system, to enable case/outcome validation for these severe outcomes; and hypoglycemic events appear to be very low, as was observed using the claims data in Phase 1, suggesting that point of care and/or patient-reported sources of clinical data are likely needed to better study the hypoglycemia outcome in future studies.

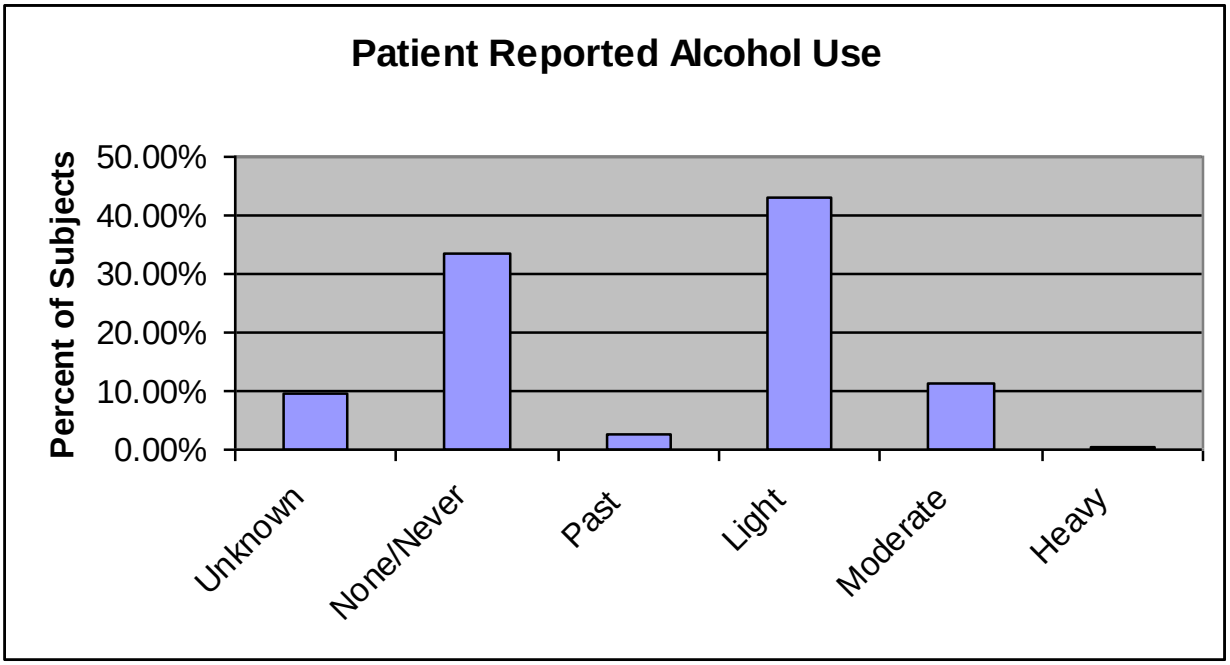
Each of the four "replication tables" (Tables B-24 through B-27) illustrate that the DARTNet system has sufficient sample size and clinical data field availability to relatively easily replicate typical claims-based comparative effectiveness and safety studies, and that further studies using additional EHR-derived data elements are likely to yield more detailed answers and more accurate estimates of the likelihood of clinical benefits and harms of ODM in the future.

C. Identification of Additional Data Elements

Our second objective in Phase 2 was to identify key additional data elements that are available in the electronic health records of DARTNet diabetic subjects, for inclusion in revised multivariable models for balancing treatment groups (i.e., propensity analysis) and for testing comparative effectiveness and safety of oral diabetes medications in subsequent work. Such data elements include: weight, BMI, family history of diabetes, duration of diabetes, smoking history, alcohol use, OTC medication use, herbal drug use, exercise, and diet. The list of data elements extracted from the DARTNet EHR data systems is currently being revised, with the review and approval of the DARTNet Board of Directors and AHRQ.

To illustrate one of the additional data elements obtained from the DARTNet EHR data extraction—patient reported alcohol use—the following bar chart (Chart B-1) displays the distribution of results for the 35,215 subjects in the replication cohort:

Chart B-1. Patient reported alcohol use



Interestingly and importantly, over 90% of subjects had actual (i.e., non-missing) data in their electronic health record indicating their self-reported level of alcohol use. Further, it appears that there is enough variation in self-reported alcohol use to enable possible use of this measure as a covariate in comparative safety analyses/models. Inclusion of the alcohol use variable, in addition to the other additional data elements that DARTNet provides when compared to traditional claims data sources, will most certainly provide opportunities to advance the science of observational comparative effectiveness and safety (OCER) research in meaningful ways—both methodologically and clinically.

In conclusion to Phase 2, we believe that the "proof of concept" work has been completed at a level meeting and exceeding our expectations, and that DARTNet is well equipped to conduct next-generation OCER research in the coming years.

VIII. List of Tables and Figures

A. Appendix B Tables

B. Appendix B Figures

IX. References

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X. Appendix B-A: List of Covariates Included in Propensity Score Models

Variable	Specifications
Age	Age (in years) at index diabetes diagnosis date
Gender	Gender
Diabetes duration	Time from Index Date to First Rx Date (in days)
Saw a diabetes nurse educator	Provider type = (610, 640, 641, 642) + ICD-9 code = 250.X
Diabetes-related physician visits	Place of service code = 11 + ICD-9 code = 250.X
Diabetes related hospitalization	Identified from admission diagnoses (either admit or discharge date during 90 days prior to index date; and either admission diagnosis or discharge diagnosis = 250.X)
Total cholesterol	LOINC: 14154-9, 2093-3, 48620-9, 5932-9, 9342-7
HDL	LOINC: 14646-4, 18263-4, 2085-9, 27340-9, 49130-8, 12771-2, 12772-0
LDL-C	LOINC: 35198-1, 39469-2, 49132-4, 12773-8, 13457-7, 14155-6, 18261-8, 18262-6, 2089-1, 22748-8
Triglycerides	LOINC: 3043-7, 14448-5, 12951-0, 14927-8, 2571-8, 28554-4
Creatinine	LOINC: 38483-4, 14682-9, 2160-0
AST	LOINC: 16325-3, 1916-6, 2325-9, 48136-6, 1920-8, 27344-1, 30239-8
ALT	LOINC: 16325-3, 1742-6, 1743-4, 1744-2, 1916-6, 48134-1
HbA1c	LOINC: 4548-4, 4549-2, 17855-8, 17856-6, 41995-2, 43150-2
Charlson Score	Used previously developed SAS macro
Antihypertensive meds	GPI: 33, 34, 36, 37
Lipid lowering meds	GPI: 39
Specific comorbidities or complications	
Hypertension	ICD-9: 401-405
Vision problems	ICD-9: 250.5, 369.X, 362.01-362.07
Myocardial infarction	ICD-9: 410
Mental disease	ICD-9: 290-314
Peripheral vascular disease	ICD-9: 443.89, 443.9, 250.7
Congestive heart failure	ICD-9: 428
Neuropathy	ICD-9: 250.6, 354.0-355.9, 337.1, 357.2
Ischemic heart disease	ICD-9: 414.8, 414.9
Renal disease	ICD-9: 583.X
Cerebral vascular disease	ICD-9: 437.X, 434.X
Cellulitis	ICD-9: 681, 682
Gangrene	ICD-9: 785.4
Amputation	ICD-9: 895-897 ; or CPT-4 : 27590-27596, 27880-27888, 28800 – 28825
Transient Ischemic attacks	ICD-9: 435.X
Liver disease	ICD-9: 573.2, 573.9
Hypoglycemia	ICD-9: 250.80, 251.2
Ketoacidosis	ICD-9: 250.12, 250.13; or LOINC: 2513-0, 32547-2, 33058-9, 38493-3, 53061-8, 11557-6, 20565-8, 34728-6, 19212-0, 19223-7, 2021-4, 2027-1, 48391-7, 2028-9
Diabetic coma	ICD-9: 250.32, 251.0
Other variables suggested by other researchers or the DARTNet Research Team	
Diagnosing MD specialty	Endocrinologist vs. PCP/other
Number of Comorbidities	CDI Score
Obesity (diagnosis)	ICD-9: 278.00, 278.01, 278.02
Eye Exam	CPT-4: 2022F
Diabetes Screening	ICD-9: V77.1
Diabetes Education	CPT-4/ICD-9: V65.3 and V65.40, 65.41 and 65.49
Region	ICHIS region variable

Total HC costs	Sum standard amount (AMT_STD) across all IP stays, medical claims and pharmacy claims
Endocrine visit	Place of service = 11 + ICD-9 = 250
Total number of drugs taken	Number of unique GPI-12 codes received
Prescription copay amount for initial ODM drug(s) received	Patient cost share amount on index diabetes Rx(s)

XI. Appendix B-B: List of Covariates Included in Comparative Effectiveness Models

Variable	Specifications
Age	Age (in years) at index diabetes diagnosis date
Gender	Gender
Persistence	Time to first change in initial ODM drug regimen
Compliance	MPR (medication posession ratio during persistence window)
Diabetes duration	Time from Index Date to First Rx Date (in days)
Hepatic dysfunction indicator	0=no, 1=yes
Renal dysfunction indiccator	0=no, 1=yes
Diabetes-related education visits	Provider type = (610, 640, 641, 642) + ICD-9 code = 250.X
Diabetes-related physician visits	Place of service code = 11 + ICD-9 code = 250.X
Total number of drugs taken	Number of unique GPI-12 codes received
Specific medications associated with risk of hypoglycemia	
Aspirin products (Rx)	GPI codes: 641000, 641099, 649910022203, 659900022203, 659910021003, 659917022003, 759900021003, 759900024003, 759900031003, 759900032003, 851599022069
ACE Inhibitors	GPI code: 361000
Angiotensin receptor blockers	GPI code: 361500
Antidepressants	GPI code: 58
Beta blockers	GPI codes: 331000 through 333000
Flouroquinolones	GPI code: 050000

XII. Appendix B-C: List of Covariates Included in Comparative Safety Models

Variable	Codes/Values
Outcomes	
1. Hypoglycemia	Diagnosis of Hypoglycemia (ICD-9: 251.0, 251.1, 251.2) **OR** Glucose < 70
2. Liver Toxicity (enzyme elevation to 3X ULN)	AST **OR** ALT ≥ 100
3. Liver Failure (diagnosis or lab result based)	Diagnosis of LF by **any** of the following ICD-9 **or** CPT-4 codes, **or** lab result combinations:
Acute hepatic failure/necrosis	ICD-9: 570
Hepatic encephalopathy/coma	ICD-9: 572.2
Toxic liver disease/hepatitis	ICD-9: 573.3
Liver transplant	ICD-9: E878.0, V42.7 **OR** CPT-4: 47135, 47136
According to Lab Test Results	AST OR ALT ≥ 100, **AND** INR ≥ 1.5, **AND** PATIENT NOT ON WARFARIN (GPI code: 832000)(during OHD Tx) **OR** AST OR ALT ≥ 100, **AND** PLT < 100K **OR** AST OR ALT ≥ 100 **AND** BILI ≥ 2.5 **OR** AST AND ALT > 350 (10X ULN)
	LOINC codes for above labs…
	GLUCOSE: 15074-8, 2339-0, 39481-7, 41651-1, 14743-9, 32016-8, 51596-5, 47995-6, 39480-9, 41652-9, 14749-6, 14768-6, 1547-9, 2345-7
	ALT: 1742-6, 1743-4, 1744-2, 48134-1
	AST: 2325-9, 48136-6, 1920-8, 27344-1, 30239-8
	INR: 34714-6, 38875-1, 46418-0, 6301-6, 27813-5, 3289-6
	PLT: 13056-7, 47284-5, 47288-6, 48705-8, 49497-1, 777-3, 778-1, 9317-9, 26515-7, 26516-5
	BILI: 14631-6, 1975-2, 34543-9, 42719-5, 47994-9, 48624-1
Exclusion Criteria (any in past year, *prior to* starting OHD therapy); these then become either **Covariates** or **Outcomes** [in brackets] *during* OHD therapy (on/after First Rx Fill Date)	
Thrombocytopenia	ICD-9: 287.3, 287.4, 287.5 **OR** PLT < 100,000 (as above)
Hepatitis B infection	ICD-9: 070.2, 070.3
Hepatitis E infection	ICD-9: 070.43, 070.53
Hepatitis C infection	ICD-9: 070.41, 070.44, 070.51, 070.54, 070.70,
HIV infection	ICD-9: 042, 079.53, V08, 795.71
CMV infection	ICD-9: 078.5
EBV infection	ICD-9: 075
Elevated Liver Enzymes	AST or ALT ≥ 100 (as above)
Elevated Bilirubin	BILI ≥ 2.5 (as above)

Abnormal Transferrin Saturation	Transferrin Saturation > 50% (LOINC codes for TrSat: 6796-7, 13452-8, 22674-6, 3034-6)
Jaundice	ICD-9: 782.4
Acute/subacute necrosis of liver	ICD-9: 570 **[outcome]**
Liver Infarction	ICD-9: 573.4
Hepatic Coma	ICD-9: 572.2 **[outcome]**
Hepatorenal syndrome	ICD-9: 572.4
Chronic liver disease, nonalcoholic	ICD-9: 571.8, 571.9
Cirrhosis of the Liver	ICD-9: 571.5
Hepatitis	*[Any of the following codes]*
Chronic Hepatitis	ICD-9: 571.40
Chronic Active Hepatitis	ICD-9: 571.49
Chronic Persistent Hepatitis	ICD-9: 571.41
Acute Alcoholic Hepatitis	ICD-9: 571.0
Viral Hepatitis	ICD-9: 070.59, 070.6, 070.9
Unspecified/cryptogenic Hepatitis	ICD-9: 571.5
Biliary tract problem	*[Any of the following codes]*
Obstruction/stricture	ICD-9: 575.2, 576.2
Stones	ICD-9: 574*, 575.10
Malignancy	ICD-9: 155.1, 156.1, 156.8, 156.9
Metastasis	ICD-9: 197.8
Primary or metastatic neoplasia of the liver and hepatic ducts	ICD-9: 153.0, 155.0, 155.2, 156.1
Hepatic encephalopathy	ICD-9: 572.2 **[outcome]**
Hereditary hemocromatosis	ICD-9: 275.0
Disorders of copper metabolism (Wilson's disease)	ICD-9: 275.1
Alpha-1 antitripsin deficiency	ICD-9: 273.4
Celiac disease	ICD-9: 579.0
Sclerosing cholangitis	ICD-9: 576.1
Primary biliary cirrhosis	ICD-9: 571.6
Liver helminth, fluke, parasite	ICD-9: 121*
Budd-Chiari syndrome	ICD-9: 453.0
Liver Transplant (prior)	ICD-9: E878.0, V42.7 **or** CPT-4: 47135, 47136 **[outcome]**
Covariates (measure these both *prior to*, and *during*, OHD use)(did not exclude on these)	
A. Diagnoses (increased risk of LI)	*According to ICD-9 codes:*
Hypercholesterolemia/dyslipidemia	ICD-9: 272*
Hyperglycemia (elevated glucose, without diagnosis of diabetes)	ICD-9: 790.2*
Albuminuria	ICD-9: 791.0
Heart Failure	ICD-9: 428*
Nonalcoholic Fatty Liver Disease	ICD-9: 571.8
Pancreatitis (acute or chronic)	ICD-9: 577.0, 577.1
B. Drugs (associated with DILI)	*According to GPI code(s):*
ACE INHIBITORS	361000
Acetaminophen (alone)	642000100001, 642000100003, 642000100004, 642000100005, 642000100009, 642000100010, 642000100018, 642000100020, 642000100052

APAP Combinations (Non-narcotic analgesics, cough/cold, etc.)	439910023003, 439910023020, 439920021003 439940, 439954, 439959, 439967035003, 439967035004, 439967035074, 439967038003, 439969037001, 439969037003, 439969037009, 439989032503, 439983042001, 439983042003, 439983042009, 649900021203, 649900030503, 649900031003, 649900031301, 649900031303, 649900032003, 649900042503, 649900044501, 649900046003, 649910021201, 649910021203, 649910023001, 649910023003, 649910023004, 649910031001, 649910031003, 649910031010, 649910031503, 649910035001
APAP Combinations (w/narcotics)	659900, 659910, 659913, 659917
Allopurinol	680000100003
Amiodarone	354000050003
Amoxicillin-Clavulanate	019900022003, 019900022005, 019900022019, 019900022074
ANABOLIC STEROIDS	231000, 232000
Azathioprine	994060
Bosentan	401600150003
Carbamazepine	594000150069, 726000200003, 726000200005, 726000200018, 726000200029, 726000200069 726000200074
Chlorpromazine	592000150052, 592000151002, 592000151003, 592000151012, 592000151013, 592000151020, 592000151029, 592000151038
Cyclophosphamide	211010200003, 211010200021
Cyclosporine	867200200016, 994020
Diltiazem	340000101003, 340000101020, 340000101069, 340000101070, 340000101170, 340000101270, 340000101275, 369915022675
Disulfiram	628020400003
Erythromycin	031000, 169900021019, 861010250042
Estrogen	240000, 249910, 249930
Ezetimibe	393000300003, 399940023003
Felbamate	721200
Fenofibrate	392000250003, 392000251001
Gemfibrozil	392000300001, 392000300003, 392000300029
Isoniazid	090000600003, 090000600012, 090000600029 099900021001, 099900032003
Ketoconazole	114040400003
Methimazole / Propylthiouracil	283000
Methotrexate	213000500003, 213000500029, 213000501003, 213000501020, 213000501021, 662500500003, 662500501003
Methyldopa	362010300003, 369950026003, 369950027003
Minocycline	040000401001, 040000401003, 040000401018, 040000401029, 040000401075
Nefazodone / Trazodone	581200
Niacin / Nicotinic Acid (Rx)	394500, 771030
Nitrofurantoin	530000500001, 530000500003, 530000500018, 530000501001, 530000501029, 530000501501
NRTIs	121050, 121060, 121080,121085
NSAIDs	661000
ORAL CONTRACEPTIVES	251000-259940 (any in this range)
Pemoline	614000300003, 614000300005
Phenobarbital (alone or in combo)	491099022501, 491099022503, 491099022504, 491099022510, 491099023403, 491099023420, 601000600003, 601000600010, 601000600029, 601000601020

Phenytoin	722000300005, 722000300018, 722000300520, 722000300529, 722000301001, 722000302001
Procainamide	351000201001, 351000201003, 351000201004, 351000201074
Pyrazinamide	090000700003, 099900032003
Quinidine	351000301004, 351000303003, 351000303004
Ranitidine	492000200503, 492000201001, 492000201003, 492000201008, 492000201012, 492000201020 492000201030, 492000201120
Rifampin	090000800001, 090000800021, 090000800029, 099900021001, 099900032003
SSRIs	581600
STATINS (HMGs)	394000-394099 (any in this range)
SULFONAMIDES	080000
Tacrine	620510501001
Tamoxifen	214026801003, 214026801020
TRICYCLIC ANTIDEPRESSANTS	582000
Terbinafine	110000801003
Tolcapone	731520
Trovafloxacin	050000751003
Valproic Acid	725000
Zafirlukast	445050800003
Zileuton	445040850003

XIII. Appendix B Tables

Table B-1. Demographic characteristics of the DARTNet diabetic cohort (N=98992)

	TOTAL		INDEX YEAR OF DIAGNOSIS 2002		2003		2004		2005		2006		2007		
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	Chi-square test for trend p-value
Total N	98992	(100.00)	100	(0.10)	11482	(11.60)	30988	(31.30)	28521	(28.81)	22235	(22.46)	5666	(5.72)	
Age															
1-24 yrs	1256	(1.27)	1	(1)	121	(1.05)	434	(1.4)	391	(1.37)	245	(1.1)	64	(1.13)	0.0049
25-34 yrs	4718	(4.77)	2	(2)	372	(3.24)	1508	(4.87)	1517	(5.32)	1102	(4.96)	217	(3.83)	< 0.0001
35-44 yrs	15197	(15.35)	13	(13)	1238	(10.78)	4929	(15.91)	4670	(16.37)	3588	(16.14)	759	(13.4)	< 0.0001
45-54 yrs	28820	(29.11)	23	(23)	2444	(21.29)	9884	(31.9)	8962	(31.42)	6909	(31.07)	1598	(28.2)	< 0.0001
55-64 yrs	31712	(32.03)	13	(13)	3002	(26.15)	10201	(32.92)	9251	(32.44)	7374	(33.16)	1871	(33.02)	< 0.0001
65-74 yrs	10582	(10.69)	27	(27)	2556	(22.26)	2716	(8.76)	2514	(8.81)	2045	(9.2)	724	(12.78)	< 0.0001
75-84 yrs	5707	(5.77)	21	(21)	1749	(15.23)	1316	(4.25)	1216	(4.26)	972	(4.37)	433	(7.64)	< 0.0001
Mean	53.63		60.04		58.68		52.77		52.65		53.07		55.21		
Median	54.00		63.00		59.00		53.00		53.00		54.00		55.00		
Range	(1-80)		(22-75)		(4-76)		(1-77)		(1-78)		(2-79)		(3-80)		
Gender															
Male	52485	(53.02)	57	(57)	6135	(53.43)	16536	(53.36)	15166	(53.17)	11664	(52.46)	2927	(51.66)	
Region															
East North Central	5760	(5.82)	0	(0)	7	(0.06)	2178	(7.03)	1992	(6.98)	1369	(6.16)	214	(3.78)	< 0.0001
East South Central	2756	(2.78)	0	(0)	3	(0.03)	1108	(3.58)	993	(3.48)	557	(2.51)	95	(1.68)	< 0.0001
Middle Atlantic	40574	(40.99)	97	(97)	10878	(94.74)	10228	(33.01)	9891	(34.68)	7315	(32.9)	2165	(38.21)	< 0.0001
Mountain	2174	(2.2)	0	(0)	8	(0.07)	791	(2.55)	640	(2.24)	540	(2.43)	195	(3.44)	< 0.0001
New England	1392	(1.41)	0	(0)	32	(0.28)	447	(1.44)	506	(1.77)	349	(1.57)	58	(1.02)	< 0.0001
Other*	18	(0.02)	0	(0)	8	(0.07)	7	(0.02)	1	(0)	2	(0.01)	0	(0)	0.0004
Pacific	886	(0.9)	0	(0)	11	(0.1)	293	(0.95)	261	(0.92)	269	(1.21)	52	(0.92)	< 0.0001
South Atlantic	31486	(31.81)	1	(1)	353	(3.07)	10975	(35.42)	9848	(34.53)	8234	(37.03)	2075	(36.62)	< 0.0001
West North Central	3717	(3.75)	0	(0)	2	(0.02)	1503	(4.85)	1202	(4.21)	840	(3.78)	170	(3)	< 0.0001
West South Central	10229	(10.33)	2	(2)	180	(1.57)	3458	(11.16)	3187	(11.17)	2760	(12.41)	642	(11.33)	< 0.0001
Diagnosing Provider Type															
Endocrinologist	3219	(3.25)	4	(4)	490	(4.27)	998	(3.22)	867	(3.04)	691	(3.11)	169	(2.98)	< 0.0001
PCP	61013	(61.63)	62	(62)	8101	(70.55)	19127	(61.72)	17129	(60.06)	13297	(59.8)	3297	(58.19)	< 0.0001
Other (known)	8373	(8.46)	14	(14)	1521	(13.25)	2539	(8.19)	2224	(7.8)	1636	(7.36)	439	(7.75)	< 0.0001
Unknown	26387	(26.66)	20	(20)	1370	(11.93)	8324	(26.86)	8301	(29.1)	6611	(29.73)	1761	(31.08)	< 0.0001
Chronic Disease Indicator															
Mean	4.07		4.05		4.38		4.23		4.01		3.82		3.73		< 0.0001
Median	4.00		4.00		4.00		4.00		4.00		3.00		3.00		
Range	(0-21)		(0-13)		(0-21)		(0-21)		(0-19)		(0-20)		(0-16)		
Charlson Index															
Mean	0.27		0.48		0.48		0.30		0.24		0.18		0.15		< 0.0001
Median	0.00		1.00		1.00		1.00		1.00		1.00		0.00		
Range	(0-8)		(0-5)		(0-8)		(0-7)		(0-7)		(0-6)		(0-6)		
Initial Drug Dispensed Following Diagnosis															
No diabetes drugs ever dispensed	46464	(46.94)	34	(34)	4407	(38.38)	12235	(39.48)	13472	(47.24)	12392	(55.73)	3924	(69.26)	< 0.0001
Insulin (alone or with oral(s))	4051	(4.09)	14	(14)	573	(4.99)	1660	(5.36)	1079	(3.78)	636	(2.86)	89	(1.57)	< 0.0001
Oral hypoglycemic drug prescribed	48477	(48.97)	52	(52)	6502	(56.63)	17093	(55.16)	13970	(48.98)	9207	(41.41)	1653	(29.17)	< 0.0001
Monotherapy	38636	(39.03)	43	(43)	5323	(46.36)	13312	(42.96)	11257	(39.47)	7374	(33.16)	1327	(23.42)	< 0.0001
Combotherapy	9841	(9.94)	9	(9)	1179	(10.27)	3781	(12.2)	2713	(9.51)	1833	(8.24)	326	(5.75)	< 0.0001
Fixed-dose combo	6320	(6.38)	4	(4)	684	(5.96)	2527	(8.15)	1637	(5.74)	1225	(5.51)	243	(4.29)	< 0.0001

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-2. Top 10 concurrent and past diagnoses for DARTNet Diabetic Cohort (2002-2007 combined)

Table B-2a. Top 10 concurrent diagnoses for DARTNet Diabetic Cohort (2002-2007 combined)

ICD-9 code	Description	N	%
272	Disorders of lipoid metabolism	45924	46.39
401	Essential hypertension	43844	44.29
780	General symptoms	15410	15.57
790	Nonspecific findings on examination of blood	15131	15.29
786	Symptoms involving respiratory system and other chest symptoms	14356	14.50
414	Other forms of chronic ischemic heart disease	7450	7.53
244	Acquired hypothyroidism	7343	7.42
719	Other and unspecified disorder of joint	6402	6.47
724	Other and unspecified disorders of back	6267	6.33
789	Other symptoms involving abdomen and pelvis	6081	6.14

*Total N = 98992

Table B-2b. Top 10 past diagnoses for DARTNet Diabetic Cohort (2002-2007 combined)

ICD-9 code	Description	N	%
401	Essential hypertension	35758	36.12
272	Disorders of lipoid metabolism	34579	34.93
786	Symptoms involving respiratory system and other chest symptoms	22215	22.44
780	General symptoms	18893	19.09
719	Other and unspecified disorder of joint	13191	13.33
790	Nonspecific findings on examination of blood	12584	12.71
724	Other and unspecified disorders of back	12269	12.39
789	Other symptoms involving abdomen and pelvis	12102	12.23
729	Other disorders of soft tissues	10354	10.46
414	Other forms of chronic ischemic heart disease	9288	9.38

*Total N = 98992

Table B-3a. Initial monotherapies for the DARTNet Diabetic Cohort members who received a single oral diabetes medication (N=38636), by year

	Total		Year of prescription 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	38636	(100.00)	7	(0.02)	2698	(6.98)	8955	(23.18)	11545	(29.88)	10982	(28.42)	4449	(11.52)	
Sulfonylureas (SU)	7987	(20.67)	3	(42.86)	894	(33.14)	2201	(24.58)	2358	(20.42)	1967	(17.91)	564	(12.68)	< 0.0001
Chlorpropamide*	10	(0.03)	0	(0)	4	(0.15)	2	(0.02)	3	(0.03)	0	(0)	1	(0.02)	0.0024
Acetohexamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Tolbutamide*	2	(0.01)	0	(0)	1	(0.04)	0	(0)	0	(0)	1	(0.01)	0	(0)	0.2267
Tolazamide*	1	(0)	0	(0)	0	(0)	0	(0)	1	(0.01)	0	(0)	0	(0)	0.7994
Glyburide	1755	(4.54)	1	(14.29)	242	(8.97)	434	(4.85)	549	(4.76)	400	(3.64)	129	(2.9)	< 0.0001
Micronized glyburide	92	(0.24)	0	(0)	12	(0.44)	34	(0.38)	20	(0.17)	22	(0.2)	4	(0.09)	0.0017
Glipizide	984	(2.55)	0	(0)	112	(4.15)	252	(2.81)	290	(2.51)	259	(2.36)	71	(1.6)	< 0.0001
Glipizide Ext Rel	2925	(7.57)	2	(28.57)	308	(11.42)	879	(9.82)	854	(7.4)	709	(6.46)	173	(3.89)	< 0.0001
Glimepiride	2221	(5.75)	0	(0)	216	(8.01)	601	(6.71)	642	(5.56)	576	(5.24)	186	(4.18)	< 0.0001
Meglitinides	533	(1.38)	0	(0)	78	(2.89)	138	(1.54)	161	(1.39)	111	(1.01)	45	(1.01)	< 0.0001
Repaglinide	235	(0.61)	0	(0)	33	(1.22)	62	(0.69)	68	(0.59)	49	(0.45)	23	(0.52)	0.0003
Nateglinide	298	(0.77)	0	(0)	45	(1.67)	76	(0.85)	93	(0.81)	62	(0.56)	22	(0.49)	< 0.0001
Alpha-glucosidase inhibitors	71	(0.18)	0	(0)	3	(0.11)	24	(0.27)	20	(0.17)	17	(0.15)	7	(0.16)	0.4167
Acarbose	46	(0.12)	0	(0)	1	(0.04)	15	(0.17)	12	(0.1)	12	(0.11)	6	(0.13)	0.5926
Miglitol	25	(0.06)	0	(0)	2	(0.07)	9	(0.1)	8	(0.07)	5	(0.05)	1	(0.02)	0.5926
Biguanides	23427	(60.64)	4	(57.14)	1339	(49.63)	5101	(56.96)	7003	(60.66)	7003	(63.77)	2977	(66.91)	< 0.0001
Metformin, IR or XR	23427	(60.64)	4	(57.14)	1339	(49.63)	5101	(56.96)	7003	(60.66)	7003	(63.77)	2977	(66.91)	< 0.0001
Thiazolidinediones	6019	(15.58)	0	(0)	384	(14.23)	1491	(16.65)	1966	(17.03)	1658	(15.1)	520	(11.69)	< 0.0001
Troglitazone	0		0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Rosiglitazone	2529	(6.55)	0	(0)	227	(8.41)	708	(7.91)	760	(6.58)	629	(5.73)	205	(4.61)	< 0.0001
Pioglitazone	3490	(9.03)	0	(0)	157	(5.82)	783	(8.74)	1206	(10.45)	1029	(9.37)	315	(7.08)	< 0.0001
GLP-1 Mimetic	310	(0.8)	0	(0)	0	(0)	0	(0)	36	(0.31)	183	(1.67)	91	(2.05)	< 0.0001
Exenatide	310	(0.8)	0	(0)	0	(0)	0	(0)	36	(0.31)	183	(1.67)	91	(2.05)	< 0.0001
DPP-IV Inhibitor	279	(0.72)	0	(0)	0	(0)	0	(0)	0	(0)	40	(0.36)	239	(5.37)	< 0.0001
Sitagliptin	279	(0.72)	0	(0)	0	(0)	0	(0)	0	(0)	40	(0.36)	239	(5.37)	< 0.0001
*Amylin Analogue**	10	(0.03)	0	(0)	0	(0)	0	(0)	1	(0.01)	3	(0.03)	6	(0.13)	< 0.0002
Pramlintide*	10	(0.03)	0	(0)	0	(0)	0	(0)	1	(0.01)	3	(0.03)	6	(0.13)	< 0.0002

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-3b. Initial monotherapies for men in the DARTNet Diabetic Cohort who received a single oral diabetes medication (N=20506), by year

	Total		Year of prescription 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	20506	(100.00)	5	(0.02)	1488	(7.26)	4745	(23.14)	6226	(30.36)	5771	(28.14)	2271	(11.07)	
Sulfonylureas (SU)	4625	(22.55)	2	(40)	527	(35.42)	1262	(26.6)	1395	(22.41)	1132	(19.62)	307	(13.52)	< 0.0001
Chlorpropamide*	6	(0.03)	0	(0)	2	(0.13)	2	(0.04)	2	(0.03)	0	(0)	0	(0)	0.1421
Acetohexamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Tolbutamide*	1	(0)	0	(0)	1	(0.07)	0	(0)	0	(0)	0	(0)	0	(0)	0.0255
Tolazamide*	1	(0)	0	(0)	0	(0)	0	(0)	1	(0.02)	0	(0)	0	(0)	0.8072
Glyburide	981	(4.78)	0	(0)	140	(9.41)	237	(4.99)	319	(5.12)	219	(3.79)	66	(2.91)	<0.0001
Micronized glyburide	58	(0.28)	0	(0)	9	(0.6)	21	(0.44)	13	(0.21)	12	(0.21)	3	(0.13)	0.0158
Glipizide	582	(2.84)	0	(0)	70	(4.7)	152	(3.2)	168	(2.7)	150	(2.6)	42	(1.85)	<0.0001
Glipizide Ext Rel	1701	(8.3)	2	(40)	179	(12.03)	500	(10.54)	513	(8.24)	409	(7.09)	98	(4.32)	<0.0001
Glimepiride	1298	(6.33)	0	(0)	127	(8.53)	351	(7.4)	380	(6.1)	342	(5.93)	98	(4.32)	<0.0001
Meglitinides	284	(1.38)	0	(0)	38	(2.55)	78	(1.64)	87	(1.4)	52	(0.9)	29	(1.28)	<0.0001
Repaglinide	128	(0.62)	0	(0)	18	(1.21)	35	(0.74)	39	(0.63)	22	(0.38)	14	(0.62)	<0.0116
Nateglinide	156	(0.76)	0	(0)	20	(1.34)	43	(0.91)	48	(0.77)	30	(0.52)	15	(0.66)	<0.0251
*Alpha-glucosidase inhibitors**	33	(0.16)	0	(0)	0	(0)	9	(0.19)	13	(0.21)	6	(0.1)	5	(0.22)	0.392
Acarbose*	22	(0.11)	0	(0)	0	(0)	6	(0.13)	9	(0.14)	3	(0.05)	4	(0.18)	0.3891
Miglitol*	11	(0.05)	0	(0)	0	(0)	3	(0.06)	4	(0.06)	3	(0.05)	1	(0.04)	0.958
Biguanides	11749	(57.3)	3	(60)	705	(47.38)	2520	(53.11)	3535	(56.78)	3521	(61.01)	1465	(64.51)	<0.0001
Metformin, IR or XR	11749	(57.3)	3	(60)	705	(47.38)	2520	(53.11)	3535	(56.78)	3521	(61.01)	1465	(64.51)	<0.0001
Thiazolidinediones	3541	(17.27)	0	(0)	218	(14.65)	876	(18.46)	1181	(18.97)	967	(16.76)	299	(13.17)	<0.0001
Troglitazone	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Rosiglitazone	1482	(7.23)	0	(0)	135	(9.07)	426	(8.98)	457	(7.34)	357	(6.19)	107	(4.71)	<0.0001
Pioglitazone	2059	(10.04)	0	(0)	83	(5.58)	450	(9.48)	724	(11.63)	610	(10.57)	192	(8.45)	<0.0001
GLP-1 Mimetic	118	(0.58)	0	(0)	0	(0)	0	(0)	14	(0.22)	68	(1.18)	36	(1.59)	<0.0001
Exenatide	118	(0.58)	0	(0)	0	(0)	0	(0)	14	(0.22)	68	(1.18)	36	(1.59)	<0.0001
DPP-IV Inhibitor	149	(0.73)	0	(0)	0	(0)	0	(0)	0	(0)	22	(0.38)	127	(5.59)	<0.0001
Sitagliptin	149	(0.73)	0	(0)	0	(0)	0	(0)	0	(0)	22	(0.38)	127	(5.59)	<0.0001
*Amylin Analogue**	7	(0.03)	0	(0)	0	(0)	0	(0)	1	(0.02)	3	(0.05)	3	(0.13)	0.0857
Pramlintide*	7	(0.03)	0	(0)	0	(0)	0	(0)	1	(0.02)	3	(0.05)	3	(0.13)	0.0857

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-3c. Initial monotherapies for women in the DARTNet Diabetic Cohort who received a single oral diabetes medication (N=18130), by year

	Total		Year of prescription 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	18130	(100.00)	2	(0.01)	1210	(6.67)	4210	(23.22)	5319	(29.34)	5211	(28.74)	2178	(12.01)	
Sulfonylureas (SU)	3362	(18.54)	1	(50)	367	(30.33)	939	(22.3)	963	(18.1)	835	(16.02)	257	(11.8)	<0.0001
Chlorpropamide*	4	(0.02)	0	(0)	2	(0.17)	0	(0)	1	(0.02)	0	(0)	1	(0.05)	0.0161
Acetohexamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Tolbutamide*	1	(0.01)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.02)	0	(0)	0.7796
Tolazamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Glyburide	774	(4.27)	1	(50)	102	(8.43)	197	(4.68)	230	(4.32)	181	(3.47)	63	(2.89)	<0.0001
Micronized glyburide	34	(0.19)	0	(0)	3	(0.25)	13	(0.31)	7	(0.13)	10	(0.19)	1	(0.05)	0.238
Glipizide	402	(2.22)	0	(0)	42	(3.47)	100	(2.38)	122	(2.29)	109	(2.09)	29	(1.33)	0.0033
Glipizide Ext Rel	1224	(6.75)	0	(0)	129	(10.66)	379	(9)	341	(6.41)	300	(5.76)	75	(3.44)	<0.0001
Glimepiride	923	(5.09)	0	(0)	89	(7.36)	250	(5.94)	262	(4.93)	234	(4.49)	88	(4.04)	<0.0001
Meglitinides	249	(1.37)	0	(0)	40	(3.31)	60	(1.43)	74	(1.39)	59	(1.13)	16	(0.73)	<0.0001
Repaglinide	107	(0.59)	0	(0)	15	(1.24)	27	(0.64)	29	(0.55)	27	(0.52)	9	(0.41)	0.0575
Nateglinide	142	(0.78)	0	(0)	25	(2.07)	33	(0.78)	45	(0.85)	32	(0.61)	7	(0.32)	<0.0001
*Alpha-glucosidase inhibitors**	38	(0.21)	0	(0)	3	(0.25)	15	(0.36)	7	(0.13)	11	(0.21)	2	(0.09)	0.1917
Acarbose*	24	(0.13)	0	(0)	1	(0.08)	9	(0.21)	3	(0.06)	9	(0.17)	2	(0.09)	0.3499
Miglitol*	14	(0.08)	0	(0)	2	(0.17)	6	(0.14)	4	(0.08)	2	(0.04)	0	(0)	0.2827
Biguanides	11678	(64.41)	1	(50)	634	(52.4)	2581	(61.31)	3468	(65.2)	3482	(66.82)	1512	(69.42)	<0.0001
Metformin, IR or XR	11678	(64.41)	1	(50)	634	(52.4)	2581	(61.31)	3468	(65.2)	3482	(66.82)	1512	(69.42)	<0.0001
Thiazolidinediones	2478	(13.67)	0	(0)	166	(13.72)	615	(14.61)	785	(14.76)	691	(13.26)	221	(10.15)	<0.0001
Troglitazone	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Rosiglitazone	1047	(5.77)	0	(0)	92	(7.6)	282	(6.7)	303	(5.7)	272	(5.22)	98	(4.5)	0.0003
Pioglitazone	1431	(7.89)	0	(0)	74	(6.12)	333	(7.91)	482	(9.06)	419	(8.04)	123	(5.65)	<0.0001
GLP-1 Mimetic	192	(1.06)	0	(0)	0	(0)	0	(0)	22	(0.41)	115	(2.21)	55	(2.53)	<0.0001
Exenatide	192	(1.06)	0	(0)	0	(0)	0	(0)	22	(0.41)	115	(2.21)	55	(2.53)	<0.0001
DPP-IV Inhibitor	130	(0.72)	0	(0)	0	(0)	0	(0)	0	(0)	18	(0.35)	112	(5.14)	<0.0001
Sitagliptin	130	(0.72)	0	(0)	0	(0)	0	(0)	0	(0)	18	(0.35)	112	(5.14)	<0.0001
*Amylin Analogue**	3	(0.02)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	3	(0.14)	0.0005
Pramlintide*	3	(0.02)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	3	(0.14)	0.0005

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-3d. Initial monotherapies for subjects age < 45 years in the DARTNet Diabetic Cohort who received a single oral diabetes medication (N=8371), by year

	Total		Year of prescription 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	8371	(100.00)	2	(0.02)	486	(5.81)	2018	(24.11)	2703	(32.29)	2330	(27.83)	832	(9.94)	
Sulfonylureas (SU)	1467	(17.52)	1	(50)	133	(27.37)	426	(21.11)	487	(18.02)	341	(14.64)	79	(9.5)	<0.0001
Chlorpropamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Acetohexamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Tolbutamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Tolazamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Glyburide	294	(3.51)	0	(0)	27	(5.56)	70	(3.47)	106	(3.92)	71	(3.05)	20	(2.4)	0.036
Micronized glyburide*	10	(0.12)	0	(0)	2	(0.41)	3	(0.15)	2	(0.07)	3	(0.13)	0	(0)	0.4036
Glipizide	184	(2.2)	0	(0)	9	(1.85)	58	(2.87)	60	(2.22)	49	(2.1)	8	(0.96)	0.0593
Glipizide Ext Rel	557	(6.65)	1	(50)	55	(11.32)	165	(8.18)	184	(6.81)	125	(5.36)	27	(3.25)	<0.0001
Glimepiride	423	(5.05)	0	(0)	40	(8.23)	130	(6.44)	136	(5.03)	93	(3.99)	24	(2.88)	<0.0001
Meglitinides	81	(0.97)	0	(0)	9	(1.85)	19	(0.94)	32	(1.18)	16	(0.69)	5	(0.6)	0.1353
Repaglinide*	26	(0.31)	0	(0)	4	(0.82)	6	(0.3)	13	(0.48)	3	(0.13)	0	(0)	0.0383
Nateglinide	55	(0.66)	0	(0)	5	(1.03)	13	(0.64)	19	(0.7)	13	(0.56)	5	(0.6)	0.9101
*Alpha-glucosidase inhibitors**	14	(0.17)	0	(0)	1	(0.21)	4	(0.2)	4	(0.15)	2	(0.09)	3	(0.36)	0.6985
Acarbose*	8	(0.1)	0	(0)	0	(0)	3	(0.15)	2	(0.07)	1	(0.04)	2	(0.24)	0.5936
Miglitol*	6	(0.07)	0	(0)	1	(0.21)	1	(0.05)	2	(0.07)	1	(0.04)	1	(0.12)	0.8623
Biguanides	5599	(66.89)	1	(50)	278	(57.2)	1287	(63.78)	1787	(66.11)	1638	(70.3)	608	(73.08)	<0.0001
Metformin, IR or XR	5599	(66.89)	1	(50)	278	(57.2)	1287	(63.78)	1787	(66.11)	1638	(70.3)	608	(73.08)	<0.0001
Thiazolidinediones	1083	(12.94)	0	(0)	65	(13.37)	282	(13.97)	386	(14.28)	275	(11.8)	75	(9.01)	0.0009
Troglitazone	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Rosiglitazone	418	(4.99)	0	(0)	37	(7.61)	121	(6)	130	(4.81)	105	(4.51)	25	(3)	0.0014
Pioglitazone	665	(7.94)	0	(0)	28	(5.76)	161	(7.98)	256	(9.47)	170	(7.3)	50	(6.01)	0.0036
GLP-1 Mimetic	83	(0.99)	0	(0)	0	(0)	0	(0)	6	(0.22)	50	(2.15)	27	(3.25)	<0.0001
Exenatide	83	(0.99)	0	(0)	0	(0)	0	(0)	6	(0.22)	50	(2.15)	27	(3.25)	<0.0001
*DPP-IV Inhibitor**	41	(0.49)	0	(0)	0	(0)	0	(0)	0	(0)	8	(0.34)	33	(3.97)	<0.0001
Sitagliptin*	41	(0.49)	0	(0)	0	(0)	0	(0)	0	(0)	8	(0.34)	33	(3.97)	<0.0001
*Amylin Analogue**	3	(0.04)	0	(0)	0	(0)	0	(0)	1	(0.04)	0	(0)	2	(0.24)	0.0431
Pramlintide*	3	(0.04)	0	(0)	0	(0)	0	(0)	1	(0.04)	0	(0)	2	(0.24)	0.0431

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-3e. Initial monotherapies for subjects age 45–64 years in the DARTNet Diabetic Cohort who received a single oral diabetes medication (N=24542), by year

	Total		Year of prescription 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	24542	(100.00)	1	(0)	1516	(6.18)	5727	(23.34)	7600	(30.97)	6834	(27.85)	2864	(11.67)	
Sulfonylureas (SU)	4560	(18.58)	0	(0)	437	(28.83)	1293	(22.58)	1475	(19.41)	1049	(15.35)	306	(10.68)	<0.0001
Chlorpropamide*	2	(0.01)	0	(0)	0	(0)	0	(0)	2	(0.03)	0	(0)	0	(0)	0.4854
Acetohexamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Tolbutamide*	1	(0)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.01)	0	(0)	0.7627
Tolazamide*	1	(0)	0	(0)	0	(0)	0	(0)	1	(0.01)	0	(0)	0	(0)	0.8166
Glyburide	950	(3.87)	0	(0)	91	(6)	256	(4.47)	343	(4.51)	196	(2.87)	64	(2.23)	<0.0001
Micronized glyburide*	62	(0.25)	0	(0)	3	(0.2)	26	(0.45)	15	(0.2)	14	(0.2)	4	(0.14)	0.0298
Glipizide	550	(2.24)	0	(0)	43	(2.84)	143	(2.5)	182	(2.39)	142	(2.08)	40	(1.4)	0.0097
Glipizide Ext Rel	1691	(6.89)	0	(0)	182	(12.01)	504	(8.8)	520	(6.84)	383	(5.6)	102	(3.56)	<0.0001
Glimepiride	1305	(5.32)	0	(0)	119	(7.85)	365	(6.37)	412	(5.42)	313	(4.58)	96	(3.35)	<0.0001
Meglitinides	318	(1.3)	0	(0)	50	(3.3)	89	(1.55)	105	(1.38)	53	(0.78)	21	(0.73)	<0.0001
Repaglinide	132	(0.54)	0	(0)	21	(1.39)	37	(0.65)	42	(0.55)	21	(0.31)	11	(0.38)	<0.0001
Nateglinide	186	(0.76)	0	(0)	29	(1.91)	52	(0.91)	63	(0.83)	32	(0.47)	10	(0.35)	<0.0001
		(0)		(0)		(0)		(0)		(0)		(0)		(0)	
Alpha-glucosidase inhibitors	44	(0.18)	0	(0)	2	(0.13)	16	(0.28)	14	(0.18)	10	(0.15)	2	(0.07)	0.3323
Acarbose*	27	(0.11)	0	(0)	1	(0.07)	8	(0.14)	8	(0.11)	8	(0.12)	2	(0.07)	0.9454
Miglitol*	17	(0.07)	0	(0)	1	(0.07)	8	(0.14)	6	(0.08)	2	(0.03)	0	(0)	0.1691
Biguanides	15272	(62.23)	1	(100)	792	(52.24)	3316	(57.9)	4627	(60.88)	4564	(66.78)	1972	(68.85)	<0.0001
Metformin, IR or XR	15272	(62.23)	1	(100)	792	(52.24)	3316	(57.9)	4627	(60.88)	4564	(66.78)	1972	(68.85)	<0.0001
Thiazolidinediones	3947	(16.08)	0	(0)	235	(15.5)	1013	(17.69)	1350	(17.76)	1010	(14.78)	339	(11.84)	<0.0001
Troglitazone	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Rosiglitazone	1635	(6.66)	0	(0)	139	(9.17)	488	(8.52)	522	(6.87)	350	(5.12)	136	(4.75)	<0.0001
Pioglitazone	2312	(9.42)	0	(0)	96	(6.33)	525	(9.17)	828	(10.89)	660	(9.66)	203	(7.09)	<0.0001
GLP-1 Mimetic	207	(0.84)	0	(0)	0	(0)	0	(0)	29	(0.38)	119	(1.74)	59	(2.06)	<0.0001
Exenatide	207	(0.84)	0	(0)	0	(0)	0	(0)	29	(0.38)	119	(1.74)	59	(2.06)	<0.0001
DPP-IV Inhibitor	188	(0.77)	0	(0)	0	(0)	0	(0)	0	(0)	27	(0.4)	161	(5.62)	<0.0001
Sitagliptin	188	(0.77)	0	(0)	0	(0)	0	(0)	0	(0)	27	(0.4)	161	(5.62)	<0.0001
*Amylin Analogue**	6	(0.02)	0	(0)	0	(0)	0	(0)	0	(0)	2	(0.03)	4	(0.14)	0.0017
Pramlintide*	6	(0.02)	0	(0)	0	(0)	0	(0)	0	(0)	2	(0.03)	4	(0.14)	0.0017

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-3f. Initial monotherapies for subjects age 65+ years in the DARTNet Diabetic Cohort who received a single oral diabetes medication (N=5723), by year

	Total		Year of prescription												Chi-square test for trend p-value
			2002		2003		2004		2005		2006		2007		
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	5723	(100.00)	4	(0.07)	696	(12.16)	1210	(21.14)	1242	(21.7)	1818	(31.77)	753	(13.16)	
Sulfonylureas (SU)	1960	(34.25)	2	(50)	324	(46.55)	482	(39.83)	396	(31.88)	577	(31.74)	179	(23.77)	<0.0001
Chlorpropamide*	8	(0.14)	0	(0)	4	(0.57)	2	(0.17)	1	(0.08)	0	(0)	1	(0.13)	0.0303
Acetohexamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Tolbutamide*	1	(0.02)	0	(0)	1	(0.14)	0	(0)	0	(0)	0	(0)	0	(0)	0.2045
Tolazamide	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Glyburide	511	(8.93)	1	(25)	124	(17.82)	108	(8.93)	100	(8.05)	133	(7.32)	45	(5.98)	<0.0001
Micronized glyburide*	20	(0.35)	0	(0)	7	(1.01)	5	(0.41)	3	(0.24)	5	(0.28)	0	(0)	0.0333
Glipizide	250	(4.37)	0	(0)	60	(8.62)	51	(4.21)	48	(3.86)	68	(3.74)	23	(3.05)	<0.0001
Glipizide Ext Rel	677	(11.83)	1	(25)	71	(10.2)	210	(17.36)	150	(12.08)	201	(11.06)	44	(5.84)	<0.0001
Glimepiride	493	(8.61)	0	(0)	57	(8.19)	106	(8.76)	94	(7.57)	170	(9.35)	66	(8.76)	0.6129
Meglitinides	134	(2.34)	0	(0)	19	(2.73)	30	(2.48)	24	(1.93)	42	(2.31)	19	(2.52)	0.8912
Repaglinide	77	(1.35)	0	(0)	8	(1.15)	19	(1.57)	13	(1.05)	25	(1.38)	12	(1.59)	0.861
Nateglinide	57	(1)	0	(0)	11	(1.58)	11	(0.91)	11	(0.89)	17	(0.94)	7	(0.93)	0.7309
*Alpha-glucosidase inhibitors**	13	(0.23)	0	(0)	0	(0)	4	(0.33)	2	(0.16)	5	(0.28)	2	(0.27)	0.7557
Acarbose*	11	(0.19)	0	(0)	0	(0)	4	(0.33)	2	(0.16)	3	(0.17)	2	(0.27)	0.7154
Miglitol*	2	(0.03)	0	(0)	0	(0)	0	(0)	0	(0)	2	(0.11)	0	(0)	0.5074
Biguanides	2556	(44.66)	2	(50)	269	(38.65)	498	(41.16)	589	(47.42)	801	(44.06)	397	(52.72)	<0.0001
Metformin, IR or XR	2556	(44.66)	2	(50)	269	(38.65)	498	(41.16)	589	(47.42)	801	(44.06)	397	(52.72)	<0.0001
Thiazolidinediones	989	(17.28)	0	(0)	84	(12.07)	196	(16.2)	230	(18.52)	373	(20.52)	106	(14.08)	<0.0001
Troglitazone	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	-
Rosiglitazone	476	(8.32)	0	(0)	51	(7.33)	99	(8.18)	108	(8.7)	174	(9.57)	44	(5.84)	0.0456
Pioglitazone	513	(8.96)	0	(0)	33	(4.74)	97	(8.02)	122	(9.82)	199	(10.95)	62	(8.23)	<0.0001
*GLP-1 Mimetic**	20	(0.35)	0	(0)	0	(0)	0	(0)	1	(0.08)	14	(0.77)	5	(0.66)	0.0009
Exenatide*	20	(0.35)	0	(0)	0	(0)	0	(0)	1	(0.08)	14	(0.77)	5	(0.66)	0.0009
DPP-IV Inhibitor	50	(0.87)	0	(0)	0	(0)	0	(0)	0	(0)	5	(0.28)	45	(5.98)	<0.0001
Sitagliptin	50	(0.87)	0	(0)	0	(0)	0	(0)	0	(0)	5	(0.28)	45	(5.98)	<0.0001
*Amylin Analogue**	1	(0.02)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.06)	0	(0)	0.8283
Pramlintide*	1	(0.02)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.06)	0	(0)	0.8283

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-4a. Initial fixed-dose combinations for the DARTNet Diabetic Cohort who received a combination of oral diabetes medications (N=6320), by year

	Total		Year of prescription												
			2002		2003		2004		2005		2006		2007		
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	Chi-square test for trend p-value
Total N	6320	(100.00)	1	(0.02)	387	(6.12)	1914	(30.28)	1763	(27.90)	1641	(25.97)	614	(9.72)	
SU/Metformin	2924	(46.27)	1	(100.00)	256	(66.15)	893	(46.66)	934	(52.98)	662	(40.34)	178	(28.99)	< 0.0001
Glyburide/metformin	2693	(42.61)	1	(100.00)	226	(58.40)	829	(43.31)	846	(47.99)	626	(38.15)	165	(26.87)	< 0.0001
Glipizide/metformin	231	(3.66)	0	-	30	(7.75)	64	(3.34)	88	(4.99)	36	(2.19)	13	(2.12)	< 0.0001
SU/TZD	292	(4.62)	0	-	0	-	0	-	0	-	239	(14.56)	53	(8.63)	< 0.0001
Glimepiride/rosiglitazone	276	(4.37)	0	-	0	-	0	-	0	-	235	(14.32)	41	(6.68)	< 0.0001
Glimepiride/pioglitazone*	16	(0.25)	0	-	0	-	0	-	0	-	4	(0.24)	12	(1.95)	< 0.0001
Biguanide/TZD	3091	(48.91)	0	-	134	(34.63)	1027	(53.66)	829	(47.02)	741	(45.16)	360	(58.63)	< 0.0001
Metformin/rosiglitazone	2435	(38.53)	0	-	134	(34.63)	1027	(53.66)	787	(44.64)	286	(17.53)	201	(32.74)	< 0.0001
Metformin/pioglitazone	656	(10.38)	0	-	0	-	0	-	42	(2.38)	455	(27.73)	159	(25.90)	< 0.0001
*DPP-IV/Biguanide**	24	(0.38)	0	-	0	-	0	-	0	-	0	-	24	(3.91)	< 0.0001
Sitagliptin/metformin*	24	(0.38)	0	-	0	-	0	-	0	-	0	-	24	(3.91)	< 0.0001

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-4b. Initial fixed-dose combinations for men in the DARTNet Diabetic Cohort who received a combination of oral diabetes medications (N=3879), by year

			Year of prescription										
	Total		2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	3879	(100.00)	1	(0.03)	235	(6.06)	1158	(29.85)	1087	(28.02)	1009	(26.01)	389	(10.03)	
SU/Metformin	1750	(45.11)	1	(100)	158	(67.23)	528	(45.6)	572	(52.62)	376	(37.26)	115	(29.56)	<0.0001
Glyburide/metformin	1606	(41.4)	1	(100)	136	(57.87)	488	(42.14)	521	(47.93)	355	(35.18)	105	(26.99)	<0.0001
Glipizide/metformin	144	(3.71)	0	(0)	22	(9.36)	40	(3.45)	51	(4.69)	21	(2.08)	10	(2.57)	<0.0001
SU/TZD	175	(4.51)	0	(0)	0	(0)	0	(0)	0	(0)	142	(14.07)	33	(8.48)	<0.0001
Glimepiride/rosiglitazone	168	(4.33)	0	(0)	0	(0)	0	(0)	0	(0)	142	(14.07)	26	(6.68)	<0.0001
Glimepiride/pioglitazone*	7	(0.18)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	7	(1.8)	<0.0001
Biguanide/TZD	1943	(50.09)	0	(0)	79	(33.62)	633	(54.66)	515	(47.38)	491	(48.66)	225	(57.84)	<0.0001
Metformin/rosiglitazone	1511	(38.95)	0	(0)	79	(33.62)	633	(54.66)	485	(44.62)	186	(18.43)	128	(32.9)	<0.0001
Metformin/pioglitazone	432	(11.14)	0	(0)	0	(0)	0	(0)	30	(2.76)	305	(30.23)	97	(24.94)	<0.0001
*DPP-IV/Biguanide**	17	(0.44)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	17	(4.37)	<0.0001
Sitagliptin/metformin*	17	(0.44)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	17	(4.37)	<0.0001

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-4c. Initial fixed-dose combinations for women in the DARTNet Diabetic Cohort who received a combination of oral diabetes medications (N=2441), by year

	Total		Year of prescription: 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	2441	(100.00)	0	(0)	152	(6.23)	756	(30.97)	676	(27.69)	632	(25.89)	225	(9.22)	
SU/Metformin	1174	(48.1)	0	(0)	98	(64.47)	365	(48.28)	362	(53.55)	286	(45.25)	63	(28)	<0.0001
Glyburide/metformin	1087	(44.53)	0	(0)	90	(59.21)	341	(45.11)	325	(48.08)	271	(42.88)	60	(26.67)	<0.0001
Glipizide/metformin	87	(3.56)	0	(0)	8	(5.26)	24	(3.17)	37	(5.47)	15	(2.37)	3	(1.33)	0.0055
SU/TZD	117	(4.79)	0	(0)	0	(0)	0	(0)	0	(0)	97	(15.35)	20	(8.89)	<0.0001
Glimepiride/rosiglitazone	108	(4.42)	0	(0)	0	(0)	0	(0)	0	(0)	93	(14.72)	15	(6.67)	<0.0001
Glimepiride/pioglitazone*	9	(0.37)	0	(0)	0	(0)	0	(0)	0	(0)	4	(0.63)	5	(2.22)	<0.0001
Biguanide/TZD	1148	(47.03)	0	(0)	55	(36.18)	394	(52.12)	314	(46.45)	250	(39.56)	135	(60)	<0.0001
Metformin/rosiglitazone	924	(37.85)	0	(0)	55	(36.18)	394	(52.12)	302	(44.67)	100	(15.82)	73	(32.44)	<0.0001
Metformin/pioglitazone	224	(9.18)	0	(0)	0	(0)	0	(0)	12	(1.78)	150	(23.73)	32	(14.22)	<0.0001
*DPP-IV/Biguanide**	7	(0.29)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	7	(3.11)	<0.0001
Sitagliptin/metformin*	7	(0.29)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	7	(11.11)	<0.0001

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-4d. Initial fixed-dose combinations for subjects age <45 years in the DARTNet Diabetic Cohort who received a combination of oral diabetes medications (N=1724), by year

	Total		Year of prescription 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	1724	(100.00)	0	(0)	90	(5.22)	561	(32.54)	482	(27.96)	429	(24.88)	162	(9.4)	
SU/Metformin	761	(44.14)	0	(0)	54	(60)	261	(46.52)	259	(53.73)	148	(34.5)	39	(24.07)	<0.0001
Glyburide/metformin	703	(40.78)	0	(0)	52	(57.78)	246	(43.85)	234	(48.55)	136	(31.7)	35	(21.6)	<0.0001
Glipizide/metformin	58	(3.36)	0	(0)	2	(2.22)	15	(2.67)	25	(5.19)	12	(2.8)	4	(2.47)	0.1396
SU/TZD	78	(4.52)	0	(0)	0	(0)	0	(0)	0	(0)	65	(15.15)	13	(8.02)	<0.0001
Glimepiride/rosiglitazone	72	(4.18)	0	(0)	0	(0)	0	(0)	0	(0)	64	(14.92)	8	(4.94)	<0.0001
Glimepiride/pioglitazone*	6	(0.35)	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.23)	5	(3.09)	<0.0001
Biguanide/TZD	889	(51.57)	0	(0)	38	(42.22)	304	(54.19)	223	(46.27)	217	(50.58)	107	(66.05)	<0.0001
Metformin/rosiglitazone	698	(40.49)	0	(0)	38	(42.22)	304	(54.19)	209	(43.36)	87	(20.28)	60	(37.04)	<0.0001
Metformin/pioglitazone	191	(11.08)	0	(0)	0	(0)	0	(0)	14	(2.9)	130	(30.3)	47	(29.01)	<0.0001
*DPP-IV/Biguanide**	3	(0.17)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	3	(1.85)	<0.0001
Sitagliptin/metformin*	3	(0.17)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	3	(1.85)	<0.0001

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-4e. Initial fixed-dose combinations for subjects age 45–64 years in the DARTNet Diabetic Cohort who received a combination of oral diabetes medications (N=4090), by year

	Total		Year of prescription 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	4090	(100.00)	1	(0.02)	246	(6.01)	1250	(30.56)	1181	(28.88)	1023	(25.01)	389	(9.51)	
SU/Metformin	1884	(46.06)	1	(100)	164	(66.67)	573	(45.84)	617	(52.24)	409	(39.98)	120	(30.85)	<0.0001
Glyburide/metformin	1725	(42.18)	1	(100)	137	(55.69)	529	(42.32)	557	(47.16)	389	(38.03)	112	(28.79)	<0.0001
Glipizide/metformin	159	(3.89)	0	(0)	27	(10.98)	44	(3.52)	60	(5.08)	20	(1.96)	8	(2.06)	<0.0001
SU/TZD	184	(4.5)	0	(0)	0	(0)	0	(0)	0	(0)	149	(14.57)	35	(9)	<0.0001
Glimepiride/rosiglitazone	174	(4.25)	0	(0)	0	(0)	0	(0)	0	(0)	146	(14.27)	28	(7.2)	<0.0001
Glimepiride/pioglitazone*	10	(0.24)	0	(0)	0	(0)	0	(0)	0	(0)	3	(0.29)	7	(1.8)	<0.0001
Biguanide/TZD	2007	(49.07)	0	(0)	83	(33.74)	679	(54.32)	564	(47.76)	465	(45.45)	216	(55.53)	<0.0001
Metformin/rosiglitazone	1594	(38.97)	0	(0)	83	(33.74)	679	(54.32)	540	(45.72)	171	(16.72)	121	(31.11)	<0.0001
Metformin/pioglitazone	413	(10.1)	0	(0)	0	(0)	0	(0)	24	(2.03)	294	(28.74)	95	(24.42)	<0.0001
*DPP-IV/Biguanide**	19	(0.46)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	19	(4.88)	<0.0001
Sitagliptin/metformin*	19	(0.46)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	19	(4.88)	<0.0001

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-4f. Initial fixed-dose combinations for subjects age 65+ years in the DARTNet Diabetic Cohort who received a combination of oral diabetes medications (N=506), by year

	Total		Year of prescription: 2002		2003		2004		2005		2006		2007		Chi-square test for trend p-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	506	(100.00)	0	(0)	51	(10.08)	103	(20.36)	100	(19.76)	189	(37.35)	63	(12.45)	
SU/Metformin	279	(55.14)	0	(0)	38	(74.51)	59	(57.28)	58	(58)	105	(55.56)	19	(30.16)	<0.0001
Glyburide/metformin	265	(52.37)	0	(0)	37	(72.55)	54	(52.43)	55	(55)	101	(53.44)	18	(28.57)	<0.0001
Glipizide/metformin*	14	(2.77)	0	(0)	1	(1.96)	5	(4.85)	3	(3)	4	(2.12)	1	(1.59)	0.6563
		(0)		(0)		(0)		(0)		(0)		(0)		(0)	
SU/TZD	30	(5.93)	0	(0)	0	(0)	0	(0)	0	(0)	25	(13.23)	5	(7.94)	<0.0001
Glimepiride/rosiglitazone	30	(5.93)	0	(0)	0	(0)	0	(0)	0	(0)	25	(13.23)	5	(7.94)	<0.0001
Glimepiride/pioglitazone	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	N/A
		(0)		(0)		(0)		(0)		(0)		(0)		(0)	
Biguanide/TZD	195	(38.54)	0	(0)	13	(25.49)	44	(42.72)	42	(42)	59	(31.22)	37	(58.73)	0.0005
Metformin/rosiglitazone	143	(28.26)	0	(0)	13	(25.49)	44	(42.72)	38	(38)	28	(14.81)	20	(31.75)	<0.0001
Metformin/pioglitazone	52	(10.28)	0	(0)	0	(0)	0	(0)	4	(4)	31	(16.4)	17	(26.98)	<0.0001
		(0)		(0)		(0)		(0)		(0)		(0)		(0)	
*DPP-IV/Biguanide**	2	(0.4)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	2	(3.17)	0.0069
Sitagliptin/metformin*	2	(0.4)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	2	(3.17)	0.0069

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-5. Top 25 initial non-fixed-dose combinations (by individual agent) for the DARTNet Diabetic Cohort who received a combination of oral diabetes medications (2002-2007, combined)

	TOTAL	
	N	(%)
2 Drug Combinations		
Metformin_IR_XR + Rosiglitazone	620	(19.35)
Glipizide_Ext_Rel + Metformin_IR_XR	500	(15.61)
Metformin_IR_XR + Pioglitazone	445	(13.89)
Glimepiride + Metformin_IR_XR	365	(11.39)
Glyburide + Metformin_IR_XR	346	(10.8)
Glipizide + Metformin_IR_XR	274	(8.55)
Glimepiride + Pioglitazone	106	(3.31)
Glimepiride + Rosiglitazone	86	(2.68)
Glipizide_Ext_Rel + Rosiglitazone	83	(2.59)
Glipizide_Ext_Rel+ Pioglitazone	74	(2.31)
Repaglinide + Metformin_IR_XR	37	(1.15)
Nateglinide + Metformin_IR_XR	36	(1.12)
Glyburide + Rosiglitazone	34	(1.06)
Metformin_IR_XR + Exanatide	30	(0.94)
Glyburide + Pioglitazone	29	(0.91)
Glipizide + Rosiglitazone	22	(0.69)
Glipizide + Pioglitazone	20	(0.62)
Metformin_IR_XR + Sitagliptin	19	(0.59)
Micronized_glyburide + Metformin_IR_XR	18	(0.56)
Nateglinide + Pioglitazone	18	(0.56)
Nateglinide + Rosiglitazone	13	(0.41)
Repaglinide + Pioglitazone	11	(0.34)
Repaglinide + Rosiglitazone	11	(0.34)
Glipizide_Ext_Rel + Repaglinide	4	(0.12)
Glimepiride + Repaglinide	3	(0.09)
Total	3204	(100)
3 Drug Combinations		
Glipizide_Ext_Rel + Metformin_IR_XR + Rosiglitazone	49	(17.69)
Glimepiride + Metformin_IR_XR + Pioglitazone	47	(16.97)
Glipizide_Ext_Rel + Metformin_IR_XR+ Pioglitazone	37	(13.36)
Glimepiride + Metformin_IR_XR + Rosiglitazone	35	(12.64)
Glyburide + Metformin_IR_XR + Rosiglitazone	29	(10.47)
Glipizide + Metformin_IR_XR + Rosiglitazone	19	(6.86)
Glyburide + Metformin_IR_XR + Pioglitazone	17	(6.14)
Glipizide + Metformin_IR_XR + Pioglitazone	8	(2.89)
Repaglinide + Metformin_IR_XR + Pioglitazone	8	(2.89)
Nateglinide + Metformin_IR_XR + Pioglitazone	6	(2.17)
Micronized_glyburide + Metformin_IR_XR + Pioglitazone	4	(1.44)
Repaglinide + Metformin_IR_XR + Rosiglitazone	3	(1.08)
Glipizide + Metformin_IR_XR + Exenatide	2	(0.72)
Nateglinide + Metformin_IR_XR + Rosiglitazone	2	(0.72)
Glimepiride + Pioglitazone + Sitagliptin	1	(0.36)
Glimepiride + Metformin_IR_XR + Exenatide	1	(0.36)
Glimepiride + Repaglinide + Miglitol	1	(0.36)
Glimepiride + Repaglinide + Pioglitazone	1	(0.36)
Glimepiride + Repaglinide + Metformin_IR_XR	1	(0.36)
Glipizide + Glimepiride + Pioglitazone	1	(0.36)
Glipizide_Ext_Rel + Acarbose + Metformin_IR_XR	1	(0.36)
Glipizide_Ext_Rel + Acarbose + Rosiglitazone	1	(0.36)
Glipizide_Ext_Rel + Metformin_IR_XR + Exenatide	1	(0.36)
Glipizide_Ext_Rel + Nateglinide + Metformin_IR_XR	1	(0.36)
Glyburide + Nateglinide + Metformin_IR_XR	1	(0.36)
Total	277	(100)

Table B-6. Initial non-fixed-dose combinations (by drug class) for the DARTNet Diabetic Cohort who received a combination of oral diabetes medications (2002-2007, combined)

	TOTAL	
2-Drug Combinations (by Drug Class)	N	(%)
Sulfonylureas + Biguanides	1505	(46.44)
Biguanides + Thiazolidinediones	1066	(32.89)
Sulfonylureas + Thiazolidinediones	459	(14.16)
Meglitinides + Biguanides	74	(2.28)
Meglitinides + Thiazolidinediones	54	(1.67)
Biguanides + GLP-1 Mimetic	30	(0.93)
Biguanides + DPP-IV Inhibitor	20	(0.62)
Sulfonylureas + Meglitinides	15	(0.46)
Sulfonylureas + Alpha-glucosidase inhibitors	4	(0.12)
Thiazolidinediones + GLP-1 Mimetic	3	(0.09)
Alpha-glucosidase inhibitors + Thiazolidinediones	3	(0.09)
Meglitinides + GLP-1 Mimetic	3	(0.09)
Alpha-glucosidase inhibitors + Biguanides	2	(0.06)
Sulfonylureas + GLP-1 Mimetic	2	(0.06)
Alpha-glucosidase inhibitors + GLP-1 Mimetic	1	(0.03)

	TOTAL	
3-Drug Combinations (by Drug Class)	N	(%)
Sulfonylureas + Biguanides + Thiazolidinediones	248	(87.94)
Meglitinides + Biguanides + Thiazolidinediones	19	(6.74)
Sulfonylureas + Biguanides + GLP-1 Mimetic	4	(1.42)
Sulfonylureas + Meglitinides + Biguanides	3	(1.06)
Biguanides + Thiazolidinediones + GLP-1 Mimetic	1	(0.35)
Alpha-glucosidase inhibitors + Biguanides + Thiazolidinediones	1	(0.35)
Meglitinides + Alpha-glucosidase inhibitors + Thiazolidinediones	1	(0.35)
Sulfonylureas + Thiazolidinediones + DPP-IV Inhibitor	1	(0.35)
Sulfonylureas + Alpha-glucosidase inhibitors + Thiazolidinediones	1	(0.35)
Sulfonylureas + Alpha-glucosidase inhibitors + Biguanides	1	(0.35)
Sulfonylureas + Meglitinides + Thiazolidinediones	1	(0.35)
Sulfonylureas + Meglitinides + Alpha-glucosidase inhibitors	1	(0.35)

Table B-7. Time to first regimen change for monotherapy and combination therapy groups

		Time to First Regimen Change (Days)			
		N	Mean	Median	Range
Monotherapy					
a	Biguanide [b, d, e, f, g, h]	23400	284.62	182.0	2.0 - 1755.0
b	SU [a, c, d, e, f]	7977	270.34	145.0	2.0 - 1759.0
c	TZD [b, d, e, f, h]	6012	284.48	177.0	2.0 - 1736.0
d	Meglitinide [a, b, c, e, f]	533	155.56	73.0	2.0 - 1378.0
e	GLP-1 Mimetic [a, b, c, d]	309	159.44	106.0	2.0 - 856.0
f	DPP-IV Inhibitor [a, b, c, d, h]	279	123.37	103.0	2.0 - 318.0
g	Alpha-glucosidase Inhibitor [a]	71	191.45	92.0	2.0 - 1230.0
h	Amylin Analogue [a, c, f]	10	50.90	32.0	26.0 - 178.8
Combination Therapy					
i	SU + Biguanide [k, l]	4209	257.46	151.0	2.0 - 1711.0
j	Biguanide + TZD [k, l]	3940	238.71	153.5	2.0 - 1643.0
k	SU + TZD [i, j]	722	194.94	120.0	2.0 - 1548.0
l	SU + TZD + Biguanide [i, j]	661	180.33	96.0	2.0 - 1237.0

a - h: Based on pair-wise Wilcoxon nonparametric tests, median time to first regimen change is statistically different across specified monotherapy groups at $p < 0.0018$ (adjusted for multiple comparisons). For example, Amylin Analogue group (group h) is statistically different from Buguanide, TZD, and DPP-IV Inhibitor groups (groups a, c, f).

i - l: Based on pair-wise Wilcoxon nonparametric tests, median time to first regimen change is statistically different across specified combination therapy groups at $p < 0.0083$ (adjusted for multiple comparisons). For example, SU+Biguanide group (group i) is statistically different from SU+TZD and SU+TZD+Biguanide groups (groups k, l).

Table B-8. Log rank tests for Kaplan-Meier plots of time to first regimen change

Plot	Drug Group	N	Log Rank chi-square	p-value
	Comination vs. Monotherapy			
1	Combination Therapy	9532	97.62	<0.0001
2	Monotherapy	38951	502.51	<0.0001
	Combination Therapies			
3	SU + Biguanide	4209	722.39	<0.0001
4	Biguanide + TZD	3940	814.52	<0.0001
5	SU + TZD	722	119.51	<0.0001
6	SU + TZD + Biguanide	661	36.38	<0.0001
	Monotherapies			
7	Biguanide	23400	4707.5	<0.0001
8	SU	7977	1777.43	<0.0001
9	TZD	6012	1261.91	<0.0001
10	Meglitinide	533	62.78	<0.0001
11	GLP-1 Mimetic	309	99.76	<0.0001
12	DPP-IV Inhibitor	279	74.84	<0.0001
13	Alpha-glucosidase Inhibitor	71	13.87	0.008
14	Amylin Analogue	10	0.77	0.68

Table B-9. Demographic characteristics of the DARTNet Oral Diabetes Medication Comparative Effectiveness Cohort (n=15161)

			Initial Oral Diabetes Medication Group																				Chi-square test for trend p-value
			Monotherapies												Combination Therapies								
	TOTAL		Biguanides		SU		Meglitinides		TZD		GLP1 Mimetic		DPP4 Inhibitors		SU + biguanide		Biguanide + TZD		SU + TZD		SU + TZD + Biguanide		
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	15161	(100.00)	7981	(100.00)	2210	(100.00)	107	(100.00)	1994	(100.00)	76	(100.00)	51	(100.00)	1214	(100.00)	1205	(100.00)	186	(100.00)	137	(100.00)	
Age																							
1-24 yrs*	68	(0.45)	49	(0.61)	5	(0.23)	0	(0)	3	(0.15)	0	(0)	0	(0)	5	(0.41)	4	(0.33)	1	(0.54)	1	(0.73)	0.1609
25-34 yrs	604	(3.98)	358	(4.49)	71	(3.21)	3	(2.8)	45	(2.26)	6	(7.89)	2	(3.92)	55	(4.53)	48	(3.98)	6	(3.23)	10	(7.3)	< 0.0001
35-44 yrs	2304	(15.2)	1272	(15.94)	243	(11)	8	(7.48)	256	(12.84)	13	(17.11)	6	(11.76)	223	(18.37)	230	(19.09)	25	(13.44)	28	(20.44)	< 0.0001
45-54 yrs	5000	(32.98)	2722	(34.11)	574	(25.97)	28	(26.17)	654	(32.8)	30	(39.47)	16	(31.37)	414	(34.1)	455	(37.76)	66	(35.48)	41	(29.93)	< 0.0001
55-64 yrs	5134	(33.86)	2702	(33.86)	731	(33.08)	45	(42.06)	730	(36.61)	23	(30.26)	18	(35.29)	378	(31.14)	395	(32.78)	62	(33.33)	50	(36.5)	0.0642
65-74 yrs	1479	(9.76)	677	(8.48)	361	(16.33)	9	(8.41)	224	(11.23)	4	(5.26)	4	(7.84)	106	(8.73)	67	(5.56)	20	(10.75)	7	(5.11)	< 0.0001
75-84 yrs	572	(3.77)	201	(2.52)	225	(10.18)	14	(13.08)	82	(4.11)	0	(0)	5	(9.8)	33	(2.72)	6	(0.5)	6	(3.23)	0	(0)	< 0.0001
Mean	53.55		52.72		57.19		58.00		54.96		50.30		55.53		52.21		51.29		54.17		50.55		< 0.0001
Median	54.00		53.00		57.00		58.00		55.00		49.50		55.00		52.00		52.00		54.00		53.00		
Range	(10-80)		(10-80)		(15-79)		(30-79)		(16-80)		(25-71)		(32-80)		(21-79)		(18-79)		(17-79)		(24-73)		
Gender																							
Male	8445	(55.7)	4102	(51.4)	1288	(58.28)	55	(51.4)	1219	(61.13)	25	(32.89)	27	(52.94)	748	(61.61)	766	(63.57)	118	(63.44)	97	(70.8)	< 0.0001
Region																							
East North Central	962	(6.35)	502	(6.29)	145	(6.56)	2	(1.87)	128	(6.42)	7	(9.21)	4	(7.84)	72	(5.93)	76	(6.31)	17	(9.14)	9	(6.57)	0.545
East South Cental	513	(3.38)	262	(3.28)	41	(1.86)	1	(0.93)	84	(4.21)	7	(9.21)	0	(0)	44	(3.62)	65	(5.39)	5	(2.69)	4	(2.92)	< 0.0001
Middle Atlantic	5943	(39.2)	2931	(36.72)	1157	(52.35)	61	(57.01)	798	(40.02)	24	(31.58)	21	(41.18)	453	(37.31)	363	(30.12)	77	(41.4)	58	(42.34)	< 0.0001
Mountain*	360	(2.37)	225	(2.82)	29	(1.31)	0	(0)	44	(2.21)	0	(0)	1	(1.96)	19	(1.57)	39	(3.24)	0	(0)	3	(2.19)	0.0002
New England*	158	(1.04)	109	(1.37)	14	(0.63)	1	(0.93)	16	(0.8)	0	(0)	0	(0)	10	(0.82)	6	(0.5)	1	(0.54)	1	(0.73)	0.0274
Pacific*	111	(0.73)	68	(0.85)	14	(0.63)	1	(0.93)	9	(0.45)	1	(1.32)	0	(0)	7	(0.58)	7	(0.58)	4	(2.15)	0	(0)	0.2264
South Atlantic	4935	(32.55)	2668	(33.43)	586	(26.52)	33	(30.84)	667	(33.45)	21	(27.63)	20	(39.22)	410	(33.77)	447	(37.1)	46	(24.73)	37	(27.01)	< 0.0001
West North Central	576	(3.8)	359	(4.5)	73	(3.3)	1	(0.93)	56	(2.81)	2	(2.63)	0	(0)	39	(3.21)	39	(3.24)	4	(2.15)	3	(2.19)	0.0015
West South Central	1603	(10.57)	857	(10.74)	151	(6.83)	7	(6.54)	192	(9.63)	14	(18.42)	5	(9.8)	160	(13.18)	163	(13.53)	32	(17.2)	22	(16.06)	< 0.0001
Diagnosing Provider Type																							
Endocrinologist	472	(3.11)	297	(3.72)	37	(1.67)	4	(3.74)	39	(1.96)	16	(21.05)	2	(3.92)	32	(2.64)	25	(2.07)	15	(8.06)	5	(3.65)	< 0.0001
PCP	10774	(71.06)	5641	(70.68)	1595	(72.17)	71	(66.36)	1397	(70.06)	44	(57.89)	33	(64.71)	885	(72.9)	868	(72.03)	136	(73.12)	104	(75.91)	0.0685
Other (known)	1075	(7.09)	512	(6.42)	213	(9.64)	12	(11.21)	166	(8.32)	2	(2.63)	2	(3.92)	80	(6.59)	68	(5.64)	9	(4.84)	11	(8.03)	< 0.0001
Unknown	2840	(18.73)	1531	(19.18)	365	(16.52)	20	(18.69)	392	(19.66)	14	(18.42)	14	(27.45)	217	(17.87)	244	(20.25)	26	(13.98)	17	(12.41)	0.0413
Chronic Disease Indicator																							
Mean	4.65		4.85		5.05		4.64		4.22		4.45		4.22		3.95		4.18		4.06		3.88		< 0.0001
Median	4.00		4.00		5.00		4.00		4.00		4.00		4.00		3.00		4.00		4.00		3.00		
Range	(0-20)		(1-20)		(1-19)		(0-18)		(0-19)		(0-12)		(0-16)		(0-15)		(0-16)		(0-14)		(0-13)		
Charlson Index																							
Mean	0.23		0.19		0.37		0.34		0.25		0.14		0.24		0.26		0.17		0.25		0.18		0.8790
Median	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00		
Range	(0-6)		(0-6)		(0-6)		(0-5)		(0-5)		(0-2)		(0-3)		(0-5)		(0-5)		(0-4)		(0-3)		

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-10. Description of baseline hemoglobin A1c values and change scores by initial oral diabetes medication group, unadjusted and adjusted [a]

		Baseline H-A1c Value			Change from Baseline H-A1c to Lowest H-A1c				Change from Baseline H-A1c to Last H-A1c			
					Unadjusted			Adjusted	Unadjusted			Adjusted
	N	Mean	Median	Range	Mean	Median	Range	Mean [a]	Mean	Median	Range	Mean [a]
Initial Oral Diabetes Medication Group												
Biguanides (Metformin)	7981	7.760	7.2	4.3 to 18.0	-1.142	-0.7	-11.7 to 7.0	-1.357	-0.947	-0.5	-11.7 to 7.0	-1.159
SU	2210	8.399	7.8	4.5 to 17.9	-1.666	-1.2	-11.0 to 11.8	-1.368	-1.364	-0.9	-10.5 to 11.8	-1.089
Meglitinides	107	7.548	7.0	5.2 to 14.4	-0.893	-0.4	-8.3 to 1.2	-1.571	-0.779	-0.4	-8.3 to 2.4	-1.375
TZD	1994	7.333	6.9	4.6 to 17.7	-0.909	-0.5	-11.2 to 14.5	-1.506	-0.728	-0.4	-11.2 to 14.5	-1.318
GLP1 Mimetic	76	7.013	6.55	5.5 to 11.3	-0.63	-0.5	-4.8 to 1.8	-1.706	-0.537	-0.5	-4.8 to 1.8	-1.510
DPP4 Inhibitors	51	7.851	7.2	6.0 to 14.2	-1.208	-0.7	-7.4 to 1.4	-1.683	-1.192	-0.7	-7.4 to 1.4	-1.519
SU + Biguanide	1214	9.641	9.4	5.1 to 20.0	-2.062	-2.3	-12.7 to 4.4	-1.447	-2.338	-2.05	-12.7 to 4.5	-1.209
Biguanide + TZD	1205	8.894	8.5	4.9 to 18.6	-2.199	-1.6	-12.0 to 5.8	-1.630	-2.083	-1.5	-12.0 to 6.9	-1.503
SU + TZD	186	9.652	9.7	5.1 to 16.5	-2.705	-2.5	-8.2 to 3.6	-1.649	-2.582	-2.3	-8.0 to 4.5	-1.492
SU + TZD + Biguanide	137	9.647	9.0	5.5 to 16.2	-2.602	-1.8	-9.4 to 1.5	-1.578	-2.469	-1.7	-8.9 to 1.7	-1.410

[a] Means adjusted for propensity score, age, gender, persistence, compliance (MPR), time from first diagnosis to first Rx, baseline A1c value, renal dysfuntion, hepatic dysfuntion, number of diabetes-related physician visits, and numberof diabetes education visits (see Tables 11 and 12)

Table B-11. Multivariable generalized linear model of the effect of initial diabetes medication group and other covariates on hemoglobin A1c change from baseline to lowest (entire cohort and by propensity score quintile)

	Entire cohort (n=15161)		Quintile 1 [a] (n=3032)		Quintile 2 [b] (n=3032)		Quintile 3 [c] (n=3033)		Quintile 4 [d] (n=3032)		Quintile 5 [e] (n=3032)	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Initial Oral Diabetes Medication Group												
Biguanides (Metformin)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SU	-0.0108	0.6708	0.0226	0.8018	-0.038	0.5492	-0.0284	0.6056	-0.0275	0.5549	-0.0655	0.1127
Meglitinides	-0.2145	0.0342	-0.25	0.1411	-0.3867	0.047	-0.082	0.813	-0.2262	0.5241	0.7963	0.0405
TZD	-0.1495	<0.0001	-0.1653	0.0108	-0.2279	<0.0001	-0.0777	0.2867	-0.0935	0.24	-0.0967	0.2378
GLP1 Mimetics	-0.3496	0.0037	-0.4237	0.0084	1.2376	0.2675	-0.00296	0.9962	-0.2153	0.5746	-0.5302	0.0949
DPP4 Inhibitors	-0.3265	0.0251	-0.2607	0.1895	-0.5714	0.6075	-0.5563	0.2133	-0.4142	0.5317	-0.3628	0.2964
SU + Biguanide	-0.0904	0.0069	0.0569	0.4935	-0.1533	0.0259	-0.1912	0.0069	-0.0935	0.2191	0.03807	0.6971
Biguanide + TZD	-0.2732	<0.0001	-0.3146	<0.0001	-0.1212	0.0829	-0.2876	0.0062	-0.0616	0.6188	-0.2386	0.0848
SU + TZD	-0.2921	0.0002	-0.234	0.0389	-0.1825	0.3938	-0.3511	0.2665	0.5189	0.2183	-0.7961	0.0123
SU + TZD + Biguanide	-0.2215	0.0154	-0.1327	0.2654	-0.5223	0.2156	0.06	0.9122	-0.3093	0.5177	0.8548	0.1194
Propensity score	-0.3158	<0.0001	---	---	---	---	---	---	---	---	---	---
Age	0.00023	0.7836	-0.0011	0.5872	0.0014	0.4771	0.00114	0.5658	-0.00167	0.3429	0.00047	0.7569
Male	-0.0565	0.0011	-0.084	0.0679	-0.3077	0.4704	-0.1302	0.0016	-0.00095	0.9799	-0.02827	0.3404
Persistence	-0.00063	<0.0001	-0.00068	<0.0001	-0.00065	<0.0001	-0.00083	<0.0001	-0.00056	<0.0001	-0.00039	<0.0001
Compliance (MPR)	-0.00767	<0.0001	-0.00683	<0.0001	-0.00864	<0.0001	-0.01049	<0.0001	-0.00835	<0.0001	-0.00486	<0.0001
Time from Dx to Rx	0.00028	<0.0001	0.00021	0.03	0.0027	0.0053	0.00037	<0.0001	0.00035	<0.0001	0.00013	0.0386
Baseline A1c value	-0.7588	<0.0001	-0.8042	<0.0001	-0.7757	<0.0001	-0.7439	<0.0001	-0.7357	<0.0001	-0.658	<0.0001
Renal dysfunction	-0.1225	0.0021	-0.0479	0.5239	-0.1723	0.0435	-0.1047	0.3273	-0.2272	0.0315	-0.2086	0.0355
Hepatic dysfunction	0.009	0.8399	-0.1492	0.2571	0.0035	0.7482	-0.0131	0.8926	-0.0254	0.7701	0.1238	0.1099
No. of diabetes-related physician visits	-0.0069	<0.0001	-0.0084	0.0003	-0.0096	<0.0001	-0.0057	0.0043	-0.00629	0.0006	-0.00414	0.0116
No. of diabetes education visits	-0.0773	<0.0001	-0.1308	0.0085	-0.0888	0.0111	-0.1146	0.0001	-0.04048	0.1116	-0.0565	0.0039

[a] Parameter estimates for quintile 1 significantly different from parameter estimates for quintile 5 based on Chow Test ($p < 0.001$)

[b] Parameter estimates for quintile 2 significantly different from parameter estimates for quintile 5 based on Chow Test ($p < 0.001$)

[c] Parameter estimates for quintile 3 significantly different from parameter estimates for quintile 5 based on Chow Test ($p < 0.001$)

[d] Parameter estimates for quintile 4 significantly different from parameter estimates for quintile 5 based on Chow Test ($p < 0.001$)

[e] Parameter estimates for quintile 5 significantly different from parameter estimates for quintiles 1 - 4 based on Chow Test ($p < 0.001$)

Table B-12. Multivariable generalized linear model of the effect of initial diabetes medication group and other covariates on hemoglobin A1c change from baseline to last (entire cohort and by propensity score quintile)

	Entire cohort (n=15161)		Quintile 1 [a] (n=3032)		Quintile 2 [b] (n=3032)		Quintile 3 [c] (n=3033)		Quintile 4 [d] (n=3032)		Quintile 5 [e] (n=3032)	
	b	p-value	b	p-value	b	p-value	b	p-value	b	p-value	b	p-value
Initial Oral Diabetes Medication Group												
Biguanides (Metformin)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SU	0.0693	0.0134	0.0716	0.4623	0.0235	0.7293	0.0461	0.4549	0.0956	0.0752	-0.007	0.8787
Meglitinides	-0.2161	0.0532	-0.3101	0.0914	-0.4101	0.0487	0.1519	0.6967	-0.2319	0.571	1.0699	0.0131
TZD	-0.1597	<0.0001	-0.1776	0.0115	-0.2846	<0.0001	-0.0315	0.7006	-0.0238	0.7951	-0.10338	0.2556
GLP1 Mimetic	-0.3515	0.0081	-0.4342	0.0126	1.2459	0.2964	-0.0146	0.9835	-0.1114	0.8011	-0.5975	0.0899
DPP4 Inhibitors	-0.3603	0.0251	-0.2906	0.1766	-0.579	0.6263	-0.5466	0.2765	-0.4176	0.5844	-0.4073	0.2909
SU + Biguanide	-0.0503	0.1731	0.1671	0.0632	-0.1418	0.054	-0.1241	0.1187	-0.1413	0.1073	0.0402	0.7111
Biguanide + TZD	-0.3445	<0.0001	-0.3680	<0.0001	-0.217	0.0037	-0.3435	0.0036	-0.1127	0.4295	-0.3041	0.0478
SU + TZD	-0.3336	0.0001	-0.2434	0.0469	-0.2865	0.2104	-0.4219	0.2349	0.4111	0.3974	-0.9609	0.0065
SU + TZD + Biguanide	-0.2512	0.0128	-0.1363	0.2907	-0.6246	0.166	-0.0214	0.9721	-0.4682	0.3857	0.8929	0.1426
Propensity score	-0.3169	<0.0001	---	---	---	---	---	---	---	---	---	---
Age	-0.0011	0.2312	-0.0011	0.6282	-0.00076	0.7188	-0.00024	0.9135	-0.0047	0.0195	-0.0001	0.9591
Male	-0.026	0.1746	-0.0645	0.1954	-0.0152	0.7394	-0.1015	0.0283	0.0385	0.3306	0.01157	0.7251
Persistence	-0.00019	<0.0001	-0.00023	0.015	-0.00022	0.0048	-0.00032	0.0002	-0.00017	0.033	0.00002	0.7952
Compliance (MPR)	-0.00752	<0.0001	-0.00736	<0.0001	-0.00792	<0.0001	-0.01085	<0.0001	-0.00812	<0.0001	-0.00419	<0.0001
Time from Dx to Rx	0.00026	<0.0001	0.00022	0.032	0.00026	0.0103	0.00032	0.0015	0.00032	0.0001	0.00008	0.2456
Baseline A1c value	-0.745	<0.0001	-0.7916	<0.0001	-0.7628	<0.0001	-0.7335	<0.0001	-0.7155	<0.0001	-0.6428	<0.0001
Renal dysfunction	-0.1035	0.0184	-0.0283	0.7278	-0.114	0.2116	-0.1105	0.3577	-0.3221	0.0082	-0.0879	0.4244
Hepatic dysfunction	0.138	0.0049	-0.1633	0.2519	0.069	0.5356	0.1893	0.0833	0.1266	0.2066	0.3411	<0.0001
No. of diabetes-related physician visits	-0.0023	0.0176	-0.0043	0.0835	-0.0049	0.0169	-0.00139	0.5255	-0.00028	0.8923	-0.00064	0.7264
No. of diabetes education visits	-0.0817	<0.0001	-0.1718	0.0014	-0.0847	0.0234	-0.1055	0.0017	-0.0478	0.1029	-0.0606	0.0052

[a] Parameter estimates for quintile 1 significantly different from parameter estimates for quintiles 4 and 5 based on Chow Test ($p < 0.001$)

[b] Parameter estimates for quintile 2 significantly different from parameter estimates for quintile 5 based on Chow Test ($p < 0.001$)

[c] Parameter estimates for quintile 3 significantly different from parameter estimates for quintile 5 based on Chow Test ($p < 0.001$)

[d] Parameter estimates for quintile 4 significantly different from parameter estimates for quintiles 1 and 5 based on Chow Test ($p < 0.001$)

[e] Parameter estimates for quintile 5 significantly different from parameter estimates for quintiles 1 - 4 based on Chow Test ($p < 0.001$)

Table B-13. Demographic characteristics of the DARTNet Oral Diabetes Medication Comparative Safety Cohorts (N=76304)

	TOTAL		CAD/Dyslipidemia Comparison Group		Diabetic/No Drug Comparison Group		Initial Oral Diabetes Medication Group																		Chi-square test for trend p-value
							Monotherapies										Combination Therapies								
							Biguanides		SU		Meglitinides		TZD		GLP1 Mimetic		DPP4 Inhibitors		SU + biguanide		Biguanide + TZD		SU + TZD		SU + TZD + Biguanide		
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total N	112918	(100.00)	37412	(100.00)	36614	(100.00)	19396	(100.00)	6228	(100.00)	430	(100.00)	4995	(100.00)	276	(100.00)	251	(100.00)	3112	(100.00)	3169	(100.00)	591	(100.00)	444	(100.00)	
Age																											
1-24 yrs*	879	(0.78)	253	(0.68)	358	(0.98)	177	(0.91)	30	(0.48)	2	(0.47)	8	(0.16)	5	(1.81)	0	(0)	21	(0.67)	21	(0.66)	2	(0.34)	2	(0.45)	< 0.0001
25-34 yrs	4839	(4.29)	1692	(4.52)	1380	(3.77)	977	(5.04)	246	(3.95)	16	(3.72)	150	(3)	16	(5.8)	5	(1.99)	156	(5.01)	155	(4.89)	31	(5.25)	15	(3.38)	< 0.0001
35-44 yrs	17238	(15.27)	6100	(16.3)	4747	(12.96)	3304	(17.03)	800	(12.85)	48	(11.16)	704	(14.09)	49	(17.75)	31	(12.35)	602	(19.34)	667	(21.05)	99	(16.75)	87	(19.59)	< 0.0001
45-54 yrs	34652	(30.69)	12026	(32.14)	10119	(27.64)	6448	(33.24)	1632	(26.2)	113	(26.28)	1588	(31.79)	100	(36.23)	77	(30.68)	1062	(34.13)	1141	(36.01)	189	(31.98)	157	(35.36)	< 0.0001
55-64 yrs	36603	(32.42)	11820	(31.59)	12538	(34.24)	6230	(32.12)	1860	(29.87)	139	(32.33)	1676	(33.55)	86	(31.16)	92	(36.65)	897	(28.82)	939	(29.63)	183	(30.96)	143	(32.21)	< 0.0001
65-74 yrs	12261	(10.86)	3761	(10.05)	4580	(12.51)	1689	(8.71)	979	(15.72)	62	(14.42)	582	(11.65)	16	(5.8)	29	(11.55)	271	(8.71)	201	(6.34)	55	(9.31)	36	(8.11)	< 0.0001
75-84 yrs	6446	(5.71)	1760	(4.7)	2892	(7.9)	571	(2.94)	681	(10.93)	50	(11.63)	287	(5.75)	4	(1.45)	17	(6.77)	103	(3.31)	45	(1.42)	32	(5.41)	4	(0.9)	< 0.0001
Mean	53.98		53.35		55.39		52.38		56.53		57.00		54.77		50.87		56.11		51.87		50.89		53.27		51.83		< 0.0001
Median	54.00		54.00		56.00		53.00		57.00		57.00		55.00		52.00		55.00		52.00		51.00		54.00		53.00		
Range	(2-82)		(11-80)		(4-80)		(6-80)		(2-80)		(21-79)		(14-80)		(17-77)		(32-80)		(17-80)		(16-80)		(17-80)		(20-78)		
Gender																											
Male	59798	(52.96)	20287	(54.23)	18399	(50.25)	9647	(49.74)	3559	(57.15)	228	(53.02)	2928	(58.62)	107	(38.77)	135	(53.78)	1892	(60.8)	1987	(62.7)	356	(60.24)	273	(61.49)	< 0.0001
Region																											
East North Central	7738	(6.85)	3499	(9.35)	1873	(5.12)	1198	(6.18)	355	(5.7)	15	(3.49)	336	(6.73)	21	(7.61)	13	(5.18)	164	(5.27)	195	(6.15)	41	(6.94)	28	(6.31)	< 0.0001
East South Cental	2998	(2.66)	1029	(2.75)	772	(2.11)	603	(3.11)	132	(2.12)	13	(3.02)	153	(3.06)	17	(6.16)	7	(2.79)	80	(2.57)	159	(5.02)	20	(3.38)	13	(2.93)	< 0.0001
Middle Atlantic	46343	(41.04)	14499	(38.75)	16769	(45.8)	7008	(36.13)	3158	(50.71)	258	(60)	1959	(39.22)	81	(29.35)	103	(41.04)	1143	(36.73)	980	(30.92)	234	(39.59)	151	(34.01)	< 0.0001
Mountain	3777	(3.34)	2146	(5.74)	601	(1.64)	629	(3.24)	103	(1.65)	2	(0.47)	118	(2.36)	5	(1.81)	3	(1.2)	62	(1.99)	85	(2.68)	7	(1.18)	16	(3.6)	< 0.0001
New England	2463	(2.18)	1441	(3.85)	570	(1.56)	258	(1.33)	58	(0.93)	4	(0.93)	64	(1.28)	3	(1.09)	1	(0.4)	25	(0.8)	30	(0.95)	4	(0.68)	5	(1.13)	< 0.0001
Pacific	2316	(2.05)	1640	(4.38)	263	(0.72)	246	(1.27)	55	(0.88)	3	(0.7)	36	(0.72)	1	(0.36)	3	(1.2)	24	(0.77)	35	(1.1)	5	(0.85)	5	(1.13)	< 0.0001
South Atlantic	30693	(27.18)	6905	(18.46)	11592	(31.66)	6226	(32.1)	1637	(26.28)	99	(23.02)	1568	(31.39)	94	(34.06)	88	(35.06)	1055	(33.9)	1110	(35.03)	173	(29.27)	146	(32.88)	< 0.0001
West North Central	4426	(3.92)	1672	(4.47)	1308	(3.57)	855	(4.41)	199	(3.2)	10	(2.33)	149	(2.98)	11	(3.99)	4	(1.59)	89	(2.86)	94	(2.97)	15	(2.54)	20	(4.5)	< 0.0001
West South Central	12139	(10.75)	4569	(12.21)	2859	(7.81)	2372	(12.23)	529	(8.49)	26	(6.05)	610	(12.21)	43	(15.58)	29	(11.55)	469	(15.07)	481	(15.18)	92	(15.57)	60	(13.51)	< 0.0001
Other*	25	(0.02)	12	(0.03)	7	(0.02)	1	(0.01)	2	(0.03)	0	(0)	2	(0.04)	0	(0)	0	(0)	1	(0.03)	0	(0)	0	(0)	0	(0)	0.828
Diagnosing Provider Type																											
Endocrinologist	2136	(1.89)	---	---	876	(2.39)	678	(3.5)	148	(2.38)	32	(7.44)	124	(2.48)	32	(11.59)	14	(5.58)	98	(3.15)	87	(2.75)	30	(5.08)	17	(3.83)	< 0.0001
PCP	46674	(41.33)	---	---	19944	(54.47)	13285	(68.49)	4237	(68.03)	284	(66.05)	3418	(68.43)	158	(57.25)	166	(66.14)	2167	(69.63)	2276	(71.82)	410	(69.37)	329	(74.1)	< 0.0001
Other (known)	6132	(5.43)	---	---	2865	(7.82)	1468	(7.57)	708	(11.37)	51	(11.86)	413	(8.27)	20	(7.25)	19	(7.57)	294	(9.45)	199	(6.28)	53	(8.97)	42	(9.46)	< 0.0001
Unknown	20564	(18.21)	---	---	12929	(35.31)	3965	(20.44)	1135	(18.22)	63	(14.65)	1040	(20.82)	66	(23.91)	52	(20.72)	553	(17.77)	607	(19.15)	98	(16.58)	56	(12.61)	< 0.0001
Chronic Disease Indicator																											
Mean	3.65		2.76		3.41		4.91		5.10		5.36		4.32		4.91		4.32		4.14		4.15		4.35		4.18		< 0.0001
Median	3.00		2.00		3.00		4.00		5.00		5.00		4.00		4.00		4.00		4.00		4.00		4.00		4.00		
Range	(0-21)		(0-19)		(0-20)		(1-19)		(1-21)		(0-21)		(0-19)		(0-13)		(0-16)		(0-17)		(0-17)		(0-18)		(0-14)		
Charlson Index																											
Mean	0.38		0.10		0.70		0.94		1.31		1.41		1.11		0.84		1.00		1.25		1.06		1.21		1.17		< 0.0001
Median	0.00		0.00		0.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		
Range	(0-7)		(0-6)		(0-7)		(0-7)		(0-7)		(0-7)		(0-5)		(0-3)		(0-4)		(0-5)		(0-5)		(0-6)		(0-4)		

* Small cell sizes are present, use caution in interpretation of chi-square test results

Table B-14a. Crude incidence rates of hypoglycemia, liver injury and liver failure events in DARTNet comparative safety cohorts (N=112918)

				Initial Oral Diabetes Medication Group									
	TOTAL	CAD/Dyslipidemia Comparison Group	Diabetic/No Drug Comparison Group	Biguanides	SU	Meglitinides	TZD	GLP1 Mimetic	DPP4 Inhibitors	SU + Biguanide	Biguanide + TZD	SU + TZD	SU + TZD + Biguanide
Total N	112918	37412	36614	19396	6228	430	4995	276	251	3112	3169	591	444
Hypoglycemia													
No. of events	1842	155	1166	167	160	6	39	2	1	99	22	11	14
No. of events per 1000 subjects	16.3	4.1	31.8	8.6	25.7	14.0	7.8	7.2	4.0	31.8	6.9	18.6	31.5
No. of person years	119174.21	27606.02	62969.48	14937.73	4613.16	186	3910.6	122.0877	84.4986	2155.17	2074.3	315.318	199.8822
No. of events per person-year of therapy/followup*	0.015	0.006	0.019	0.011	0.035	0.032	0.010	0.016	0.012	0.046	0.011	0.035	0.070
Liver Injury													
No. of events	1083	109	597	178	87	4	22	1	0	56	21	6	2
No. of events per 1000 subjects	9.6	2.9	16.3	9.2	14.0	9.3	4.4	3.6	0.0	18.0	6.6	10.2	4.5
No. of person years	119174.21	27606.02	62969.48	14937.73	4613.16	186	3910.6	122.0877	84.4986	2155.17	2074.3	315.318	199.8822
No. of events per person-year of therapy/followup*	0.009	0.004	0.009	0.012	0.019	0.022	0.006	0.008	0.000	0.026	0.010	0.019	0.010
Liver Failure													
No. of events	888	107	586	95	42	1	21	2	0	14	18	2	0
No. of events per 1000 subjects	7.9	2.9	16.0	4.9	6.7	2.3	4.2	7.2	0.0	4.5	5.7	3.4	0.0
No. of person years	119174.21	27606.02	62969.48	14937.73	4613.16	186	3910.6	122.0877	84.4986	2155.17	2074.3	315.318	199.8822
No. of events per person-year of therapy/followup*	0.007	0.004	0.009	0.006	0.009	0.005	0.005	0.016	0.000	0.006	0.009	0.006	0.000

* Person-years of therapy refer to duration of exposure to ODM for subjects in diabetic/receiving drug groups; and refer to followup time (not exposed to ODM, by definition) for those in CAD/Dyslipidemia and diabetic/no drug comparison groups.

Table B-14b. Crude incidence rates of hypoglycemia, liver injury, and liver failure events in DARTNet Comparative Safety Cohorts: statin users only (N=37613)

				Initial Oral Diabetes Medication Group									
	TOTAL	CAD/Dyslipidemia Comparison Group	Diabetic/No Drug Comparison Group	Biguanides	SU	Meglitinides	TZD	GLP1 Mimetic	DPP4 Inhibitors	SU + Biguanide	Biguanide + TZD	SU + TZD	SU + TZD + Biguanide
Total N	37613	8708	13388	7865	2277	140	2221	84	90	1171	1245	235	189
Hypoglycemia													
No. of events	622	51	348	63	68	2	19	0	0	50	9	5	7
No. of events per 1000 subjects	16.5	5.9	26.0	8.0	29.9	14.3	8.6	0.0	0.0	42.7	7.2	21.3	37.0
No. of person years	48590.02	8668.8	24695.28	7996.37	2323.49	85.79	2293.5	48.72	37.54	1090.85	1081	160.58	108.13
No. of events per person-year of therapy/followup*	0.013	0.006	0.014	0.008	0.029	0.023	0.008	0.000	0.000	0.046	0.008	0.031	0.065
Liver Injury													
No. of events	336	31	188	57	25	1	9	1	0	16	7	1	0
No. of events per 1000 subjects	6.4	2.9	2.9	9.2	14.0	9.3	4.4	3.6	0.0	18.0	6.6	10.2	4.5
No. of person years	48590.02	8668.8	24695.28	7996.37	2323.49	85.79	2293.5	48.72	37.54	1090.85	1081	160.58	108.13
No. of events per person-year of therapy/followup*	0.007	0.004	0.008	0.007	0.011	0.012	0.004	0.021	0.000	0.015	0.006	0.006	0.000
Liver Failure													
No. of events	308	29	192	44	15	0	14	0	0	4	9	1	0
No. of events per 1000 subjects	6.4	2.9	2.9	4.9	6.7	2.3	4.2	7.2	0.0	4.5	5.7	3.4	0.0
No. of person years	48590.02	8668.8	24695.28	7996.37	2323.49	85.79	2293.5	48.72	37.54	1090.85	1081	160.58	108.13
No. of events per person-year of therapy/followup*	0.006	0.003	0.008	0.006	0.006	0.000	0.006	0.000	0.000	0.004	0.008	0.006	0.000

* Person-years of therapy refer to duration of exposure to ODM for subjects in diabetic/receiving drug groups; and refer to followup time (not exposed to ODM, by definition) for those in CAD/Dyslipidemia and diabetic/no drug comparison groups.

Table B-14c. Crude incidence rates of hypoglycemia, liver injury, and liver failure events in DARTNet Comparative Safety Cohorts: non-statin users only (N=75305)

				Initial Oral Diabetes Medication Group									
	TOTAL	CAD/Dyslipidemia Comparison Group	Diabetic/No Drug Comparison Group	Biguanides	SU	Meglitinides	TZD	GLP1 Mimetic	DPP4 Inhibitors	SU + Biguanide	Biguanide + TZD	SU + TZD	SU + TZD + Biguanide
Total N	75305	28704	23226	11531	3951	290	2774	192	161	1941	1924	356	255
Hypoglycemia													
No. of events	1220	104	818	104	92	4	20	2	1	49	13	6	7
No. of events per 1000 subjects	16.2	3.6	35.2	9.0	23.3	13.8	7.2	10.4	6.2	25.2	6.8	16.9	27.5
No. of person years	70584.19	18937.22	38274.21	6491.36	2289.67	100.214	1617.1	73.373	46.962	1064.32	993.3	154.74	91.748
No. of events per person-year of therapy/followup*	0.017	0.005	0.021	0.016	0.040	0.040	0.012	0.027	0.021	0.046	0.013	0.039	0.076
Liver Injury													
No. of events	747	78	409	121	62	3	13	0	0	40	14	5	2
No. of events per 1000 subjects	9.9	2.7	17.6	10.5	15.7	10.3	4.7	0.0	0.0	20.6	7.3	14.0	7.8
No. of person years	70584.19	18937.22	38274.21	6491.36	2289.67	100.214	1617.1	73.373	46.962	1064.32	993.3	154.74	91.748
No. of events per person-year of therapy/followup*	0.011	0.004	0.011	0.019	0.027	0.030	0.008	0.000	0.000	0.038	0.014	0.032	0.022
Liver Failure													
No. of events	580	78	394	51	27	1	7	2	0	10	9	1	0
No. of events per 1000 subjects	7.7	2.7	17.0	4.4	6.8	3.4	2.5	10.4	0.0	5.2	4.7	2.8	0.0
No. of person years	70584.19	18937.22	38274.21	6491.36	2289.67	100.214	1617.1	73.373	46.962	1064.32	993.3	154.74	91.748
No. of events per person-year of therapy/followup*	0.008	0.004	0.010	0.008	0.012	0.010	0.004	0.027	0.000	0.009	0.009	0.006	0.000

* Person-years of therapy refer to duration of exposure to ODM for subjects in diabetic/receiving drug groups; and refer to followup time (not exposed to ODM, by definition) for those in CAD/Dyslipidemia and diabetic/no drug comparison groups.

Table B-15. Multivariable Cox proportional hazards model of the effect of initial diabetes medication group and other covariates on relative hazard of hypoglycemic Events (entire cohort and by propensity score quintile) [a]

	Entire cohort (n=38887)		Quintile 1 (n=7777)		Quintile 2 (n=7778)		Quintile 3 (n=7777)		Quintile 4 (n=7778)		Quintile 5 (n=7777)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Initial Oral Diabetes Medication Group												
Biguanides (Metformin)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SU	3.231	(2.581, 4.045)	3.113	(1.278, 7.582)	3.286	(1.801, 5.993)	3.095	(1.860, 5.151)	3.567	(2.264, 5.620)	3.222	(2.179, 4.765)
Meglitinides	2.305	(0.995, 5.338)	2.859	(0.893, 9.156)	---	---	---	---	---	---	5.330	(0.723, 39.320)
TZD	1.031	(0.713, 1.491)	1.145	(0.486, 2.699)	1.112	(0.563, 2.194)	1.589	(0.695, 3.633)	0.371	(0.051, 2.702)	---	---
GLP1 Mimetic	1.140	(0.279, 4.654)	0.794	(0.098, 6.425)	11.433	(1.491, 87.666)	---	---	---	---	---	---
DPP4 Inhibitors	0.843	(0.117, 6.076)	---	---	11.98	(1.577, 91.030)	---	---	---	---	---	---
SU + Biguanide	4.434	(3.413, 5.760)	3.985	(1.686, 9.417)	4.706	(2.620, 8.454)	4.122	(2.389, 7.076)	6.305	(3.703, 10.733)	4.516	(2.245, 9.085)
Biguanide + TZD	0.932	(0.578, 1.503)	1.061	(0.426, 2.642)	0.577	(0.193, 1.726)	1.209	(0.353, 4.135)	3.111	(0.936, 10.338)	---	---
SU + TZD	2.871	(1.523, 5.413)	3.997	(1.520, 10.511)	---	---	2.751	(0.365, 20.767)	---	---	8.930	(1.220, 65.340)
SU + TZD + Biguanide	5.968	(3.307, 10.772)	7.013	(2.879, 17.085)	---	---	---	---	---	---	---	---
Propensity score	1.543	(0.935, 2.549)	---	---	---	---	---	---	---	---	---	---
Age	0.987	(0.979, 0.995)	0.996	(0.978, 1.104)	0.979	(0.961, 0.996)	0.994	(0.975, 1.014)	0.979	(0.960, 0.997)	0.987	(0.969, 1.006)
Male	0.802	(0.669, 0.962)	1.080	(0.699, 1.667)	0.771	(0.508, 1.170)	0.901	(0.590, 1.376)	0.686	(0.458, 1.025)	0.733	(0.487, 1.103)
Persistence	0.999	(0.998, 0.999)	0.997	(0.996, 0.998)	0.999	(0.998, 1.000)	0.998	(0.997, 0.999)	0.999	(0.998, 1.000)	0.999	(0.998, 1.000)
Compliance (MPR)	1.109	(0.725, 1.697)	1.430	(0.536, 3.818)	0.684	(0.260, 1.799)	1.571	(0.593, 4.161)	0.837	(0.333, 2.104)	1.477	(0.557, 3.915)
Renal dysfunction	3.089	(2.344, 4.072)	2.299	(1.308, 4.043)	3.749	(2.200, 6.391)	2.707	(1.353, 5.416)	2.575	(1.159, 5.721)	3.779	(1.859, 7.680)
Hepatic dysfunction	1.058	(0.650, 1.722)	0.507	(0.070, 3.666)	0.459	(0.111, 1.899)	2.098	(0.903, 4.878)	0.581	(0.142, 2.370)	1.765	(0.752, 4.146)
No. of diabetes-related physician visits	1.007	(1.001, 1.014)	1.007	(0.985, 1.029)	1.009	(0.994, 1.023)	1.003	(0.984, 1.022)	1.019	(1.003, 1.034)	1.007	(0.990, 1.023)
No. of diabetes education visits	1.131	(1.062, 1.205)	1.293	(1.154, 1.449)	1.211	(0.958, 1.532)	1.099	(0.963, 1.253)	1.036	(0.814, 1.320)	1.102	(0.893, 1.360)
No. of unique drugs	1.057	(1.040, 1.074)	1.102	(1.061, 1.145)	1.068	(1.032, 1.105)	1.04	(0.995, 1.086)	1.044	(1.004, 1.085)	1.034	(1.002, 1.067)

[a] Cox proportional hazard model also adjusted for receipt of the following drugs/classes associated with hypoglycemia: ACE inhibitors, angiotensin receptor blockers, antidepressants, aspirin products (Rx), beta blockers, and fluoroquinolones (none of these drugs/classes had HR estimates that were statistically different from 1.0)

Table B-16. Multivariable Cox proportional hazards model of the effect of initial diabetes medication group and other covariates on relative hazard of liver injury events (entire cohort and by propensity score quintile) [a]

	Entire cohort (n=38887)		Quintile 1 (n=7777)		Quintile 2 (n=7778)		Quintile 3 (n=7777)		Quintile 4 (n=7778)		Quintile 5 (n=7777)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Initial Oral Diabetes Medication Group												
Biguanides (Metformin)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SU	1.512	(1.154, 1.980)	3.208	(1.227, 8.384)	1.563	(0.843, 2.896)	1.583	(0.968, 2.589)	1.095	(0.575, 2.083)	1.768	(0.924, 3.838)
Meglitinides	1.089	(0.386, 3.067)	2.464	(0.613, 9.912)	1.284	(0.165, 10.018)	---	---	---	---	---	---
TZD	0.426	(0.265, 0.685)	0.708	(0.278, 1.804)	0.347	(0.149, 0.809)	0.267	(0.061, 1.171)	0.872	(0.206, 3.699)	0.860	(0.117, 6.345)
GLP1 Mimetic	0.365	(0.049, 2.705)	0.951	(0.117, 7.755)	---	---	---	---	---	---	---	---
DPP4 Inhibitors	---	---	---	---	---	---	---	---	---	---	---	---
SU + Biguanide	1.660	(1.204, 2.288)	2.487	(1.062, 5.827)	1.971	(1.104, 3.519)	1.228	(0.653, 2.309)	1.293	(0.481, 3.479)	1.885	(0.426, 8.344)
Biguanide + TZD	0.548	(0.334, 0.900)	0.427	(0.154, 1.182)	0.714	(0.309, 1.650)	0.599	(0.139, 2.571)	2.630	(0.764, 9.050)	---	---
SU + TZD	0.864	(0.368, 2.028)	1.692	(0.538, 5.316)	---	---	---	---	---	---	---	---
SU + TZD + Biguanide	0.444	(0.107, 1.837)	0.551	(0.109, 2.796)	---	---	---	---	---	---	---	---
Statin use	0.522	(0.410, 0.666)	0.552	(0.298, 1.022)	0.359	(0.205, 0.628)	0.476	(0.289, 0.782)	0.552	(0.305, 0.997)	0.820	(0.456, 1.474)
Propensity score	0.437	(0.238, 0.803)	---	---	---	---	---	---	---	---	---	---
Age	0.965	(0.955, 0.974)	0.958	(0.936, 0.980)	0.959	(0.941, 0.978)	0.959	(0.940, 0.978)	0.977	(0.953, 1.002)	0.953	(0.929, 0.978)
Male	1.344	(1.067, 1.693)	1.616	(0.883, 2.957)	1.395	(0.836, 2.327)	1.205	(0.754, 1.926)	0.965	(0.563, 1.656)	1.630	(0.918, 2.892)
Persistence	0.999	(0.998, 0.999)	0.998	(0.996, 0.999)	0.999	(0.998, 1.000)	0.999	(0.998, 1.000)	0.997	(0.995, 0.998)	0.999	(0.998, 1.000)
Compliance (MPR)	1.287	(0.772, 2.144)	3.665	(1.162, 11.561)	0.542	(0.195, 1.505)	1.024	(0.356, 2.949)	1.623	(0.463, 5.689)	1.387	(0.323, 5.951)
Renal dysfunction	1.985	(1.306, 3.017)	1.370	(0.545, 3.445)	1.215	(0.455, 3.246)	1.180	(0.414, 3.368)	3.499	(1.288, 9.504)	5.047	(1.859, 13.704)
No. of diabetes-related physician visits	1.016	(1.009, 1.024)	1.050	(1.027, 1.073)	1.014	(0.997, 1.032)	1.003	(0.984, 1.021)	1.018	(0.995, 1.043)	1.014	(0.998, 1.031)
No. of diabetes education visits	0.998	(0.854, 1.168)	---	---	0.871	(0.480, 1.580)	1.119	(0.9443, 1.328)	0.943	(0.675, 1.316)	0.910	(0.597, 1.387)
Other Drugs Associated with Liver Injury												
APAP combinations (non-narcotic)	2.741	(1.309, 5.739)	5.332	(0.657, 43.303)	5.080	(0.639, 40.359)	8.720	(2.875, 26.453)	1.533	(0.196, 11.979)	1.034	(0.119, 8.950)
Allopurinol	0.407	(0.166, 0.997)	---	---	0.417	(0.055, 3.193)	0.803	(0.184, 3.505)	0.564	(0.071, 4.455)	0.519	(0.069, 3.932)
Amiodarone	4.158	(1.622, 10.660)	4.579	(0.836, 25.077)	---	---	9.762	(2.106, 45.250)	5.185	(0.559, 48.111)	---	---
Quinidine	30.597	(4.214, 222.15)	112.098	(12.979, 968.199)	---	---	---	---	---	---	---	---
Other Diagnoses Associated with Liver Injury												
Hepatitis C infection	12.045	(7.251, 20.009)	6.579	(0.855, 50.647)	25.107	(9.587, 65.750)	11.107	(4.322, 28.545)	9.439	(1.929, 46.195)	14.706	(3.064, 70.595)
Hepatitis D infection	2.673	(1.077, 6.636)	33.695	(3.830, 296.420)	1.944	(0.203, 18.638)	16.689	(3.977, 70.029)	---	---	4.575	(0.421, 49.696)
EBV infection	13.005	(1.563, 108.195)	---	---	---	---	142.828	(16.630, 1226.66)	---	---	---	---
Jaundice	6.097	(1.699, 21.874)	---	---	86.041	(2.157, 3431.9)	9.902	(1.225, 80.036)	---	---	---	---
Chronic liver disease	10.531	(2.586, 42.875)	---	---	---	---	28.513	(6.263, 129.804)	---	---	---	---
Primary/metastatic neoplasia	6.044	(1.456, 25.095)	---	---	---	---	8.692	(1.246, 60.662)	60.403	(7.659, 476.395)	---	---
Sclerosing cholangitis	6.700	(1.006, 44.635)	---	---	---	---	26.776	(1.440, 497.899)	---	---	---	---
Hypercholesterolemia	1.298	(1.021, 1.649)	1.071	(0.608, 1.887)	1.653	(1.007, 2.714)	1.130	(0.697, 1.830)	1.183	(0.653, 2.141)	1.963	(0.941, 4.092)

[a] Cox proportional hazard models also adjusted for other diagnoses and drugs that have been reported to be associated with liver injury or failure (see Appendix E); HR estimates are not presented for those diagnoses or drugs that had zero events, were not estimable, or were not statistically significant ($p<0.05$ individually).

Table B-17. Multivariable Cox proportional hazards model of the effect of initial diabetes medication group and other covariates on relative hazard of liver failure events (entire cohort and by propensity score quintile)[a]

	Entire cohort (n=38887)		Quintile 1 (n=7777)		Quintile 2 (n=7777)		Quintile 3 (n=7777)		Quintile 4 (n=7778)		Quintile 5 (n=7777)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Initial Oral Diabetes Medication Group												
Biguanides (Metformin)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SU	1.313	(0.887, 1.942)	0.424	(0.068, 2.650)	1.044	(0.367, 2.970)	1.976	(0.965, 4.046)	1.137	(0.500, 2.586)	1.563	(0.626, 3.906)
Meglitinides	0.735	(0.100, 5.409)	0.967	(0.085, 11.025)	---	---	---	---	---	---	---	---
TZD	1.010	(0.590, 1.699)	1.019	(0.338, 3.037)	0.162	(0.032, 0.809)	0.853	(0.194, 3.745)	3.829	(1.424, 10.296)	2.140	(0.442, 10.365)
GLP1 Mimetic	2.084	(0.479, 9.067)	---	---	---	---	36.152	(4.475, 292.047)	---	---	17.803	(2.162, 146.600)
DPP4 Inhibitors	---	---	---	---	---	---	---	---	---	---	---	---
SU + Biguanide	0.947	(0.528, 1.697)	0.811	(0.154, 4.276)	0.994	(0.323, 3.057)	0.390	(0.086, 1.768)	0.948	(0.249, 3.600)	3.775	(0.861, 16.553)
Biguanide + TZD	1.502	(0.841, 2.684)	1.214	(0.378, 3.904)	1.274	(0.425, 3.819)	2.395	(0.671, 8.549)	1.722	(0.223, 13.289)	---	---
SU + TZD	0.721	(0.164, 3.167)	1.503	(0.278, 8.125)	---	---	---	---	---	---	---	---
SU + TZD + Biguanide	---	---	---	---	---	---	---	---	---	---	---	---
Statin use	0.826	(0.602, 1.133)	0.769	(0.345, 1.716)	0.965	(0.418, 2.224)	0.580	(0.288, 1.169)	0.860	(0.419, 1.762)	0.866	(0.409, 1.831)
Propensity score	1.581	(0.656, 3.810)	---	---	---	---	---	---	---	---	---	---
Age	1.001	(0.987, 1.015)	1.002	(0.966, 1.038)	0.990	(0.956, 1.026)	1.021	(0.992, 1.052)	0.984	(0.953, 1.016)	0.997	(0.960, 1.036)
Male	1.131	(0.824, 1.552)	0.964	(0.415, 2.241)	1.346	(0.554, 3.266)	1.479	(0.724, 3.022)	0.767	(0.385, 1.528)	0.802	(0.369, 1.742)
Persistence	0.998	(0.997, 0.999)	0.999	(0.997, 1.001)	0.997	(0.995, 0.999)	0.998	(0.977, 1.000)	0.996	(0.994, 0.998)	0.999	(0.997, 1.001)
Compliance (MPR)	0.696	(0.342, 1.418)	2.863	(0.556, 14.739)	0.151	(0.028, 0.822)	0.551	(0.114, 2.667)	0.679	(0.141, 3.275)	0.729	(0.110, 4.840)
Renal dysfunction	1.902	(1.075, 3.365)	0.988	(0.252, 3.872)	2.833	(0.804, 9.979)	2.538	(0.811, 7.939)	2.967	(0.671, 13.113)	4.122	(0.783, 21.688)
No. of diabetes-related physician visits	1.010	(0.997, 1.023)	0.998	(0.958, 1.039)	1.027	(0.999, 1.055)	1.027	(1.002, 1.054)	1.017	(0.986, 1.050)	0.969	(0.921, 1.020)
No. of diabetes education visits	0.934	(0.708, 1.231)	---	---	0.779	(0.229, 2.654)	0.882	(0.533, 1.457)	0.886	(0.396, 1.984)	0.973	(0.613, 1.543)
Other Drugs Associated with Liver Injury												
Isoniazid	8.302	(1.100, 62.629)	---	---	--	---	---	---	---	---	54.576	(4.936, 603.429)
Methotrexate	4.457	(1.606, 12.371)	---	---	--	---	13.484	(2.838, 64.058)	8.197	(1.726, 38.931)	---	---
Other Diagnoses Associated with Liver Injury												
Hepatitis B infection	7.780	(2.009, 30.132)	---	---	92.178	(16.839, 504.587)	105.79	(13.330, 839.600)	---	---	---	---
Hepatitis C infection	11.739	(5.861, 23.510)	---	---	102.275	(28.251, 370.261)	21.143	(6.868, 65.085)	17.617	(1.910, 162.527)	23.895	(3.643, 156.719)
Hepatitis D infection	2.999	(1.014, 8.866)	16.572	(1.531, 179.330)	1.444	(0.119, 17.591)	34.621	(3.871, 309.671)	---	---	18.473	(1.145, 298.150)
EBV infection	57.696	(11.049, 301.281)	---	---	---	---	286.36	(27.850, 2944.412)	---	---	---	---
Chronic liver disease	14.530	(3.506, 60.214)	---	---	74.045	(7.416, 739.294)	14.284	(1.660, 122.918)	---	---	---	---
Biliary tract problem	2.608	(1.012, 6.724)	15.538	(3.079, 78.423)	4.793	(0.765, 30.027)	0.730	(0.009, 56.412)	---	---	---	---
Hypercholesterolemia	1.733	(1.213, 2.477)	2.025	(0.815, 5.032)	1.679	(0.691, 4.083)	1.462	(0.687, 3.111)	1.613	(0.764, 3.407)	2.202	(0.843, 5.753)

[a] Cox proportional hazard models also adjusted for other diagnoses and drugs that have been reported to be associated with liver injury or failure (see Appendix E); HR estimates are not presented for those diagnoses or drugs that had zero events, were not estimable, or were not statistically significant ($p<0.05$ individually).

Table B-18. Description of baseline hemoglobin A1c values and change scores by initial oral diabetes medication group, unadjusted and adjusted [a]

		Baseline H-A1c Value			Change from Baseline H-A1c to Lowest H-A1c				Change from Baseline H-A1c to Last H-A1c			
					Unadjusted			Adjusted	Unadjusted			Adjusted
	N	Mean	Median	Range	Mean	Median	Range	Mean [a]	Mean	Median	Range	Mean [a]
Initial Oral Diabetes Medication Group												
Biguanides (Metformin)	7981	7.760	7.2	4.3 to 18.0	-1.142	-0.7	-11.7 to 7.0	-1.359	-0.947	-0.5	-11.7 to 7.0	-1.161
SU	2210	8.399	7.8	4.5 to 17.9	-1.666	-1.2	-11.0 to 11.8	-1.399	-1.364	-0.9	-10.5 to 11.8	-1.127
Meglitinides	107	7.548	7.0	5.2 to 14.4	-0.893	-0.4	-8.3 to 1.2	-1.527	-0.779	-0.4	-8.3 to 2.4	-1.331
TZD	1994	7.333	6.9	4.6 to 17.7	-0.909	-0.5	-11.2 to 14.5	-1.479	-0.728	-0.4	-11.2 to 14.5	-1.282
GLP1 Mimetic	76	7.013	6.6	5.5 to 11.3	-0.63	-0.5	-4.8 to 1.8	-1.511	-0.537	-0.5	-4.8 to 1.8	-1.298
DPP4 Inhibitors	51	7.851	7.2	6.0 to 14.2	-1.208	-0.7	-7.4 to 1.4	-1.654	-1.192	-0.7	-7.4 to 1.4	-1.48
SU + Biguanide	1214	9.641	9.4	5.1 to 20.0	-2.062	-2.3	-12.7 to 4.4	-1.448	-2.338	-2.05	-12.7 to 4.5	-1.209
Biguanide + TZD	1205	8.894	8.5	4.9 to 18.6	-2.199	-1.6	-12.0 to 5.8	-1.619	-2.083	-1.5	-12.0 to 6.9	-1.496
SU + TZD	186	9.652	9.7	5.1 to 16.5	-2.705	-2.5	-8.2 to 3.6	-1.599	-2.582	-2.3	-8.0 to 4.5	-1.437
SU + TZD + Biguanide	137	9.647	9.0	5.5 to 16.2	-2.602	-1.8	-9.4 to 1.5	-1.645	-2.469	-1.7	-8.9 to 1.7	-1.48

[a] Means adjusted for multiple propensity scores, age, gender, persistence, compliance (MPR), time from first diagnosis to first Rx, baseline A1c value, renal dysfuntion, hepatic dysfuntion, number of diabetes-related physician visits, and number of diabetes education visits.

Note: this table corresponds to Table 10 of the primary analyses.

Table B-19. Multivariable generalized linear model of the effect of initial diabetes medication group and other covariates on hemoglobin A1c change from baseline to lowest[a]

	Entire cohort (n=15161)	
	β	p-value
Initial Oral Diabetes Medication Group		
Biguanides (Metformin)	Ref	Ref
SU	-0.0399	0.1234
Meglitinides	-0.1683	0.0956
TZD	-0.1201	<0.0001
GLP1 Mimetics	-0.1515	0.219
DPP4 Inhibitors	-0.2948	0.0438
SU + Biguanide	-0.0890	0.0078
Biguanide + TZD	-0.2600	<0.0001
SU + TZD	-0.2395	0.0029
SU + TZD + Biguanide	-0.2864	0.0025
Age	-0.0005	0.5429
Male	-0.0873	<0.0001
Persistence	-0.0006	<0.0001
Compliance (MPR)	-0.7422	<0.0001
Time from Dx to Rx	0.0003	<0.0001
Baseline A1c value	-0.7700	<0.0001
Renal dysfunction	-0.1230	0.0022
Hepatic dysfunction	0.0045	0.9191
No. of diabetes-related physician visits	-0.0072	<0.0001
No. of diabetes education visits	-0.0759	<0.0001

[a] Adjusted for multiple propensity scores (estimates not reported in table).

Note: this table corresponds to Table 11 of the primary analyses.

Table B-20. Multivariable generalized linear model of the effect of initial diabetes medication group and other covariates on hemoglobin A1c change from baseline to last[a]

	Entire cohort (n=15161)	
	β	p-value
Initial Oral Diabetes Medication Group		
Biguanides (Metformin)	Ref	Ref
SU	0.0349	0.2219
Meglitinides	-0.1695	0.1286
TZD	-0.1208	0.0002
GLP1 Mimetic	-0.1369	0.3147
DPP4 Inhibitors	-0.3184	0.0486
SU + Biguanide	-0.0476	0.1983
Biguanide + TZD	-0.3342	<0.0001
SU + TZD	-0.2757	0.0019
SU + TZD + Biguanide	-0.3181	0.0023
Age	-0.0019	0.0464
Male	-0.0584	0.0026
Persistence	-0.0002	<0.0001
Compliance (MPR)	-0.7245	<0.0001
Time from Dx to Rx	0.0003	<0.0001
Baseline A1c value	-0.7587	<0.0001
Renal dysfunction	-0.1072	0.0156
Hepatic dysfunction	0.1341	0.0062
No. of diabetes-related physician visits	-0.0027	0.0046
No. of diabetes education visits	-0.0805	<0.0001

[a] Adjusted for multiple propensity scores (estimates not reported in table).

Note: this table corresponds to Table 12 of the primary analyses.

Table B-21. Multivariable Cox proportional hazards model of the effect of initial diabetes medication group and other covariates on relative hazard of hypoglycemic events[a]

	Entire cohort (n=38887)	
	HR	(95% CI)
Initial Oral Diabetes Medication Group		
Biguanides (Metformin)	Ref	Ref
SU	3.353	(2.659, 4.228)
Meglitinides	2.134	(0.914, 4.981)
TZD	0.979	(0.667, 1.436)
GLP1 Mimetic	0.506	(0.108, 2.374)
DPP4 Inhibitors	0.558	(0.075, 4.181)
SU + Biguanide	4.613	(3.529, 6.030)
Biguanide + TZD	0.896	(0.550, 1.458)
SU + TZD	2.821	(1.485, 5.357)
SU + TZD + Biguanide	5.471	(2.828, 10.583)
Age	0.987	(0.978, 0.996)
Male	0.834	(0.694, 1.003)
Persistence	0.999	(0.998, 0.999)
Compliance (MPR)	1.107	(0.722, 1.696)
Renal dysfunction	3.206	(2.415, 4.255)
Hepatic dysfunction	1.074	(0.659, 1.750)
No. of diabetes-related physician visits	1.015	(0.975, 1.057)
No. of diabetes education visits	1.136	(1.066, 1.211)
No. of unique drugs	1.058	(1.041, 1.076)

[a] Cox proportional hazard model also adjusted for multiple propensity scores and receipt of the following drugs/classes associated with hypoglycemia: ACE inhibitors, angiotensin receptor blockers, antidepressants, aspirin products (Rx), beta blockers, and fluoroquinolones (none of these drugs/classes had HR esimates that were statistically different from 1.0)

Note: this table corresponds to Table 15 of the primary analyses.

Table B-22. Multivariable Cox proportional hazards model of the effect of initial diabetes medication group and other covariates on relative hazard of liver injury events[a]

	Entire cohort (n=38887)	
	HR	(95% CI)
Initial Oral Diabetes Medication Group		
Biguanides (Metformin)	Ref	Ref
SU	1.365	(1.033, 1.802)
Meglitinides	1.365	(0.487, 3.823)
TZD	0.501	(0.308, 0.816)
GLP1 Mimetic	0.507	(0.064, 4.000)
DPP4 Inhibitors	---	---
SU + Biguanide	1.568	(1.138, 2.160)
Biguanide + TZD	0.762	(0.460, 1.262)
SU + TZD	1.294	(0.543, 3.081)
SU + TZD + Biguanide	0.713	(0.158, 3.229)
Statin use	0.559	(0.438, 0.713)
Age	0.963	(0.953, 0.972)
Male	1.242	(0.980, 1.574)
Persistence	0.999	(0.998, 0.999)
Compliance (MPR)	1.409	(0.851, 2.334)
Renal dysfunction	1.751	(1.139, 2.691)
No. of diabetes-related physician visits	1.048	(1.004, 1.094)
No. of diabetes education visits	1.009	(0.859, 1.185)
Other Drugs Associated with Liver Injury		
APAP combinations (non-narcotic)	2.763	(1.312, 5.820)
Allopurinol	0.415	(0.168, 1.027)
Amiodarone	4.467	(1.739, 11.478)
Quinidine	39.638	(5.409, 290.451)
Other Diagnoses Associated with Liver Injury		
Hepatitis C infection	11.477	(6.897, 19.099)
Hepatitis D infection	2.927	(1.167, 7.337)
EBV infection	11.68	(1.392, 98.00)
Jaundice	5.866	(1.579, 21.797)
Chronic liver disease	9.508	(2.324, 38.897)
Primary/metastatic neoplasia	5.148	(1.197, 22.142)
Sclerosing cholangitis	5.801	(0.852, 39.518)
Hypercholesterolemia	1.383	(1.088, 1.757)

[a] Cox proportional hazard model also adjusted for multiple propensity scores and other diagnoses and drugs that have been reported to be associated with liver injury or failure (see Appendix E); HR estimates are not presented for those diagnoses or drugs that had zero events, were not estimable, or were not statistically significant ($p<0.05$ individually).

Note: this table corresponds to Table 16 of the primary analyses.

Table B-23. Multivariable Cox proportional hazards model of the effect of initial diabetes medication group and other covariates on relative hazard of liver failure events[a]

	Entire cohort (n=38886)	
	HR	(95% CI)
Initial Oral Diabetes Medication Group		
Biguanides (Metformin)	Ref	Ref
SU	1.192	(0.794, 1.791)
Meglitinides	0.782	(0.106, 5.778)
TZD	1.068	(0.616, 1.852)
GLP1 Mimetic	2.429	(0.516, 11.427)
DPP4 Inhibitors	---	---
SU + Biguanide	0.995	(0.554, 1.790)
Biguanide + TZD	1.790	(0.989, 3.239)
SU + TZD	0.963	(0.217, 4.270)
SU + TZD + Biguanide	---	---
Statin use	0.835	(0.608, 1.148)
Age	0.993	(0.978, 1.008)
Male	1.082	(0.783, 1.494)
Persistence	0.998	(0.997, 0.999)
Compliance (MPR)	0.725	(0.355, 1.477)
Renal dysfunction	1.683	(0.934, 3.032)
No. of diabetes-related physician visits	0.981	(0.911, 1.057)
No. of diabetes education visits	0.948	(0.720, 1.247)
Other Drugs Associated with Liver Injury		
Isoniazid	7.147	(0.893, 57.195)
Methotrexate	4.262	(1.529, 11.879)
Other Diagnoses Associated with Liver Injury		
Hepatitis B infection	8.402	(2.230, 31.649)
Hepatitis C infection	11.815	(5.881, 23.737)
Hepatitis D infection	3.310	(1.135, 9.655)
EBV infection	48.496	(9.289, 253.191)
Chronic liver disease	12.357	(2.950, 51.757)
Biliary tract problem	2.550	(0.981, 6.628)
Hypercholesterolemia	1.854	(1.299, 2.646)

[a] Cox proportional hazard model also adjusted for multiple propensity scores and other diagnoses and drugs that have been reported to be associated with liver injury or failure (see Appendix E); HR estimates are not presented for those diagnoses or drugs that had zero events, were not estimable, or were not statistically significant ($p<0.05$ individually).

Note: this table corresponds to Table 17 of the primary analyses.

Table B-24. Demographic characteristics of the DARTNet Diabetes Replication Cohort (N=35,215)

	TOTAL		Year of Index Diabetes Diagnosis															
			2000		2001		2002		2003		2004		2005		2006		2007		2008	
	N	(%)							N	(%)	N	(%)	N	(%)					N	(%)
Total N	35,215	(100%)	980	(100%)	1,935	(100%)	2,834	(100%)	3,844	(100%)	3,461	(100%)	3,726	(100%)	4,683	(100%)	5,285	(100%)	8,467	(100%)
Age																				
1-24 yrs	697	(2.0%)	5	(<1%)	7	(<1%)	28	(<1%)	66	(1.7%)	107	(3.1%)	90	(2.4%)	122	(2.6%)	160	(3.0%)	112	(1.3%)
25-34 yrs	1,850	(5.3%)	32	(3.3%)	70	(3.6%)	122	(4.3%)	254	(6.6%)	281	(8.1%)	214	(5.7%)	270	(5.8%)	303	(5.7%)	304	(3.6%)
35-44 yrs	4,070	(11.6%)	87	(8.9%)	207	(10.7%)	348	(12.3%)	514	(13.4%)	477	(13.8%)	473	(12.7%)	544	(11.6%)	643	(12.2%)	777	(9.2%)
45-54 yrs	7,732	(22.0%)	228	(23.3%)	475	(24.5%)	704	(24.8%)	947	(24.6%)	844	(24.4%)	845	(22.7%)	988	(21.1%)	1,126	(21.3%)	1,575	(18.6%)
55-64 yrs	9,298	(26.4%)	309	(31.5%)	546	(28.2%)	786	(27.7%)	1,019	(26.5%)	887	(25.6%)	929	(24.9%)	1,232	(26.3%)	1,308	(24.7%)	2,282	(27.0%)
65-74 yrs	7,341	(20.8%)	223	(22.8%)	451	(23.3%)	568	(20.0%)	685	(17.8%)	576	(16.6%)	784	(21.0%)	963	(20.6%)	1,083	(20.5%)	2,008	(23.7%)
75-84 yrs	3,478	(9.9%)	80	(8.2%)	139	(7.2%)	245	(8.6%)	299	(7.8%)	241	(7.0%)	334	(9.0%)	469	(10.0%)	512	(9.7%)	1,159	(13.7%)
Mean	57.24		58.55		57.99		56.82		55.44		53.97		56.31		56.90		56.73		60.12	
Median	58.00		59.00		58.00		57.00		56.00		55.00		57.00		58.00		58.00		61.00	
Range	3 - 95		12 - 87		7 - 88		0 - 89		3 - 90		0 - 91		1 - 92		0 - 93		0 - 94		0 - 95	
Gender																				
Male	16,983	(48.2%)	540	(55.1%)	1,052	(54.4%)	1,459	(51.5%)	1,821	(47.4%)	1,568	(45.3%)	1,781	(47.8%)	2,220	(47.4%)	2,443	(46.2%)	4,099	(48.4%)
Chronic Disease Indicator																				
Mean	4.11		4.72		4.14		4.18		4.02		3.92		4.10		4.08		3.96		4.22	
Median	4.00		4.00		4.00		4.00		4.00		4.00		4.00		4.00		4.00		4.00	
Range	0 - 18		0 - 14		0 - 14		0 - 15		0 - 15		0 - 15		0 - 14		0 - 16		0 - 17		0 - 18	
Time from Diabetes Diagnosis to time of first Rx (days)																				
Mean	268.09		4.72		4.14		4.18		4.02		3.92		4.10		4.08		3.96		4.22	
Median	0.00		4.00		4.00		4.00		4.00		4.00		4.00		4.00		4.00		4.00	
Range	0 - 2,994		0 - 2,994		0 - 2,883		0 - 2,475		0 - 2,127		0 - 1,711		0 - 1,400		0 -1,032		0 - 682		0 - 308	
Initial Drug Dispensed Following Diagnosis																				
No diabetes drugs ever dispensed	7,854	(22.3%)	179	(18.3%)	389	(20.1%)	534	(18.8%)	1,188	(30.9%)	687	(19.8%)	835	(22.4%)	1,027	(21.9%)	1,164	(22.0%)	1,851	(21.9%)
Insulin (alone or with orals)	7,272	(20.7%)	164	(16.7%)	356	(18.4%)	484	(17.1%)	673	(17.5%)	904	(26.1%)	843	(22.6%)	1,084	(23.1%)	1,204	(22.8%)	1,560	(18.4%)
Oral hypoglycemic drug prescribed	20,089	(57.0%)	637	(65.0%)	1,190	(61.5%)	1,816	(64.1%)	1,983	(51.6%)	1,870	(54.0%)	2,048	(55.0%)	2,572	(54.9%)	2,917	(55.2%)	5,056	(59.7%)
Monotherapy	15,569	(44.2%)	554	(56.5%)	994	(51.4%)	1,450	(51.2%)	1,594	(41.5%)	1,436	(41.5%)	1,621	(43.5%)	1,933	(41.3%)	2,133	(40.4%)	3,854	(45.5%)
Combotherapy	4,520	(12.8%)	83	(8.5%)	196	(10.1%)	366	(12.9%)	389	(10.1%)	434	(12.5%)	427	(11.5%)	639	(13.6%)	784	(14.8%)	1,202	(14.2%)
Fixed-dose combo	1,529	(4.3%)	27	(2.8%)	89	(4.6%)	192	(6.8%)	168	(4.4%)	172	(5.0%)	144	(3.9%)	203	(4.3%)	198	(3.7%)	336	(4.0%)

Note: this table corresponds to Table 1 of the primary analyses (but applies now to subjects from the DARTNet population, using EHR-derived data)

Table B-25. Time to first regimen change for monotherapy and combination therapy groups, in the DARTNet Diabetes Replication Cohort

			Time to First Regimen Change (Days)		
		N	Mean	Median	Range
Monotherapy					
a	Biguanide	8467	199.75	30.0	1.0 - 2842.0
b	SU	3864	254.78	30.0	1.0 - 2976.0
c	TZD	1915	219.03	30.0	1.0 - 2698.0
d	Meglitinide [a,b,c,f]	251	257.37	81.0	3.0 - 2064.0
e	GLP-1 Mimetic [a,b,c,f]	359	165.74	88.0	2.0 - 981.0
f	DPP-IV Inhibitor	371	109.70	36.0	1.0 - 639.0
g	Alpha-glucosidase Inhibitor [a,b,c,f]	19	232.58	62.0	28.0 - 1450.0
h	Amylin Analogue [a,b,c,f]	22	172.09	79.5	1.0 - 617.0
Combination Therapy					
i	SU + Biguanide	2035	214.99	30.0	1.0 - 3745.0
j	Biguanide + TZD	1263	151.69	30.0	1.0 - 1773.0
k	SU + TZD	353	184.35	30.0	1.0 - 1904.0
l	SU + TZD + Biguanide	385	119.60	30.0	1.0 - 19.52

a-h: Based on pair-wise Wilcoxon nonparametric tests, median time to first regimen change is statistically different across specified monotherapy groups at $p < 0.05$ (adjusted for multiple comparisons). For example, Amylin Analogue group (group h) is statistic

i-l: Based on pair-wise Wilcoxon nonparametric tests, median time to first regimen change is not statistically different across specified combination therapy groups ($p>0.05$)

Note: this table corresponds to Table 7 of the primary analyses (but applies now to subjects from the DARTNet population, using EHR-derived data)

Table B-26. Description of baseline hemoglobin A1c values and change scores by initial oral diabetes medication group (unadjusted), in the DARTNet Diabetes Replication Cohort

		Baseline H-A1c Value			Change from Baseline H-A1c to Lowest H-A1c (Unadjusted)			Change from Baseline H-A1c to Last H-A1c (Unadjusted)		
	N	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Initial Oral Diabetes Medication Group										
Biguanides (Metformin)	428	7.30		3.6 to 16.7	-0.770	-0.5	-9.6 to 7.4	-0.496	-0.3	-9.4 to 7.4
SU	179	7.48		4.0 to 16.1	-0.805	-0.5	-8.0 to 6.5	-0.360	-0.2	-7.7 to 7.0
Meglitinides	115	7.45		5.2 to 14.0	-0.571	-0.3	-6.7 to 2.7	-0.232	0.0	-6.0 to 3.4
TZD	878	7.38		4.4 to 17.6	-0.787	-0.5	-11.2 to 6.7	-0.431	-0.3	-11.2 to 6.7
GLP1 Mimetic	244	7.30		4.7 to 14.0	-0.527	-0.4	-7.8 to 5.4	-0.037	-0.1	-7.8 to 6.8
DPP4 Inhibitors	263	7.43		5.0 to 14.3	-0.660	-0.5	-6.6 to 6.5	-0.407	-0.3	-6.6 to 6.5
SU + Biguanide	798	7.98		4.2 to 15.8	-0.991	-0.5	-9.5 to 3.5	-0.600	-0.2	-8.3 to 4.7
Biguanide + TZD	601	7.75		4.9 to 15.5	-1.025	-0.5	-9.2 to 5.9	-0.759	-0.3	-8.9 to 5.9
SU + TZD	140	7.66		5.1 to 14.0	-0.684	-0.4	-5.7 to 4.9	-0.274	-0.2	-5.3 to 4.9
SU + TZD + Biguanide	110	8.25		4.7 to 16.0	-0.962	-0.4	-9.7 to 5.3	-0.619	-0.3	-9.2 to 5.3

Note: this table corresponds to Table 10 of the primary analyses (but applies now to subjects from the DARTNet population, using EHR-derived data)

Table B-27. Crude incidence rates of hypoglycemia, liver injury and liver failure events in the DARTNet Diabetes Replication Cohort

			Initial Oral Diabetes Medication Group									
	TOTAL	Diabetic/No Drug Comparison Group	Biguanides	SU	Meglitinides	TZD	GLP1 Mimetic	DPP4 Inhibitors	SU + Biguanide	Biguanide + TZD	SU + TZD	SU + TZD + Biguanide
Total N	27,158	7,854	8,467	3,864	251	1,915	359	371	2,035	1,263	353	385
Number of Person-Years	34,949.88	24,128.65	4,561.53	2,669.00	176.08	1,139.14	161.89	109.92	1,176.18	510.34	174.40	120.51
Hypoglycemia												
No. of events	206	135	20	20	11	9	0	0	6	1	3	1
No. of events per 1000 subjects	7.6	17.2	2.4	5.2	43.8	4.7	0	0	2.9	0.8	8.5	2.6
No. of events per person-year of therapy/followup*	0.0059	0.0056	0.0044	0.0075	0.0625	0.0079	0	0	0.0051	0.0020	0.0172	0.0083
Liver Injury												
No. of events	743	449	132	97	1	6	4	3	34	11	2	3
No. of events per 1000 subjects	27.4	57.2	15.6	25.1	4.0	3.1	11.1	8.1	16.7	8.7	5.7	5.2
No. of events per person-year of therapy/followup*	0.0213	0.0186	0.0289	0.0363	0.0057	0.0053	0.0247	0.0273	0.0289	0.0216	0.0115	0.0166
Liver Failure												
No. of events	177	133	18	13	0	3	0	1	6	3	0	0
No. of events per 1000 subjects	6.5	16.9	2.1	3.4	0	1.6	0	2.7	2.9	2.4	0	0
No. of events per person-year of therapy/followup*	0.0051	0.0055	0.0039	0.0049	0	0.0026	0	0.0091	0.0051	0.0059	0	0

* Person-years of therapy refer to duration of exposure to ODM for subjects in diabetic/receiving drug groups; and refer to followup time (not exposed to ODM, by definition) for those in diabetic/no drug comparison group.

Note: this table corresponds to Table 14a of the primary analyses (but applies now to subjects from the DARTNet population, using EHR-derived data).

XIV. Appendix B Figures

Figure B-1. CONSORT chart

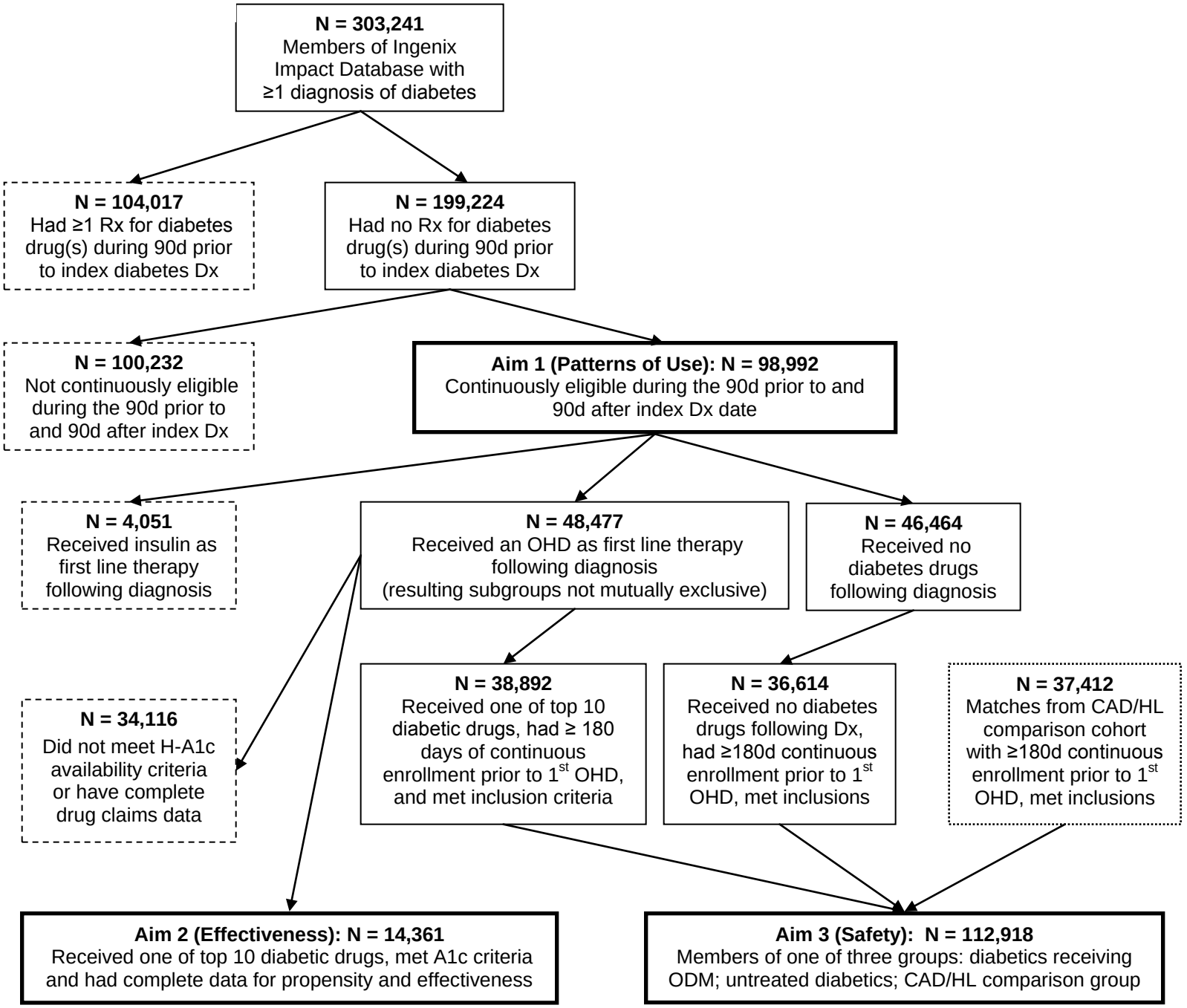

Figure B-2. Time to first regimen change for diabetic subjects starting on ODM combination therapy

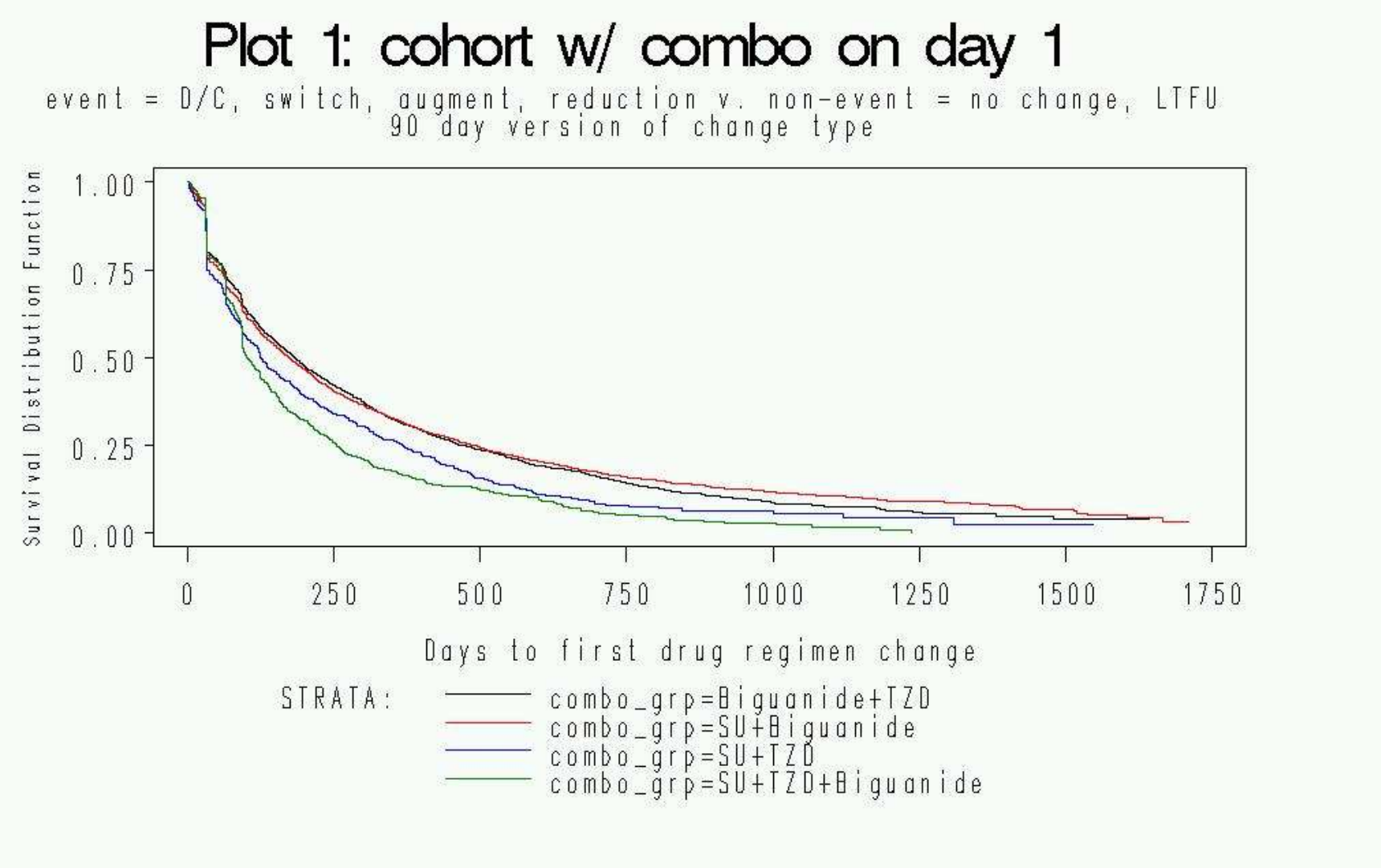

Figure B-3. Time to first regimen change for diabetic subjects starting on ODM monotherapy

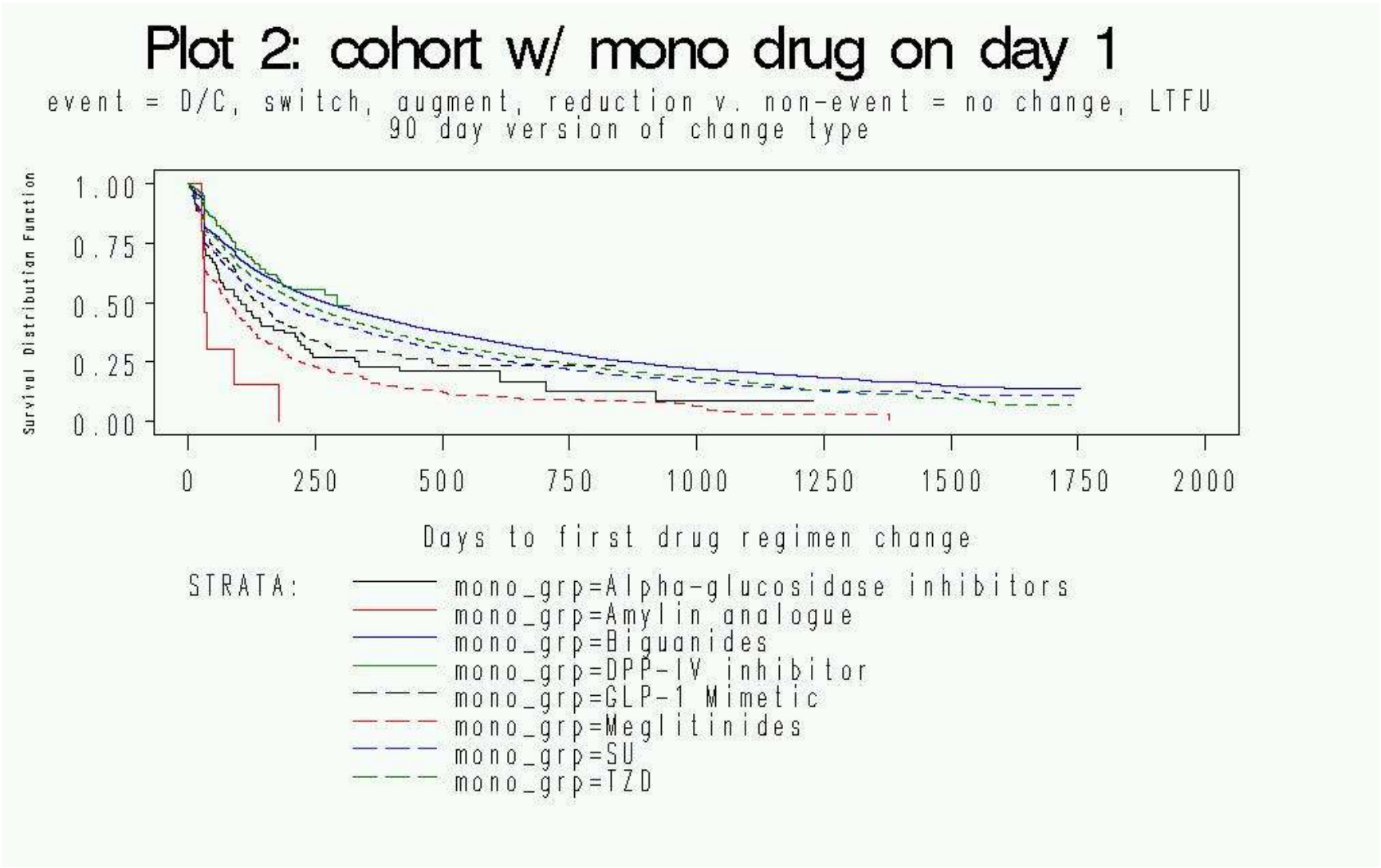

Figure B-4. Time to first regimen change: SU + biguanide combination therapy

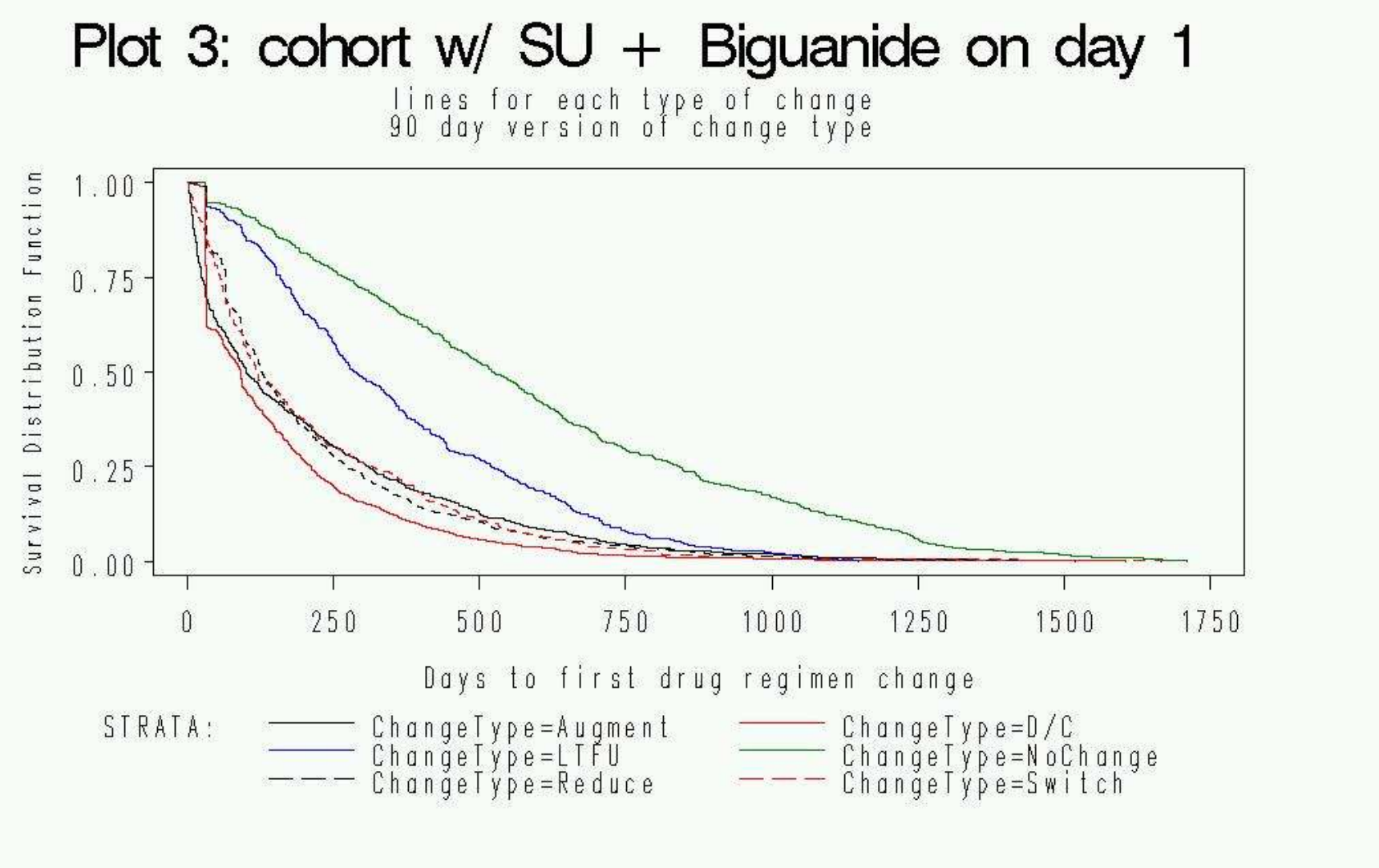

Figure B-5. Time to first regimen change: biguanide + TZD combination therapy

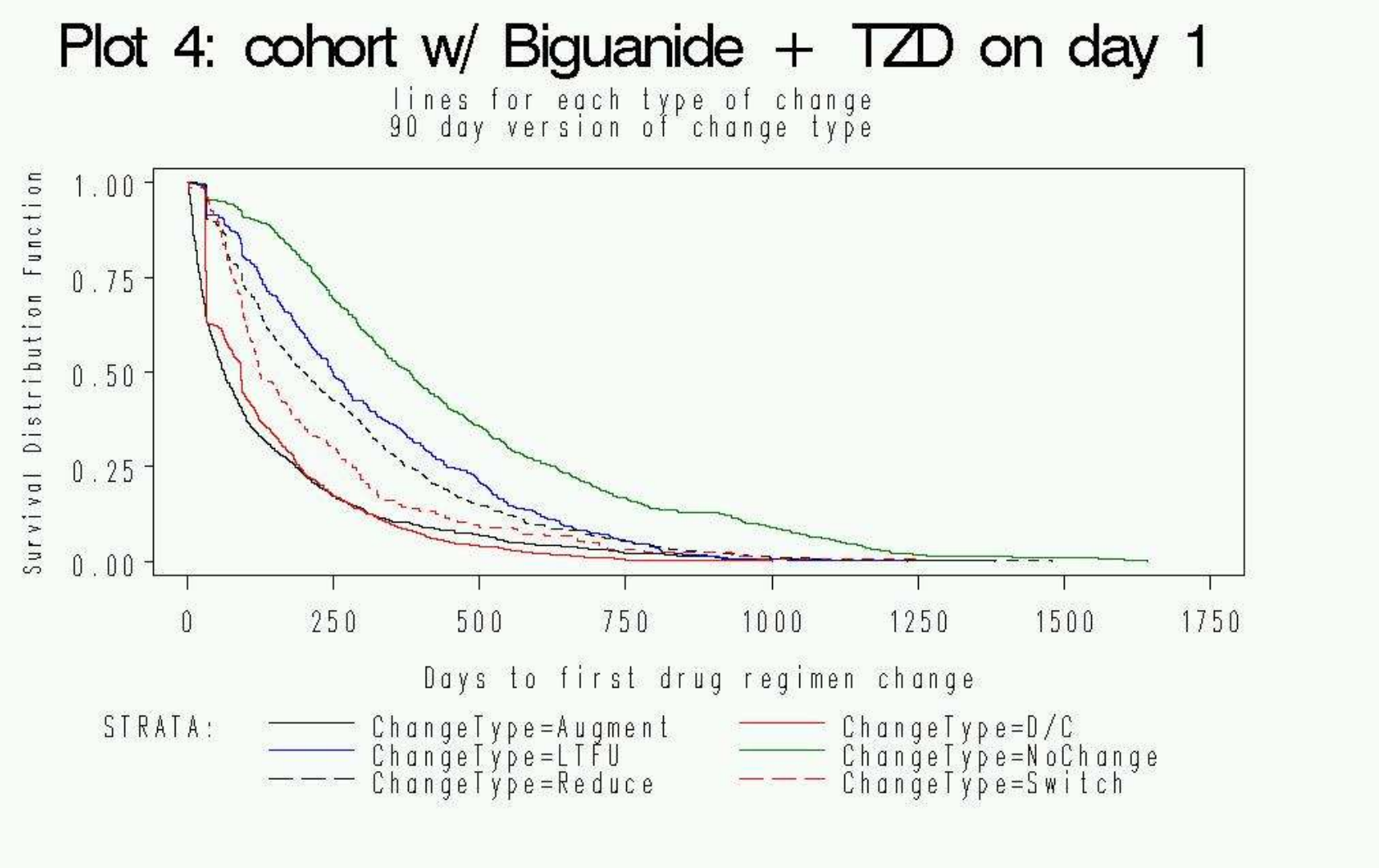

Figure B-6. Time to first regimen change: SU + TZD combination therapy

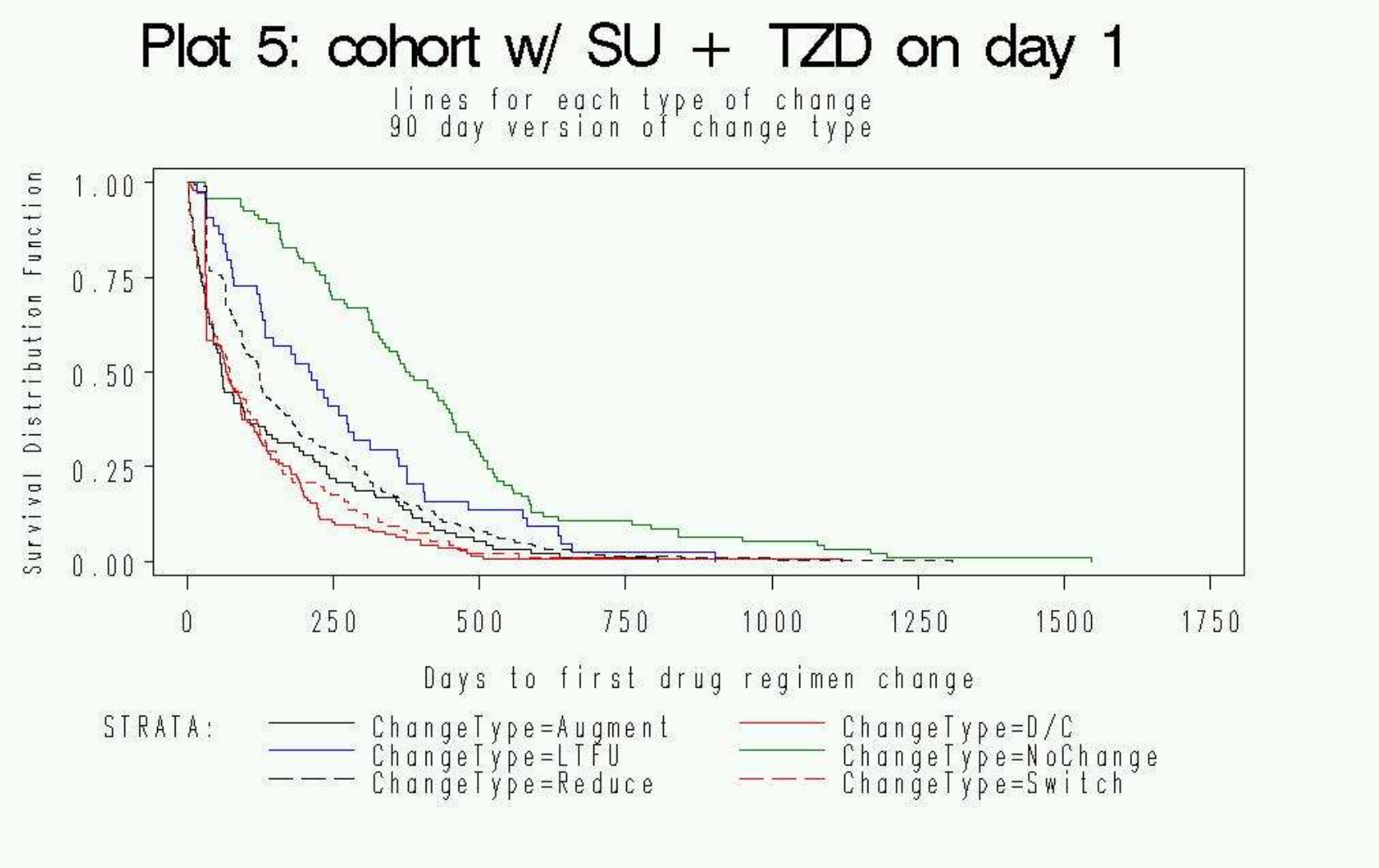

Figure B-7. Time to first regimen change: SU + TZD + biguanide combination therapy

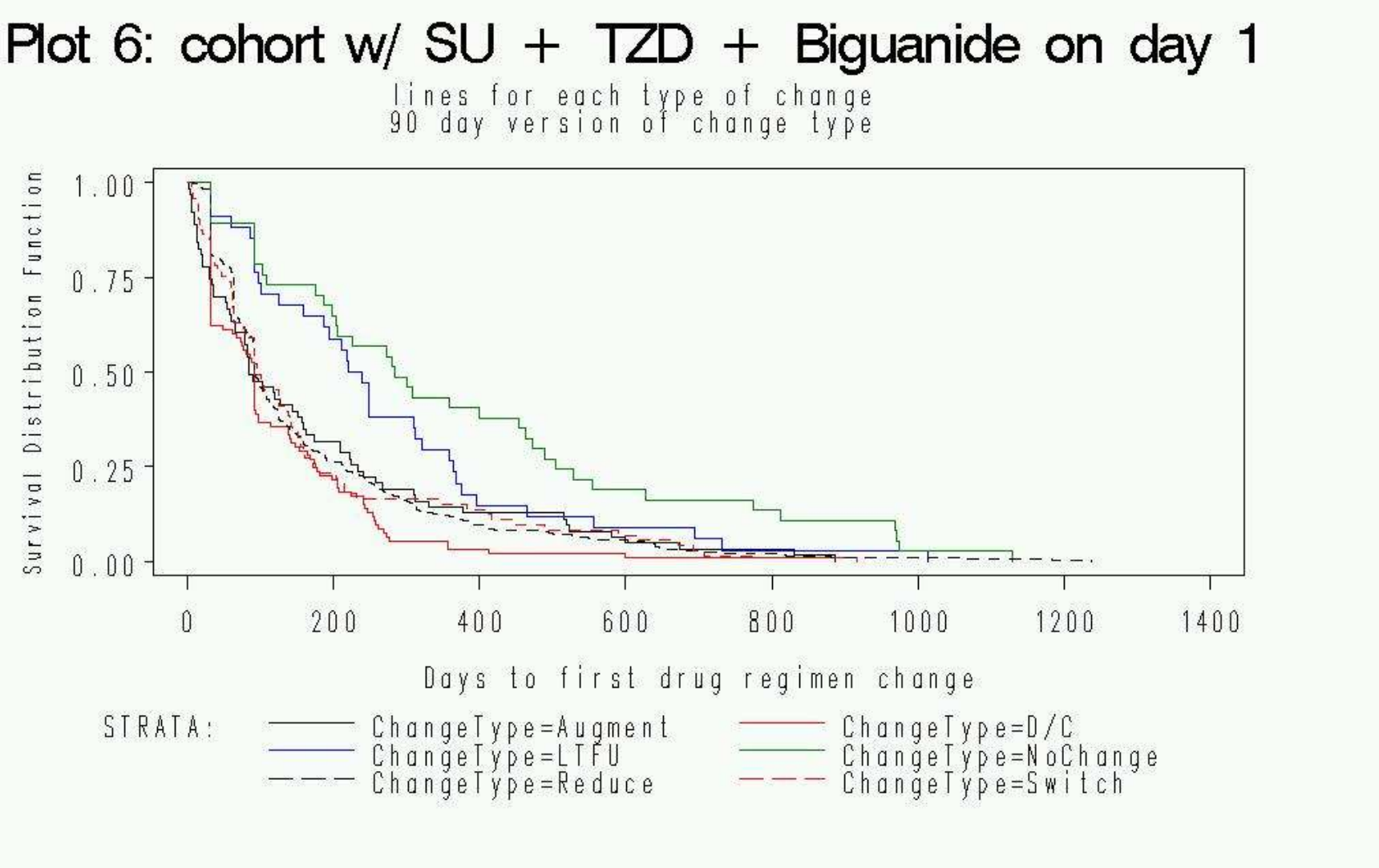

Figure B-8. Time to first regimen change: biguanide monotherapy

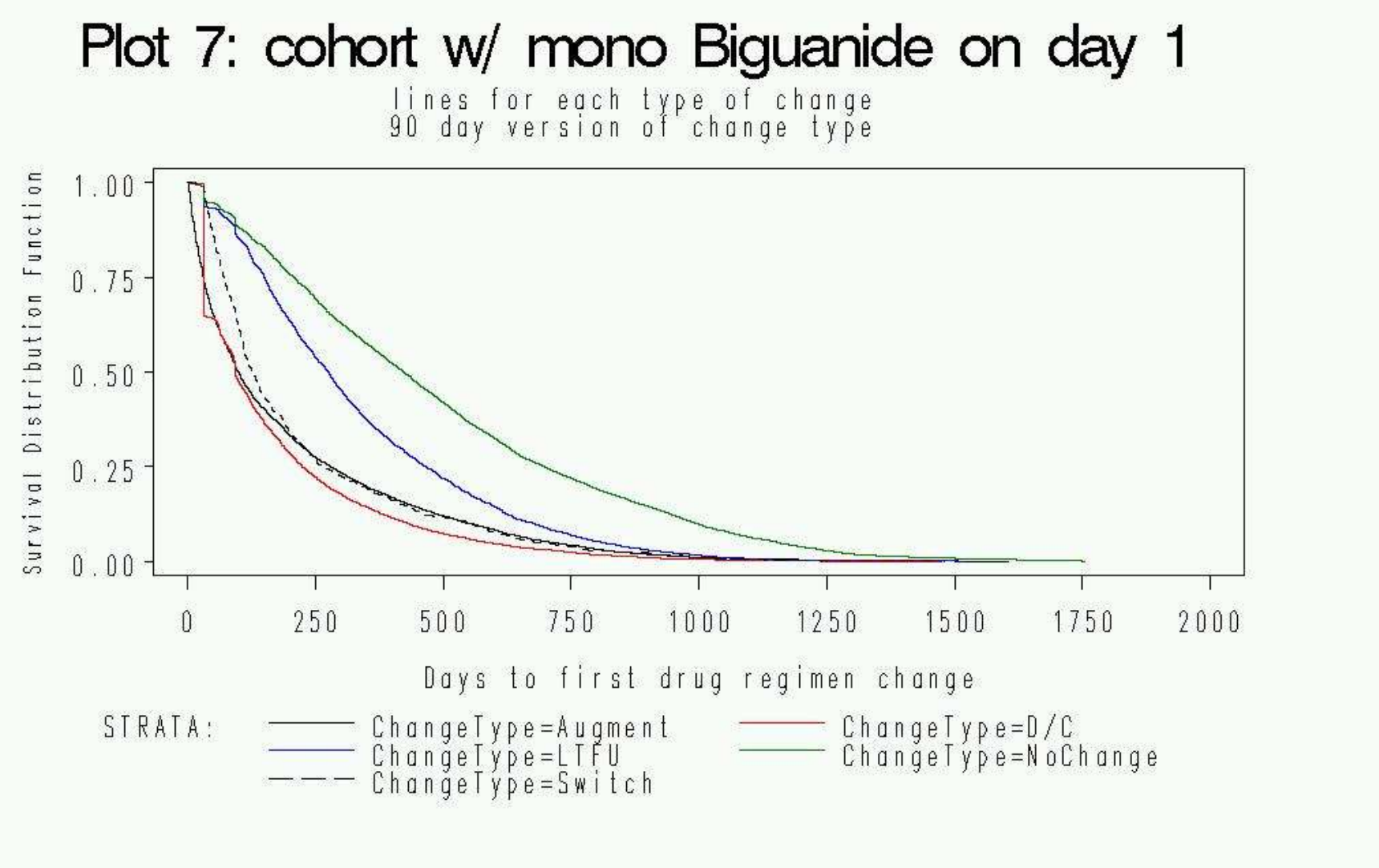

Figure B-9.Time to first regimen change: SU monotherapy

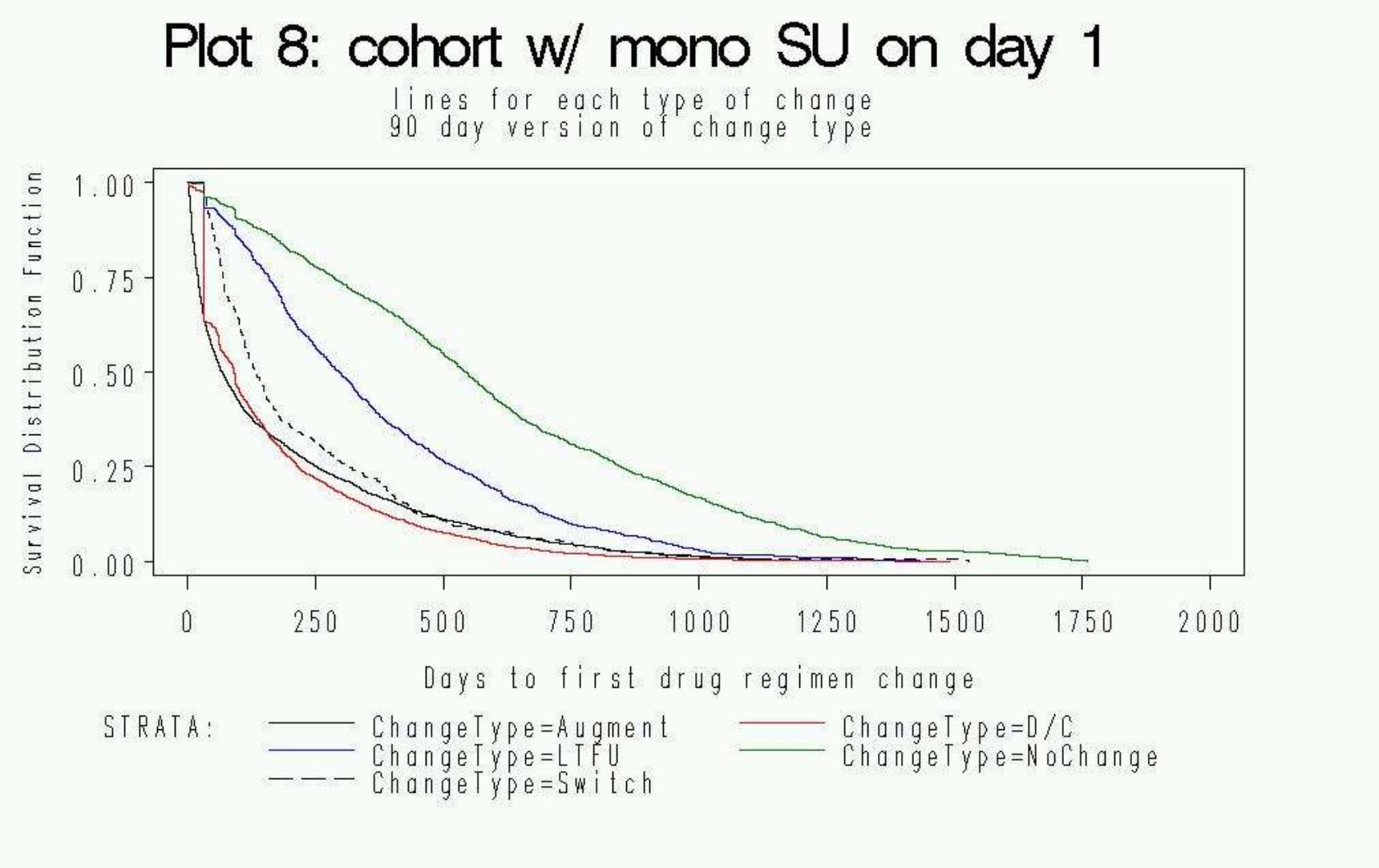

Figure B-10.Time to first regimen change: TZD monotherapy

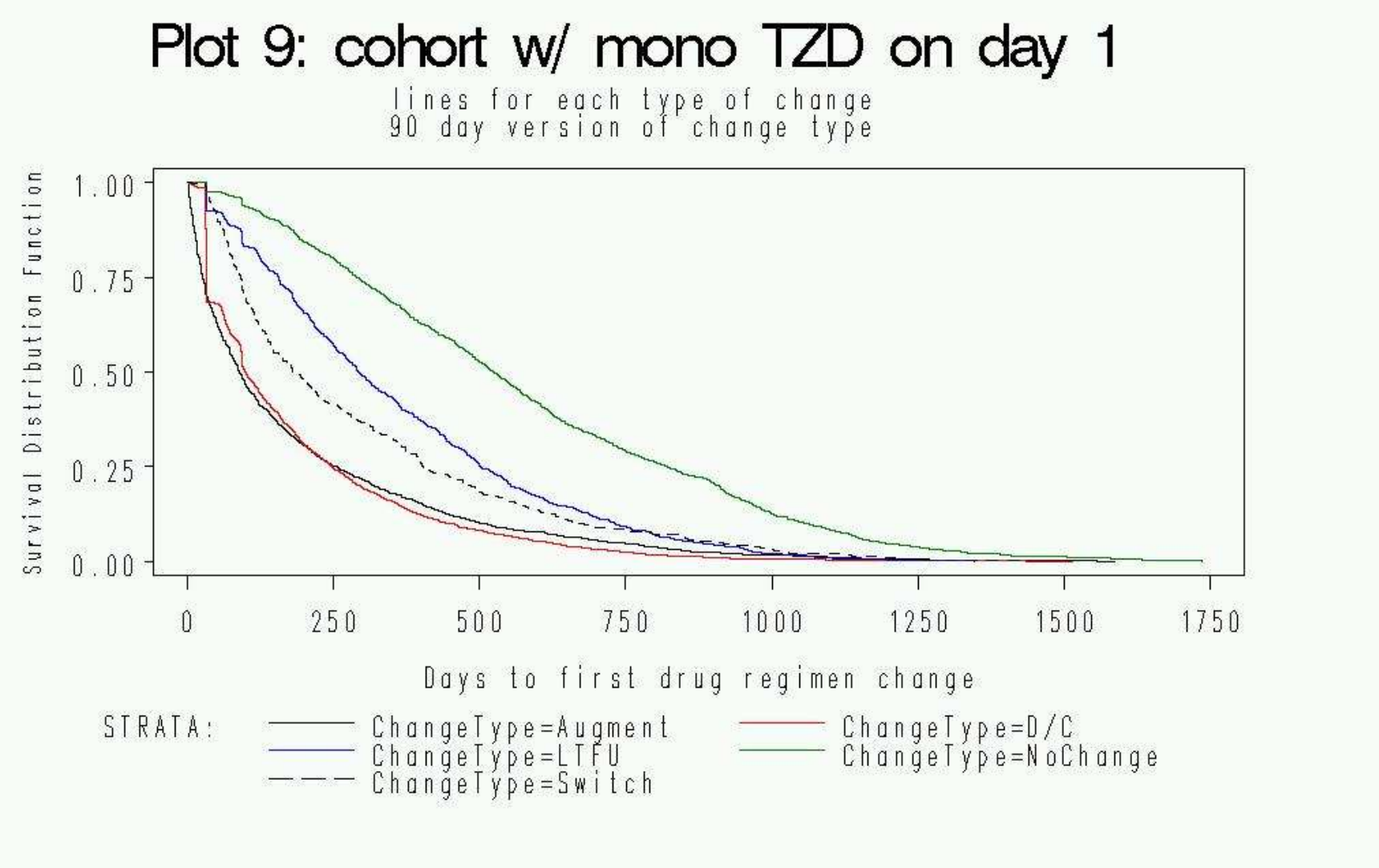

Figure B-11.Time to first regimen change: meglitinide monotherapy

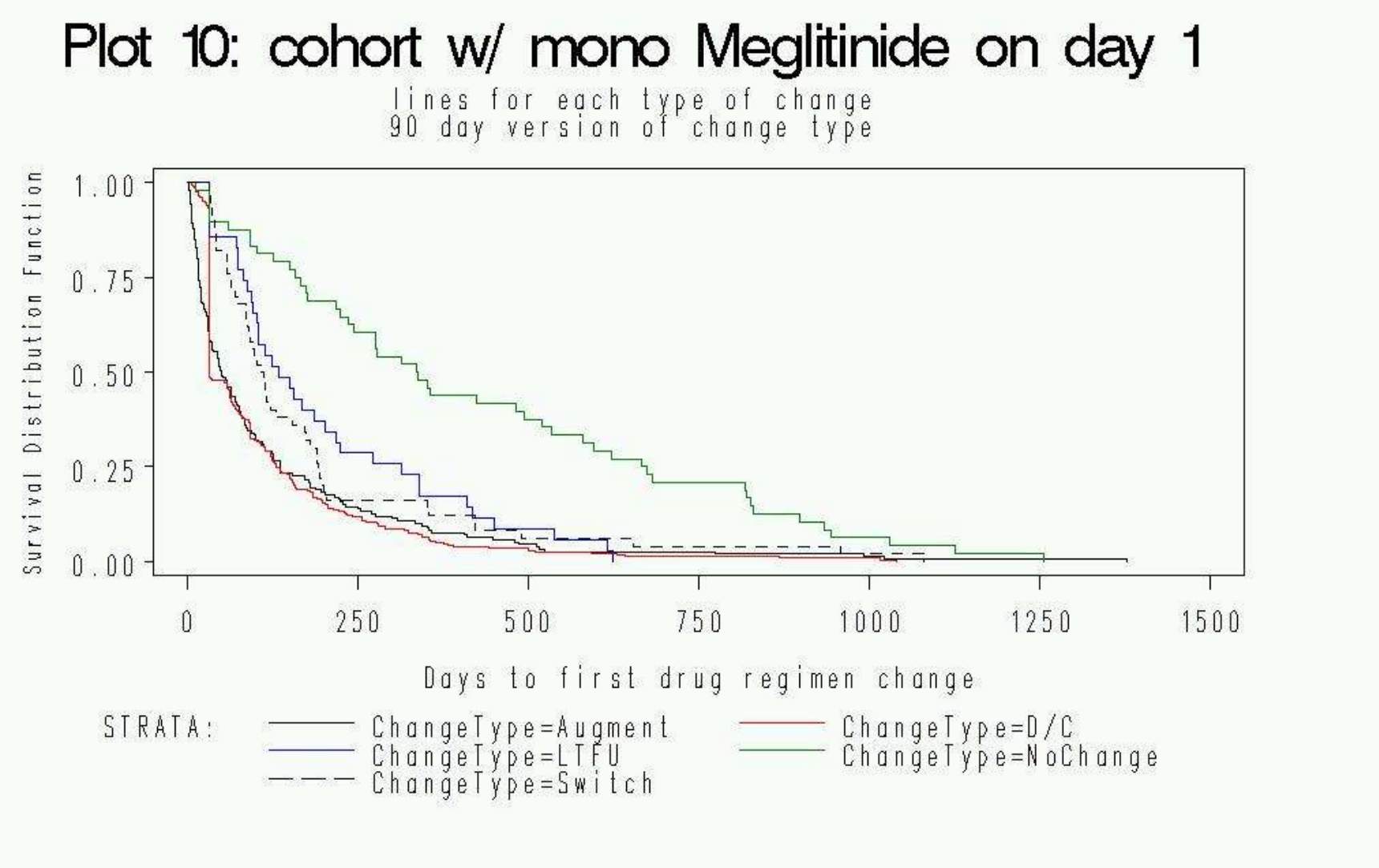

Figure B-12.Time to first regimen change: GLP-1 mimetic monotherapy

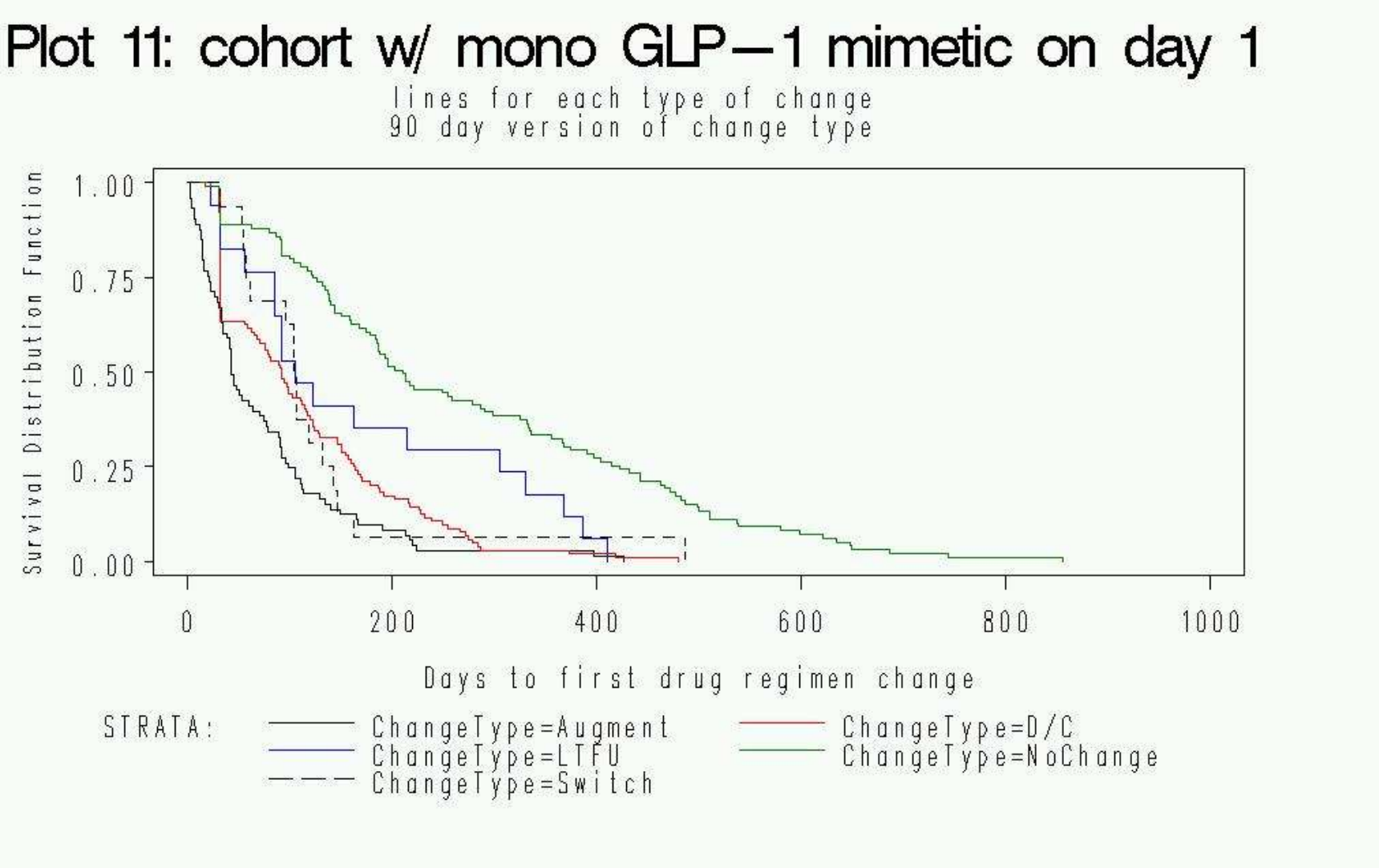

Figure B-13. Time to first regimen change: DPP-IV inhibitor monotherapy

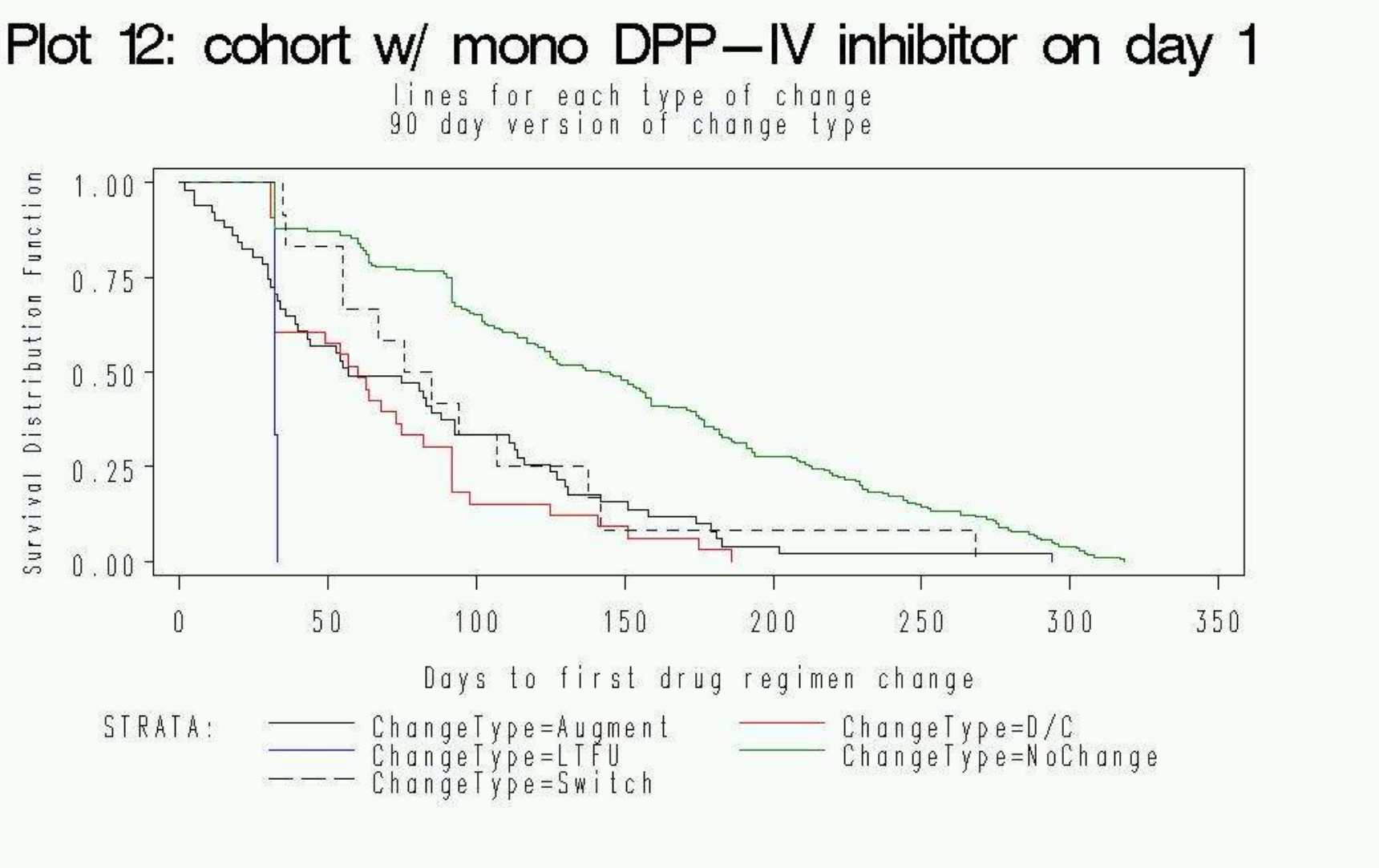

Figure B-14.Time to first regimen change: alpha-glucosidase inhibitor monotherapy

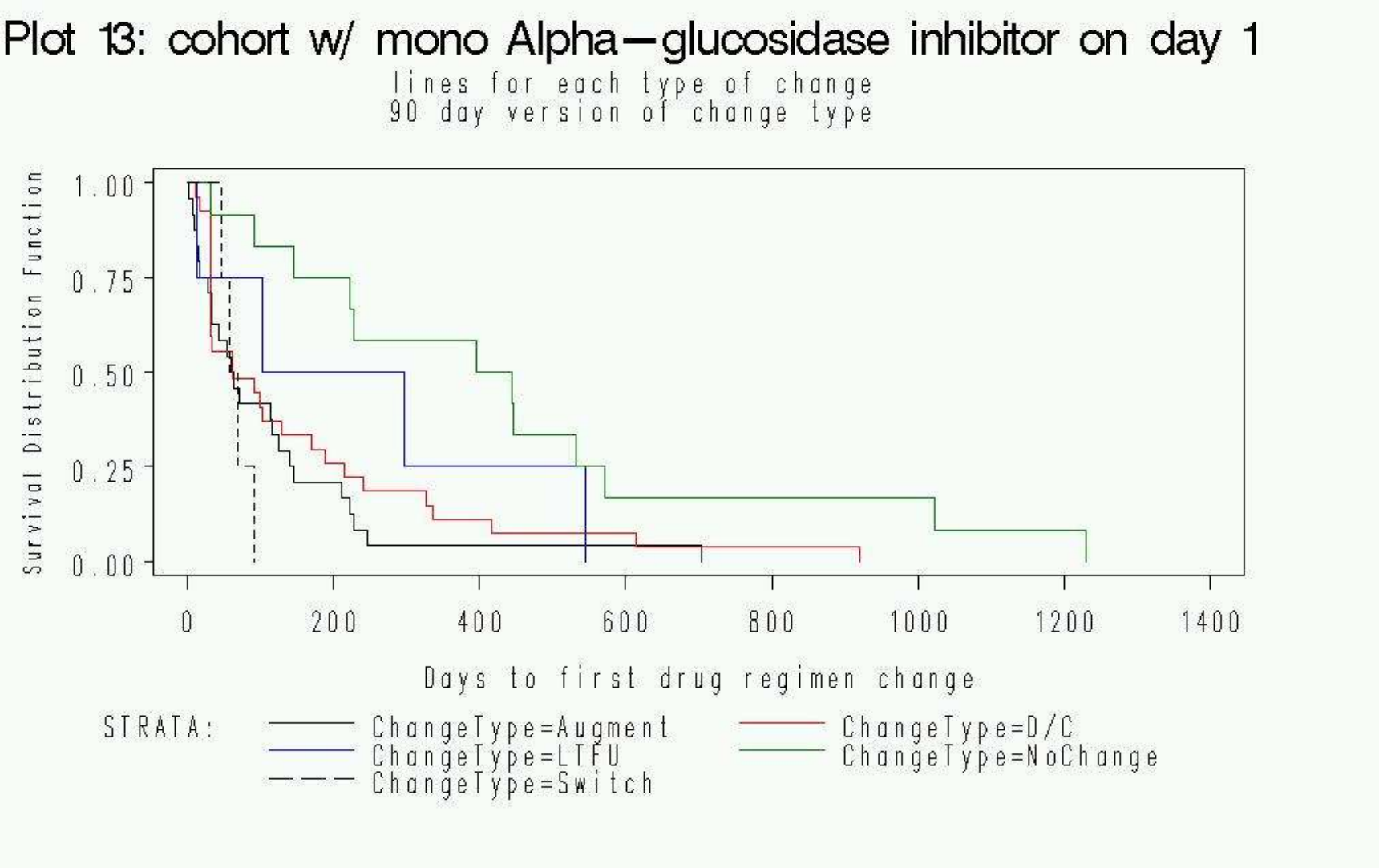

Figure B-15. Time to first regimen change: amylin analogue monotherapy