

PROJECT PERIODIC REPORT

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ABBREVIATIONS

The following abbreviations are used in this report:

- **AEDRS** – Adverse Events Drug Reporting System
- **AMI** – Acute Myocardial Infarction
- **CI** – Confidence Interval
- **CV** - Cardiovascular
- **DB** - Database
- **DPP** – Dipeptidyl Peptidase
- **DUS** – Drug Utilization Studies
- **ENCePP** – European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
- **Eudravigilance** – European Union Drug Regulating Authorities Pharmacovigilance
- **GLP** – Glucagon-Like Peptide
- **ICPE** – International Society for Pharmacoepidemiology
- **MedDRA** – Medical Dictionary for Regulatory Activities
- **NIBGLD** - Non-Insulin Blood Glucose Lowering Drugs
- **NOS** – Newcastle Ottawa Scale
- **PhVWP** – Pharmacovigilance Working Party
- **PPV** – Positive Predictive Value
- **RCT** – Randomized Controlled Trials
- **RRE** – Remote Research Environment
- **SGLT** – Sodium –Glucose Transporter
- **SMQs** – Standardised MedDRA Queries
- **T2DM** – Type 2 Diabetes Mellitus
- **TM** – Total Mortality
- **TZD** - Thiazolidinedione
- **UMLS** – Unified Medical Language System

1. FINAL PUBLISHABLE SUMMARY REPORT

1.1. EXECUTIVE SUMMARY

SAFEGUARD was set up to assess and further quantify and understand the cardio/cerebrovascular and pancreatic safety of blood glucose lowering agents, in particular the TZDs and the novel incretin-based drugs and amylin analogues in T2DM patients. A multidisciplinary consortium comprising 14 partners in 9 countries was set up to answer the various objectives and to provide evidence for regulatory and clinical decision making. A common list of 10 different outcomes and more than 30 non-insulin glucose lowering drugs was studied across the different work packages and evidence from spontaneous reports, epidemiological studies, literature and mechanistic trials was generated and assembled in an innovative fashion towards a common goal. The size and scale and breath of studies is unprecedented



The literature review was conducted on 6,952 articles describing RCTs and 2,421 articles describing observational studies for the SAFEGUARD drugs and outcomes. Analysis of clinical trials, which mainly focused on intermediary endpoints showed that it is not possible to draw definitive conclusions on the CV and cancer safety of new blood glucose-lowering agents from these studies, although positive effects on intermediate CV endpoints were observed. Among the 44 observational studies included in the systematic review for CV outcomes, we identified 329 comparisons between blood glucose-lowering drugs (including subgroup analyses). Results suggested a higher risk of AMI and stroke in users of rosiglitazone than in users of pioglitazone. The risk of AMI also seemed to be greater in users of rosiglitazone or sulphonylureas than in users of metformin, while the risk in users of pioglitazone seemed to be similar. Patients using either glitazones or sulphonylureas also might be at increased risk of heart failure compared with metformin users. Observational studies reporting on the risk of CV events associated with glitazones, metformin, and sulphonylureas are scarce and heterogeneous. Lack of a common reference category for the evaluation of all potential exposures limits direct comparison of effect estimates. Studies evaluating the CV safety of newer blood glucose-lowering agents were not identified. For pancreatic outcomes results were inconclusive due to small number of papers and large variation on methods

Analysis of 123,930 case reports related to diabetes medication in FAERS and 93,596 reports in EUDRAVIGILANCE. The following known signals were identified: pioglitazone and bladder cancer. pioglitazone and heart failure; rosiglitazone and all of the cardiovascular outcomes and cerebrovascular outcomes; newer incretin-based therapies and pancreatic outcomes. No new signals were observed for the incretin based therapies.

Within the 9 healthcare databases a cohort of almost 1.8 million diabetes type 2 patients could be analysed. Biguanides and sulfonylureas were the most frequently used products although in Italian, US and Spanish databases incretin based treatments increased as well in the last years. Nested case control studies on 9 events of interest (Myocardial infarction 25,979 cases, heart failure 27,773 cases, ventricular arrhythmia 3702 cases, sudden cardiac death 3017 cases, ischaemic stroke 22,420 cases haemorrhagic stroke 3817 cases, acute pancreatitis 3990 cases, pancreatic cancer 5141 cases, bladder cancer 6150 cases) and a cohort study on total mortality showed use of the following drugs as compared to current use of metformin plus a sulfonylurea were associated:

Use of rosiglitazone and repaglinide monotherapy are associated with a significant increased risk of myocardial infarction. Current use of glipizide, pioglitazone, repaglinide, nateglinide, rosiglitazone and sitagliptin were associated with an increased risk of heart failure in the one stage pooling. Current monotherapy with glibenclamide, gliclazide, glimepiride, glipizide, repaglinide was associated with an increased risk of ventricular arrhythmia in a one stage pooling. The risk associated with repaglinide was strongest as monotherapy and in combination with metformin. Current use of glimepiride, glipizide, nateglinide and repaglinide are associated with an increased risk of sudden cardiac death in a one stage pooling. For the cerebrovascular endpoints: Current use of glipizide monotherapy and metformin plus repaglinide were associated with an increased risk of ischemic stroke. Current use of repaglinide monotherapy was associated with an increased risk of ischemic stroke. For the pancreatic events: Current monotherapy with glipizide is associated with an increased risk of acute pancreatitis in a one stage pooling, but this was based on the USA only. Results on pancreatic cancer were inconclusive. Extended use of biguanides is associated with an increase of bladder cancer.

The mechanistic studies done in 4 clinical trials including the effects of 2 separate GLP-1 receptor agonists (i.e. exenatide and liraglutide) and DPP-4 inhibitors (i.e. sitagliptin and linagliptin), are novel, timely and needed. Pancreatitis: despite increases in pancreatic enzyme levels, no changes occur in exocrine physiology or anatomy. While a small-sized study in a small number of patients, there were no signs demonstrating pancreatic adverse effects. Heart rate acceleration: The increase in heart rate with GLP-1 receptor agonists does not appear to be caused by chronic increases in sympathetic activity. Moreover, heart rate variability (which is inversely associated with mortality) does not change. Based on these mechanistic data, there is no evidence of harm. In contrast, there is even a reduction in blood pressure with GLP-1 receptor agonists. Heart failure: The studied DPP-4 inhibitors had no evident cardiovascular effect, which supports the findings that sitagliptin and linagliptin have no effect on heart failure. Renal failure: None of the agents affected renal function in a negative manner. However, the natriuresis which occurred with acute GLP-1 receptor agonist intervention could potentially, in combination with other factors which reduce circulating volume, lead to pre-renal failure.

Integration of evidence was conducted using a Dempster Sahfer model and all workpackages categorized the evidence in high medium and low risk. This allows for easy comparison of risk which may be weighted or just listed for regulatory and clinical decision making.

SAFEGUARD promised 9 key areas of innovation beyond the current state of the art all of which have been achieved with the highest standards and quality in the various deliverables.

1. generation of EU-country-specific and pooled rates and risks of the different cardiac and cerebrovascular safety outcomes in T2DM patients
2. federation of different databases between EU and USA using distributed model
3. provision of data about the form of the relationship between intensity of the exposure to T2DM drugs (i.e. duration of the treatment and the daily and cumulative dose of the prescribed drug) and the risk of the safety outcomes of interest
4. mining of international pharmacovigilance databases to assess disproportionalities in the reporting of CV and pancreatic events of interest, and potential new safety signals for the incretin-based therapies

5. meta-analysis of cardiovascular, cerebrovascular and pancreatic events and intermediate CV markers especially for the novel incretin-based therapies, and the exploration and understanding of the differences in the meta-analyses of CV safety in TZDs
6. detailing of the effects of incretin-based therapies, both GLP-1RA and DPP-4 inhibitors on the CV, kidney and digestive system in T2DM patients
7. the scale on which we will be able to quantify the absolute and relative risks of acute pancreatitis during use of the novel incretin-based therapies and the TZD
8. the research into the association between incretin-based therapies and pancreas cancer, and whether these therapies would act as inducing or promoting factors
9. the ability to rapidly study newly occurring safety issues for T2DM drugs by having a large scale, harmonized platform for the conduct of epidemiological studies

The output of this work will be made available to the European Medicines Agency for further regulatory decision making and for future reference.

1.2. DESCRIPTION OF PROJECT CONTEXT AND OBJECTIVES

SAFEGUARD addressed a specific question of the European Commission included in the topic “Responding to EU policy needs” within the 7th Framework Programme Cooperation Work Programme Health 2011. This topic contributes to the support and follow-up of the policies and requests from the Pharmacovigilance Working Party (currently PRAC) at the European Medicines Agency with regards to all member states.

Nowadays, diabetes affects over 366 million people worldwide. For decades, insulin secretagogues (sulfonylurea derivatives: glibenclamide, gliclazide, glipizide, glimepiride) and the insulin sensitizing biguanides such as metformin, have been the only oral therapeutic options available for the treatment of T2DM. Both drug classes have maintained good benefit-risk profiles throughout their life cycle and recent evidence suggests that metformin may even reduce the risk of cancer. In the quest of agents that could halt the progression of T2DM, several novel diabetes drugs have become available over the last 10-15 years, all on the basis of their ability to reduce blood glucose levels but with different mechanisms of action: insulin sensitisers - thiazolidinediones (also called peroxisome-proliferator-activated receptor gamma ((PPAR- γ) agonists), alpha-glucosidase inhibitors (reducing glucose absorption from intestine) and the incretin-based therapies, including the injectable glucagon-like peptide-1 receptor agonists (GLP-1RA) exenatide and liraglutide and the oral dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin)⁵⁻¹⁶. Amylin analogues (such as pramlintide) exert their effect by slowing down gastric emptying and increasing satiety. Many more drugs with different mechanisms of action are in the pipeline. The average glucose-lowering effect of the major classes of T2DM drugs is broadly similar (averaging a 1-2% reduction in glycated haemoglobin HbA1c), depending on pre-treatment HbA1c-levels.

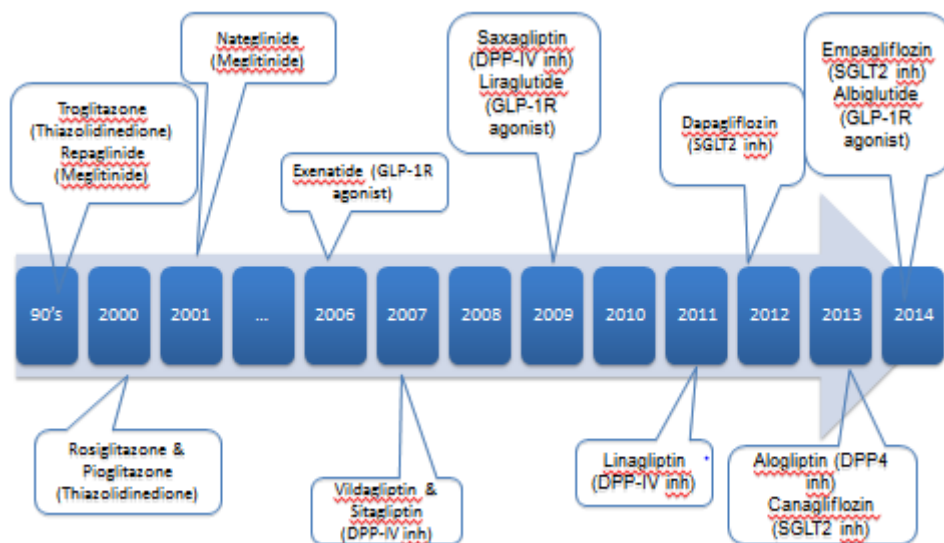


Figure 1 Overview of new non-insulin glucose lowering drug launches till 2014

Several safety risks associated with drugs used for treating diabetes have appeared over the last decade (such as the increased cardiovascular risks of rosiglitazone and the risk of pancreatitis with incretin based therapies) (see figure 2).

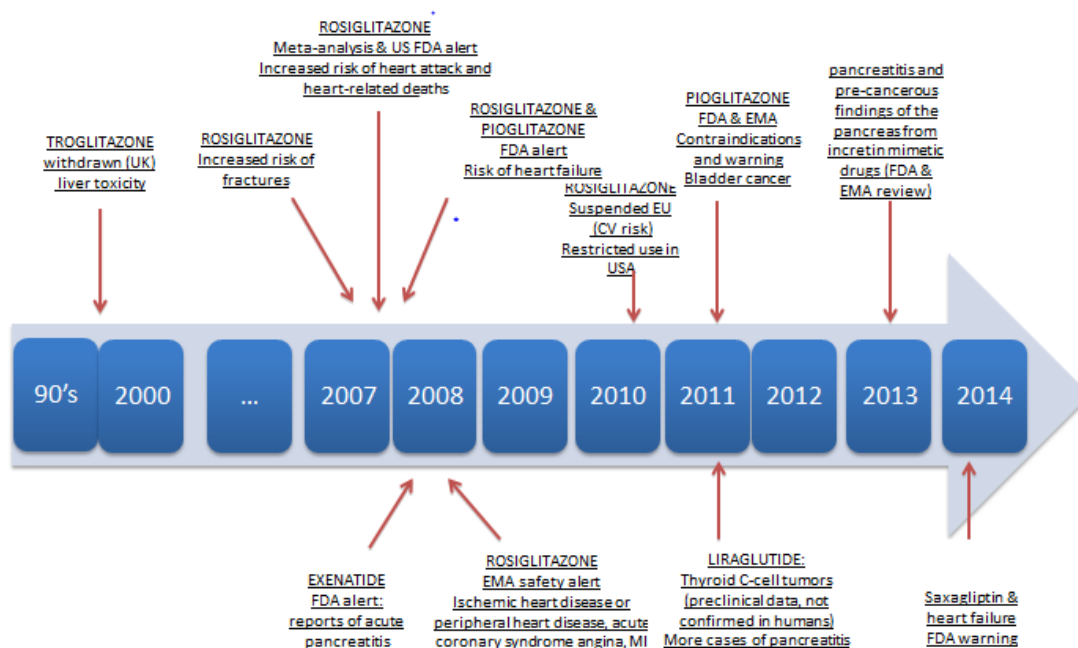


Figure 2 Overview of safety issues with new non-insulin glucose lowering drugs

The European Medicines Agency asked the European Commission to tender for a proposal that would address the safety of all the non-insulin blood glucose lowering agents for regulatory

decision making. Table 1 shows the drug classes that have been investigated, many of the products also could be use as combination

Table 1 Drugs of primary interest in SAFEGUARD

Approval	Active substance	Authorisation date	ATC code
A10BA	Biguanides		
not centralized	Metformin	National	A10BA02
A10BB	Sulfonamides, urea		
not centralized	Glibenclamide	National	A10BB01
not centralized	Tolbutamide	National	A10BB03
not centralized	Gliclazide	National	A10BB09
not centralized	Glimepiride	National	A10BB12
A10BD	Combinations		
not centralized	Metformin/glibenclamide	National	A10BD02
not centralized	Metformin/rosiglitazon	National	A10BD03
Centralized	rosiglitazone / glimepiride	27-06-2006	A10BD04
Centralized	pioglitazone / metformin hydrochloride	28-07-2006	A10BD05
Centralized	pioglitazone / glimepiride	08-01-2007	A10BD06
Centralized	sitagliptin / metformin hydrochloride	16-07-2008	A10BD07
Centralized	Vildagliptin / metformin hydrochloride	14-11-2007	A10BD08
A10BF	Alpha _glucosidase inhibitors		
not centralized	Acarbose	National	A10BF01
A10BG	Thiazolidinones (TZDs)		
REMOVED	Rosiglitazone	11-07-2000	A10BG02
Centralized	Pioglitazone	11-10-2000	A10BG03
A10BH	DPP-4		
Centralized	Sitagliptin	21-03-2007	A10BH01
Centralized	Vildagliptin	26-09-2007	A10BH02
Centralized	Saxagliptin	01-10-2009	A10BH03
A10BX	other		
Centralized	Repaglinide	17-08-1998	A10BX02
Centralized	Nateglinide	03-04-2001	A10BX03
Centralized	Exenatide	20-11-2006	A10BX04
ONLY USA	Pramlintide		A10BX05
REMOVED	Benfluorex	2009 removed	A10BX06
Centralized	Liraglutide	30-06-2009	A10BX07

The SAFEGUARD project aimed to assess and further quantify and understand the effects of all existing non-insulin blood glucose lowering agents in humans by means of the analysis of anonymised and aggregated data from diabetes patients in Europe and the US, the revision of published observational studies and clinical trials, and the implementation of state-of-the-art mechanistic studies. Only a collaborative undertaking allying experts from different research disciplines and including medical information for a large number of patients from several countries was permitting this undertaking which is required for improving the understanding on how drugs act in T2DM treated patients.

The primary aim of the SAFEGUARD project was to assess and further quantify and understand the cardio/cerebrovascular and pancreatic safety of blood glucose lowering

agents, in particular the TZDs and the novel incretin-based drugs and amylin analogues in T2DM patients

The specific objectives related with this primary aim are:

1. To determine and compare the (background) incidence rates of cardiovascular, cerebrovascular and pancreatic events of interest in T2DM patients
2. To assess the risk of outcomes of interest during different T2DM treatments and to assess the effect of dose and duration on the risk
3. To identify risk factors for developing outcomes of interest in patients treated with T2DM drugs
4. To detail the clinical effects of incretin-based therapies and whether or not they can promote or induce pancreas cancer
5. To detail the clinical effects of incretin-based agents on the cardiovascular, renal and digestive function and to unravel the underlying mechanism
6. To develop prognostic models for identifying patients at risk of the safety outcomes of interest
7. To integrate the information to assist clinicians in better treatment choices and regulatory agencies in their decision making.

The work plan was designed as displayed in figure 3. Key aspects to the overall success were the scientific (WP1) and project management packages (WP2). These packages included activities such as ethical surveillance, project quality, reporting and risk assessment. Work packages 3-7 were the main knowledge generating and scientific work packages, whereas work package 8 dealt with dissemination and exploitation. Overall the strategy has been to have each work package deal with different data substrates: analysis of spontaneous reports (WP3), conduct of new epidemiological studies with health care databases (WP4), review of the literature (WP5), and mechanistic studies (WP6), by using a common list of outcomes (Myocardial Infarction, Heart Failure, Ventricular arrhythmia, Sudden cardiac death, Cerebrovascular, Hemorrhagic stroke, Ischemic stroke, Pancreatic events, Acute pancreatitis, Pancreas cancer, Bladder cancer and total mortality) and a common list of study drugs. Each of these work packages was supported by the statistical expertise from WP7 and delivered results to WP7 for integration into various decision models

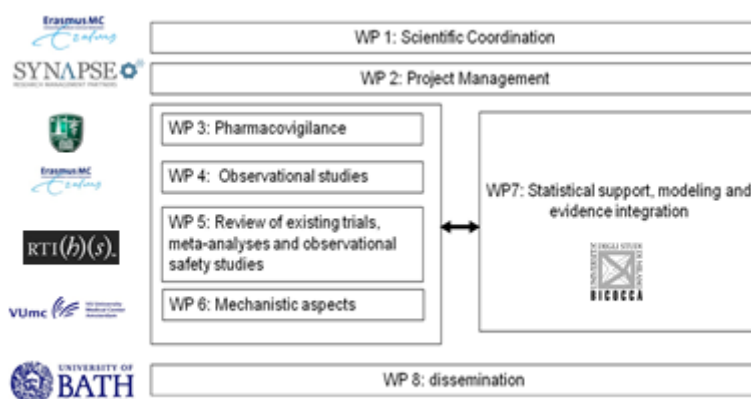


Figure 3 Strategy of the project and organizations leading the work packages.

Partnership

The SAFEGUARD Consortium brought together 14 partners from 7 countries (including the USA) with the following areas of expertise: healthcare database holders, (pharmaco)epidemiologists, medical informaticians, biostatisticians, pharmacologists, pharmacovigilance experts, decision analysts, clinicians, endocrinologists, and regulators. Each of the partners was well recognized for its scientific excellence in methods and content area, they all have a proven track record, a proven capability to effectively cooperate in European and International projects, and had enthusiasm for the ultimate objectives of the call. It was exceptional to start out (non-intentional) with a complete female steering committee, who were the work package leaders. Several changes happened throughout the project, Michaela Diamant from VUMc, who was the work package leader of WP6 passed away, and was replaced by Mark Smits, Corinne de Vries who was work package leader of WP 8 left University of Bath and WP leadership was taken over by Erasmus and Synapse. Mario Negri Sud went bankrupt after they had finished key work.



Figure 4 SAFEGUARD steering committee at Kick off.

1.3. DESCRIPTION OF THE MAIN S&T RESULTS/FOREGROUND

In order to achieve the aims and objectives of the project, we developed a knowledge integration framework to which each of the data generating work packages (3-7) were contributing. Figure 5 shows this model. Three streams are distinguished: one stream that reviewed published data the second stream was analysing data from healthcare databases that participated in SAFEGUARD as well as data from two international spontaneous reporting database. Data from these two streams were combined in a traffic light system to compile all the results and provide easy support for regulatory and clinical decision making. The third stream were mechanistic studies that could inform potential findings from the literature and observational data.

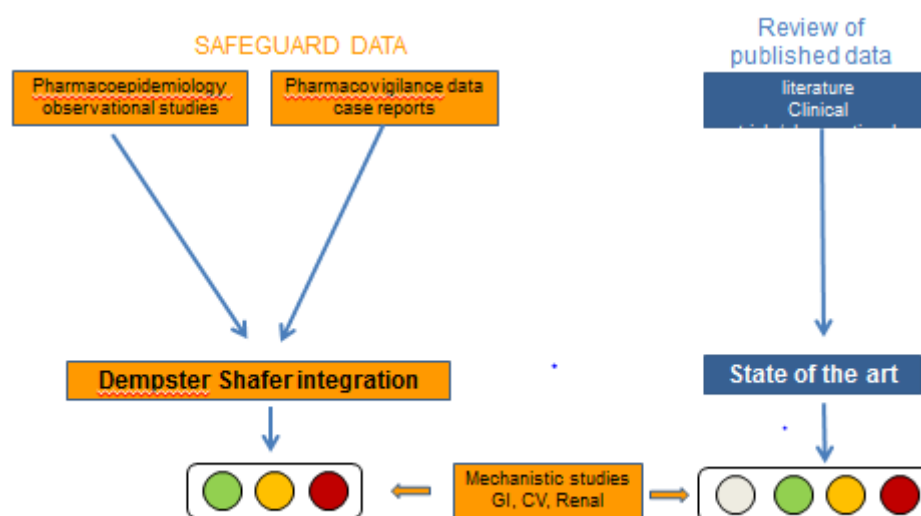


Figure 5 Data integration framework in SAFEGUARD

REVIEW OF PUBLISHED STUDIES (WP5 &7)

Research partners collaborating in this work were CMNS, DSRU, UNIMIB, VUA, and RTI-Health Solutions. The objectives were

- To systematically review published, randomised controlled trials (RCT) to provide overall effect estimates for cardiovascular (CV), cancer, and pancreatic outcomes of drug therapies in type 2 diabetes mellitus (T2DM).
- To systematically review published pharmacoepidemiology studies on the safety of therapies for T2DM; synthesise the evidence; and, where possible, provide a summary effect estimate for the effect on CV and pancreatic outcomes.
- To identify methodological issues and research gaps of published pharmacoepidemiology studies on these topics.

The first task of WP5 involved the description of the systematic process used to identify and select RCTs (D5.1) and observational studies (D5.2) on the use of blood glucose-lowering drugs (except insulin) and the risk of cardiovascular (CV) and pancreatic outcomes in patients with T2DM. The literature search was conducted in MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (for RCTs), and the Cochrane collaboration (for observational studies); bibliographic cross-referencing was also performed. The systematic search identified 6.952 articles describing RCTs and 2.421 articles describing observational studies. Among the latter, 1.929 reported on CV events and 492 on pancreatic events (pancreatic cancer and acute pancreatitis).

The CV outcomes included in the literature search of observational studies were acute myocardial infarction (AMI) or acute coronary syndrome or serious coronary heart disease, heart failure, acute stroke (ischemic or hemorrhagic), ventricular arrhythmias, sudden cardiac death, cardiovascular mortality, and a composite endpoint including any of the previous. Mortality from all causes was an eligible outcome only in studies performed in high-risk subjects. Intermediate CV outcomes (blood pressure, lipid profiles, body weight, and heart

rate) were also included in the systematic review of RCTs. After eliminating non-relevant publications by reviewing titles and abstracts, we identified 1.123 RCTs and 121 observational studies (77 articles for CV outcomes and 44 for pancreatic events) that were eligible for full-text review.

Key methodological information and results from each selected study were abstracted using Microsoft Access databases designed by UNIMIB. Data abstraction and quality assessment of included studies was done separately for RCTs (D5.3-Part A), observational studies of CV events, and observational studies of pancreatic events (D5.3-Part B).

The review of clinical trials was focused on all published studies enrolling patients with T2DM and comparing any blood glucose-lowering agent, other than insulin, against placebo, no treatment, or another blood glucose-lowering agent other than insulin. After screening the full text of selected papers, 156 RCTs, reported in 165 publications, met the inclusion criteria. Methodological quality of each clinical trial was assessed using standardised criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (<http://handbook.cochrane.org/>).

For the review of observational studies on CV outcomes, we included studies in patients with T2DM evaluating the risk of CV outcomes associated with any blood glucose-lowering medication other than insulin compared with any other blood glucose-lowering medication except insulin. Upon full-text review, 33 of the 77 articles were found to not meet eligibility criteria, leaving a total of 44 articles with CV endpoints for data abstraction. The quality of observational studies was assessed simultaneously with the data abstraction using the Newcastle-Ottawa Scale (NOS) and the RTI item bank quality assessment scale.

For pancreatic outcomes, we included studies that compared users of T2DM medication with users of other blood glucose-lowering medication (which may have included insulin), patients without T2DM (general population), or other patients with T2DM who may have been untreated with medication or may have had type 1 (insulin-dependent) diabetes. Upon full-text review, 32 of the 44 articles were found to not meet eligibility criteria, leaving a total of 13 articles for data abstraction plus an additional publication found by cross-referencing. The quality of these observational studies was also assessed at the time of data abstraction with both the NOS and the RTI item bank quality assessment scale.

D5.4 – Part A described the results of the quality assessment of the reviewed CV (n=44) and pancreatic (n=13) observational studies, the methodological issues and research gaps identified in the systematic review, and recommendations for conducting additional studies within the SAFEGUARD consortium. Methodological aspects related to the applicability of the two quality assessment tools, the NOS and the RTI item bank, the inter-rater agreement with the RTI item bank and the correlation between quality assessments with the two tools were described. For CV endpoints, the list of methodological issues was classified according to 1) study population, 2) exposure, 3) outcome, 4) analysis, 5) immortal-time bias, 6) unmeasured confounding and confounding by indication, and 7) formulary restrictions. For pancreatic endpoints, the methodological issues were classified by 1) study design, 2) analysis, and 3) handling of confounders. The main methodological issues were related to the heterogeneity of exposures of interest, exposures used as the reference category, and the endpoints evaluated and the potential for remaining confounding, immortal-time bias, and confounding by indication. The variety of medications used as references in the published studies rendered a summary of the available data very challenging for both CV and pancreatic outcomes.

Information on the influence of dose and duration on the CV and pancreatic safety of blood glucose-lowering agents was very scarce.

D5.4 – Part B described the results of the quality assessment of reviewed RCTs, which assessed studies' risk of bias with the Cochrane Collaboration's tool. Six domains were evaluated: adequacy of sequence generation, concealment of allocation, blinding, completeness of follow-up, and absence of reporting bias. A high percentage of papers did not report sufficient detail to assess the risk of selection bias. On the other hand, risk of performance bias was low, since almost all the trials were double-blinded. More than half of the studies were considered at low risk of detection bias, since outcomes were assessed by blinded researchers or clinical parameters were evaluated by central laboratories. Only one-third of studies had low attrition bias due to the low percentage of patients lost to follow-up. Finally, almost half of the trials did not report a trial registration number or the protocol was not previously published; thus, no evaluation of reporting bias could be performed.

D5.5 provided the summary relative risks from the meta-analyses of clinical trials (part A, n = 156 studies) and observational studies (part B) for CV events (n = 44 studies) and pancreatic events (n = 13 studies) in users of these medications.

The meta-analysis of RCTs reported results on clinical and intermediate CV outcomes of dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA), and sodium-glucose transporter 2 (SGLT2) inhibitors. In addition, data on thiazolidinediones, sulphonylureas, biguanides, incretin-based therapies and overall cancer, site-specific cancers including pancreatic cancer, and acute pancreatitis were evaluated. The main message was that it is not possible to draw definitive conclusions on the CV and cancer safety of new blood glucose-lowering agents, although positive effects on intermediate CV endpoints were observed. Data on cancer reduction or induction by the oldest blood glucose-lowering agent need to be interpreted with caution.

Among the 44 observational studies included in the systematic review for CV outcomes, we identified 329 comparisons between blood glucose-lowering drugs (including subgroup analyses). In total, 25 studies providing at least three independent data estimates for 16 between-drug comparisons (main or subgroups analyses) and were included in meta-analyses. The following six main comparisons, by outcome, were analyzed:

- Rosiglitazone versus pioglitazone (12 studies) for AMI, heart failure, stroke and all-cause mortality
- Rosiglitazone versus metformin (7 studies) for AMI and heart failure
- Pioglitazone versus metformin (4 studies) for AMI and heart failure
- Rosiglitazone versus sulphonylureas (5 studies) for AMI
- Pioglitazone versus sulphonylureas (3 studies) for AMI and heart failure
- Sulphonylureas versus metformin (11 studies) for AMI, heart failure, CV mortality, and all-cause mortality

Results suggested a higher risk of AMI and stroke in users of rosiglitazone than in users of pioglitazone. The risk of AMI also seemed to be greater in users of rosiglitazone or sulphonylureas than in users of metformin, while the risk in users of pioglitazone seemed to be similar. Patients using either glitazones or sulphonylureas also might be at increased risk of

heart failure compared with metformin users. We must note, though, that observational studies reporting on the risk of CV events associated with glitazones, metformin, and sulphonylureas are scarce and heterogeneous. Lack of a common reference category for the evaluation of all potential exposures limits direct comparison of effect estimates. Studies evaluating the CV safety of newer blood glucose-lowering agents were not identified.

For pancreatic outcomes, evidence was even scarcer, and a formal meta-analysis was not considered appropriate due to the small number of eligible studies identified (n=13). Instead, a descriptive narrative synthesis provided a qualitative and semiquantitative summary of the study results. For acute pancreatitis, at least 3 studies reported on sitagliptin (DPP-4 inhibitor), exenatide (GLP-1 agonist), sulphonylureas, and metformin. With exception of one study on glibenclamide, there was generally no evidence of an increased risk of acute pancreatitis in users of the T2DM drugs. Indeed, a small number of studies reported a lower risk in users of some drugs compared with non-users

For pancreatic cancer, 3 or more studies reported on metformin, sulphonylureas, and thiazolidinediones. The reference group in each of these studies were non-users of the medication evaluated, but included heterogeneous subgroups of treated or untreated patients with diabetes. The evidence was inconclusive, with some studies reporting a lower risk in users of metformin compared with the study reference category and some studies reporting a small increase in risk. A trend toward an increased risk of pancreatic cancer was observed in sulphonylurea users compared with the study reference category. These findings must be interpreted with caution since they are based on very few studies, which in some cases provided conflicting results. These associations (or lack of associations) might represent biased estimates since most studies were not able to control for all possible confounders or might be affected by channelling bias, protopathic bias, or immortal-time bias. Indeed, the overall direction of bias was unclear due to the potential for different, competing biases from different study designs and limitations. There are still unanswered questions that require further study to clarify these findings.

Regarding the integration of evidence generated from the review of the literature (WP5) with evidence generated from pharmacovigilance (WP3), observational studies (WP4), we defined an uncertainty score based on volume, precision, consistency, internal and external validity of the evidence; obtained one score per drug/outcome comparison (for cardiovascular and pancreatic outcomes) and summarized our results in tabular format showing each comparison's risk (high/intermediate/low/inconclusive risk denoted by traffic light colors) and uncertainty score. This was included in deliverable 7.5.

Publications

- Margulis AV, Pladevall M, Riera-Guardia N, Varas-Lorenzo C, Hazell L, Berkman ND, Viswanathan M, Perez-Gutthann S. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle-Ottawa Scale and the RTI item bank. *Clinical epidemiology*. 2014;6:359-68. Link: <http://shar.es/13ME2X>

Here we reported our experience applying the RTI item bank and the NOS to assess the methodological quality of identified studies in the systematic review of observational studies of on CV outcomes associated with NIGLD. Two reviewers assessed the quality of the 44 included studies with both tools and agreed on which responses conveyed low, unclear, or

high risk of bias. Chance-adjusted inter-rater agreement was estimated with the AC1 statistic. The NOS required less tailoring and was easier to use than the RTI item bank but the RTI item bank produced a more thorough assessment. Median observed inter-rater agreement for the RTI-IB was 75% (25th percentile [p25]=61%; p75=89%); median AC1 statistic was 0.64 (p25=0.51; p75=0.86). The observed agreement and AC1 statistic in this study were higher than those reported by the developers of the RTI item bank.

- Varas-Lorenzo C, Margulis AV, Pladevall M, Riera-Guardia N, Calingaert B, Hazell L, Romio S, Perez-Gutthann S. The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies. *BMC cardiovascular disorders*. 2014;14:129. Link: <http://www.biomedcentral.com/1471-2261/14/129>

Here we reported on the results of our quantitative systematic review of published cohort and case-control studies in patients with T2DM users of NIGLD and assessed the risk of heart failure. (<http://www.biomedcentral.com/1471-2261/14/129>). The summary relative risk (sRR; 95% CI) of heart failure for the identified comparisons were the following: for rosiglitazone users versus pioglitazone users, 1.16 (1.05-1.28) (I² = 66%) and 1.21 (1.14-1.30) (I² = 31%) when the analysis was restricted to new users; for rosiglitazone versus metformin, 1.36 (95% CI, 1.17-1.59); for sulfonylureas users versus metformin users, 1.17 (95% CI, 1.06-1.29) (I² = 24%) and 1.22 (1.02-1.46) when the analysis was restricted to new users. Information on dose and duration of treatment effects was lacking for most comparisons. Few studies accounted for disease severity; therefore, confounding by indication might be present in the majority of the within-study comparisons of this meta-analysis. No studies were available on newer NIGLD. In summary, use of glitazones and sulfonylureas was associated with an increased risk of heart failure compared with metformin use. However, indication bias cannot be ruled out.

- Pladevall M, Riera-Guardia N, Margulis AV, Varas-Lorenzo C, Calingaert B, Perez-Gutthann S. Cardiovascular risk associated with the use of glitazones, metformin and sulfonylureas: meta-analysis of published observational studies (under review with *BMC Cardiovascular Disorders*).

This manuscript presents the results from our meta-analysis of observational studies in patients with type 2 diabetes mellitus treated with non-insulin glucose-lowering drugs and the risk of AMI or stroke events. The summary relative risk (sRR; 95% CI) of AMI for rosiglitazone versus pioglitazone was 1.13 (1.04-1.24) (I²=55%). In the sensitivity analysis, heterogeneity was reduced (I²=16%). The sRR (95% CI) of stroke for rosiglitazone versus pioglitazone was 1.18 (1.02-1.36) (I²=42%). There was strong evidence of heterogeneity related to study quality in the comparisons of rosiglitazone versus metformin and rosiglitazone versus sulfonylureas (I²≥70%). The sRR (95% CI) of AMI for sulfonylurea versus metformin was 1.24 (1.14-1.34) (I²=41%) and for pioglitazone versus metformin was 1.02 (0.75-1.38) (I²=17%). Sensitivity analyses decreased heterogeneity in most comparisons. In summary, there were no differences in the risk of AMI when comparing pioglitazone with metformin; sulfonylureas increased the risk of AMI by 24% when compared with metformin. The presence of heterogeneity precludes any conclusions on the other comparisons. The quality assessment was valuable in identifying methodological problems in the individual studies and analysing potential sources of heterogeneity.

Indirect comparisons: network meta-analysis

In collaboration with WP 7 network met-analyses were conducted which allows for comparison of Non-insulin blood glucose lowering drugs (NIBGLDs) that were not directly compared in the scientific literature. The network meta-analysis is a statistical technique which allows: i) assessing the relative efficacy or safety of two treatments when they have not been compared directly in a randomized trial but have each been compared to other treatments, ii) expanding the concept of heterogeneity evaluating both heterogeneity and inconsistency between trials, iii) ranking the different drugs in terms of efficacy and safety.

The data used in this analysis were those already collected by CMNS for the meta-analysis of randomized controlled trials. The following outcomes were considered: pancreatic cancer, ventricular arrhythmia, haemorrhagic stroke, bladder cancer, overall cancer, cancer death, myocardial infarction, heart failure, ischemic stroke, composite cardiovascular endpoint, cardiovascular death, sudden cardiac death and pancreatitis. For all outcomes exposure to GLP-1RA, DPP-4 inhibitors, Amylin analogues, SGLT2 inhibitors were considered, while exposure to biguanides, sulphonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones and benfluorex were considered only for cancers and acute pancreatitis. The inclusion/exclusion criteria were the same of the meta-analysis of randomized controlled trials but were additionally excluded studies reporting safety information only on secondary cardiovascular outcome and those reporting as reference category no treatment, pioglitazone and metformin or sulphonylureas (SU), placebo and glipizide. After the application of all exclusion criteria 104 studies were included in the network meta-analysis.

For each considered outcome was reported the network visual representation of the direct comparison (i.e. comparisons available in the scientific literature) (see figure), a table reporting the relative risk related to the direct and indirect comparisons and the ranking of the drugs according to their safety profile.

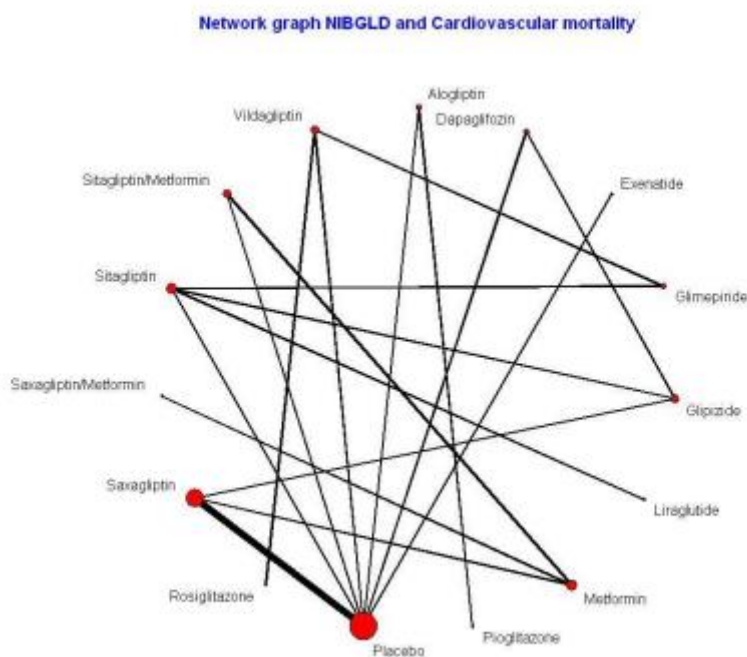


Figure 6 example for network graph for trials looking at cardiovascular mortality

After the observation of the visual representation of the network, the analyses were not performed for pancreatic cancer, haemorrhagic stroke and ventricular arrhythmia because no common comparator drug was available preventing the possibility of computing indirect comparisons.

Regarding the evaluation of cardiovascular outcomes, the comparisons evaluated through the results of the SAFEGUARD systematic review of RCTs cannot be applied to the older available NIBGLD (i.e. SUs, metformin, etc.) because clinical trials evaluating cardiovascular outcomes for those drugs were explicitly excluded from the review. The review misses then all relevant comparisons among the oldest NIBGLD (e.g., metformin and sulfonylureas) that evaluated cardiovascular outcomes.

Most of the results of the network meta-analyses are affected by strong limitations. First of all, the number of cases available for each outcome is very low leading to huge random variability in the estimates and consequently very large confidence intervals. In case of strong variability, it is not possible to determine if the lack of association is due to a real absence of risk effect between the treatments being compared or due to a too large random error. Moreover, the number of studies which investigate specific comparisons for each outcome was very low affecting also the variability of the effect estimates. Often, for each comparison, only one study was available and consequently no pooled estimate could be calculated. In this situation, the indirect comparisons were based on only one effect estimate.

The probability of being the safest treatment depends on the number of comparisons available for each outcome. Most of the comparisons were based on few direct comparisons available and very imprecise effect estimates, therefore ranking the safest treatment option was not informative. Effects estimated may be biased when indirect comparisons are based on low-quality trials.

For the evaluation of the cardiovascular composite endpoint pioglitazone was associated with an increased risk of a cardio and cerebrovascular composite outcome as compared with exenatide and vildagliptin.

ANALYSIS OF SPONTANEOUS REPORTS (WP3)

This work was led by DSRU with input from BIPS, EMC, F-SIMG and UNIMIB. The objectives of the work were:

- To obtain access to international pharmacovigilance databases of spontaneous adverse reaction/adverse event reports on which to perform the study.
- To define and list cardiovascular, cerebrovascular and pancreatic events in spontaneous reports for anti-diabetic drugs.
- To assess potential associations between T2DM drugs and cardiovascular, cerebrovascular and pancreatic events using disproportionality analyses.
- To identify new potential safety signals for the SAFEGUARD study drugs.

An additional objective evolved during the course project in response to changes in the overall evidence integration aspect of the project provided in WP7. A metric was developed that could be used to integrate the results of disproportionality analysis with evidence from the results of observational studies performed within WP4.

In WP3 there were two formal deliverables D3.1 and D3.2, which were completed and delivered to the European Commission. D3.1 was concerned with a full description of the methodology used whilst D3.2 described the quantitative results from disproportionality analysis performed in this WP.

Description of Methods, Data Sources and Overlap

Selection of databases: The first objective was to select and access large pharmacovigilance databases in which to perform analysis of spontaneous reports. Three large databases were initially considered including the FDA-AERS (FAERS) database in the US, the European equivalent, Eudravigilance (EV) and the WHO-Vigibase. Two of these databases (FAERS and EV) were selected after considering several factors including: accessibility, format of data for research purposes and cost implications (including both financial and resourcing aspects). The WHO-Vigibase, was not included, since it was considered that there may be significant overlap between this database and the other two databases, and further, that access to this data may be cost-prohibitive.

Access to databases: For the FAERS database, dataset files are published on-line every quarter. These files were downloaded and transferred into a Microsoft SQL Server database at the DSRU for the purposes of data cleaning and analysis. Data were available up to the end of 2012. Under the terms of the Eudravigilance Access Policy, an extract of Eudravigilance data was supplied to the DSRU. These data included all spontaneous reports received by EV where a blood glucose lowering drug (as per list of SAFEGUARD drugs of interest) is classified as a suspect (or interacting) drug. Aggregate denominator data were also provided for each outcome in order to facilitate disproportionality analysis.

Overlap of data sources: It was acknowledged from the outset that there would be a degree of duplication within databases and also overlap between FAERS and EV databases. After discussion within WP3 partners, it was considered beyond the scope of this project to develop a reliable method for de-duplication within or between ad-hoc datasets since, in comparison to source data; these datasets have limited fields available on which to automate such a process. Removal or merging of duplicate reports was limited to those that are readily identifiable within datasets, for example, due to follow up reports or reports on the same case from different reporters that have been identified at source and flagged as duplicates in the dataset.

Table 2: Characteristics of the DM case reports in FAERS and Eudravigilance

	FAERS	Eudravigilance
Total number of unique cases in DM_subset	123,930	93,596
Median age in years (inter-quartile range, number with non-missing age)	61 (53-69, 91,028)	64 (55-73, 40,636)
Number of males (% of DM_subset, number with non-missing gender)	52,706 (44.7%, 117,789)	43,448 (51.0%, 85,226)

Definition of SAFEGUARD Outcomes of Interest: In FAERS and EV, reported adverse drug reactions are coded using the hierarchical MedDRA terminology dictionary. For each outcome, one or more lists of MedDRA terms (at the 'preferred term' level) were selected to define a

narrow (specific) case definition that was harmonised with the definitions derived from other terminologies in WP4 and a broader more inclusive (sensitive) case definition aimed towards signal detection. A manual review process was adopted, involving all WP3 partners and some additional partners from WP4 (AEMPS, UBATH, CMNS). The case definitions were developed by considering the clinical event definitions agreed within the Consortium, any Standardised MedDRA Queries (SMQs) that already exist for these outcomes and the database codes selected for analysis of healthcare record databases (in WP4).

Identification of T2DM Drugs in FAERS and EV databases: Within the FAERS database, suspect drugs are coded according to the FDA Drug Dictionary or entered verbatim. Thus, drug names appear as generic, trade names or combinations and often contain spelling variations. A major task was undertaken by the DSRU to identify as many T2DM drugs as possible within the database by mapping the reported drug name field to a master archive of global trade names for all T2DM drugs derived from an on-line reference source (Martindale). A similar process was completed, at source, during the preparing of Eudravigilance data extract. Drugs were therefore coded either by generic name (if identifiable as a T2DM drug) or a non-DM drug.

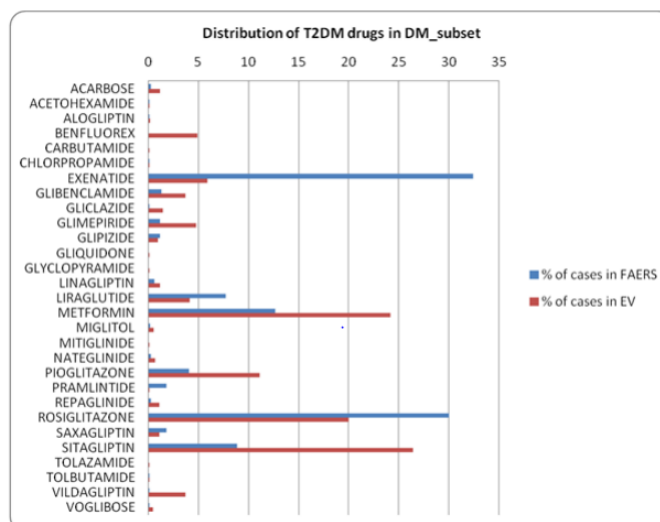


Figure 7 number of reports for the SAFEGUARD study drugs in FAERS and Eudravigilance

Method for detection of disproportionality analysis: Disproportionality analysis is used to look for associations (signals) of adverse drug reactions in pharmacovigilance databases. The method compares the reporting proportion for a drug-outcome pair with that of other drug-outcome pairs in the database. First we looked at time patterns of case reports by study drug (see figures below) since safety alerts may trigger reporting.

Several statistical techniques are available which produce a metric that can be used to detect signals of disproportionate reporting (SDRs). For the primary analysis, the metric used was the proportional reporting ratio (PRR) as this is relatively simple from a computational and interpretation aspect. An individual drug-outcome pair was classified as a SDR if the lower 95% confidence interval for the PRR was greater than 1 and the number of cases was greater than or equal to 3. Additional metrics were also used (Reporting Odds Ratio and False Discovery Rate) in sensitivity analyses. Disproportionality analyses were performed 8 times for each drug-outcome pair of interest. This comprised analysis in both FAERs and EV, using narrow and

broad case definitions and, in each case, using two different comparators (all other drugs in database and only other diabetes drugs).

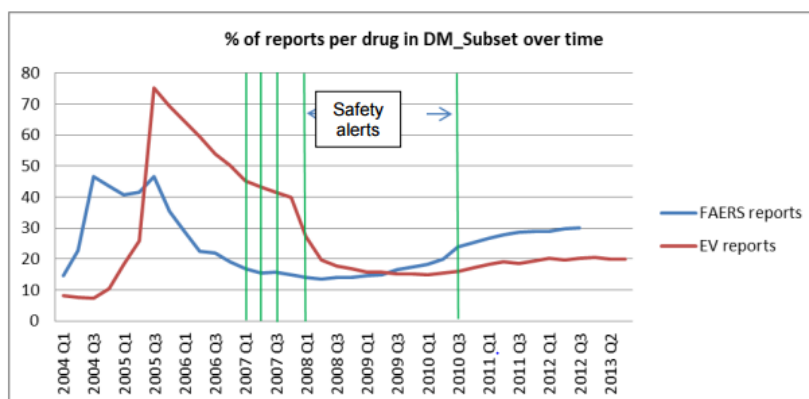


Figure 8 Proportion of Reports in DM_Subsets Over Time for Rosiglitazone

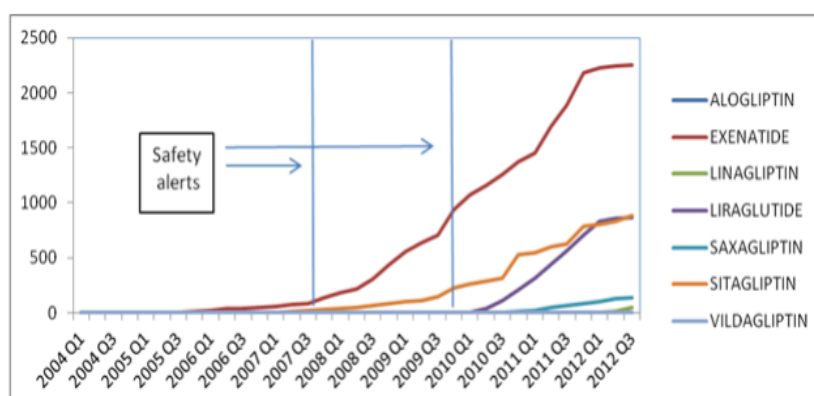


Figure 9 Reports of acute pancreatitis for incretin based therapies in FAERS

Analysis of disproportionality was also performed over time to assess whether a particular database or case definition led to earlier detection of associations. A more generalised signal screening analysis to identify previously unrecognised ADRs for the newer incretin-based therapies was also performed by calculating the PRR for all reported preferred terms for this subgroup of drugs.

List of Cardiovascular, Cerebrovascular and Pancreatic Events and New Signals for T2DM Drugs

In the primary analysis for the SAFEGUARD outcomes of interest, disproportionality was identified for many drug-outcome combinations. This was often found when reporting was compared to that of all other drugs but disappeared when compared only to that of other T2DM drugs. This may be explained as evidence of confounding by indication whereby the reporting for cardiovascular and pancreatic outcomes is higher in users of T2DM drugs because of the underlying diabetes, a condition that independently predisposes patients to such outcomes. Comparisons made within the diabetes subset of reports may be considered a more

appropriate comparator. Using this diabetes subset revealed disproportionality for several drug–outcome combinations including:

- pioglitazone and bladder cancer
- pioglitazone and heart failure
- rosiglitazone and all of the cardiovascular outcomes and cerebrovascular outcomes
- newer incretin-based therapies and pancreatic outcomes.

These findings were largely expected, since it is these specific safety issues that have led to the call for further investigation in the form of the SAFEGUARD project.

Although the FAERS and EV databases are not independent due to a degree of overlap we found differences in the two databases in terms of the distribution of reporters, seriousness of reports and drugs reported. In the analysis over time within the diabetes subset, disproportionality was found for a total of 65 drug–outcome pairs at some point during the period of observation (approximately one decade). Most were detectable in FAERS only or detectable earlier in FAERS. For around half, there was no difference in the detectability whether narrow or broad case definitions were used. The broader case definitions detected disproportionality earlier in around 20% of the 65 pairs.

In the open-ended analysis for incretin-based therapies, disproportionality was found most frequently for events within the ‘Gastrointestinal’ and ‘Skin’ System Organ Classes for the gliptins and within the ‘Gastrointestinal’ and ‘General’ disorders System Organ Classes for the GLP–agonists.

Additional activities in this work package were aimed at developing a suitable output for the purposes of integrating the results with those generated from the pharmacoepidemiology studies in WP4. This output had two dimensions: the first was based on transforming the numerical results into a categorical result (low, medium, high or unclear evidence of association) and the second was to qualify this categorical result with a numerical measure of the degree of ‘uncertainty’ that may exist in the data leading to this categorisation.

Based on the different circumstances in which disproportionality was identified, an algorithm was developed to categorise the results into low, medium, high or unclear evidence of association. If disproportionality was found in any of the eight disproportionality analyses then this result was classified as ‘medium’ evidence of an association. Results were upgraded to ‘high’ if disproportionality was identified in either database using a narrow (specific) outcome definition when using other T2DM drugs only as the comparator. If no disproportionality was detected in any analysis this result was classified as ‘low’ evidence of association. Of the 261 pairs evaluated, twenty-two (8.4%) were classified as ‘high’ evidence of an association, 48 (18.4%) as ‘medium’, 122 (46.7%) as ‘low’ and 69 (26.4%) as unclear. Those pairs classified as ‘high’ were largely as expected (see table 2)

Table 3 Drugs with high evidence of association using EUDRAVIGILANCE and FAERS

Outcome	Drug	Uncertainty Score*
Acute Pancreatitis	Exenatide	0.429
	Liraglutide	0.286
	Alogliptin	0.500
	Linagliptin	0.250
	Saxagliptin	0.375
	Sitagliptin	0.286
	Vildagliptin	0.625
Pancreatic Cancer	Exenatide	0.286
	Liraglutide	0.250
	Saxagliptin	0.375
	Sitagliptin	0.286
	Vildagliptin	0.250
Bladder Cancer	Pioglitazone	0.143
Haemorrhagic Stroke	Rosiglitazone	0.143
Ischaemic Stroke	Rosiglitazone	0.143
Heart Failure	Pioglitazone	0.571
	Rosiglitazone	0.143
Myocardial Infarction	Rosiglitazone	0.143
Ventricular Arrhythmia	Metformin	0.375
	Rosiglitazone	0.125
Sudden Cardiac Death	Nateglinide	0.500
	Rosiglitazone	0.143

A systematic and objective assessment was performed to evaluate whether various sources of uncertainty may have affected these results. Up to 10 uncertainty factors were considered in the computation of an overall uncertainty score. The score represents the proportion of these 10 uncertainty factors that applied to results for each individual drug-outcome pair. A full description of the criteria used to define uncertainty is provided in D7.5.

The 10 uncertainty factors considered for each result were as follows:

- Time the drug has been on the market,
- Level of drug use of the drug,
- Effects of multiple statistical testing,
- Influence of the reporter type,
- Issues such as notoriety bias (due to safety alerts in the media),
- Competition bias (due to high reporting rates for certain drugs that can mask potential signals for other drugs),
- Use of different thresholds to define disproportionality,
- Removal of rule of ‘minimum of three reports’ to define a signal,
- Specificity of the outcome definitions used,
- Consistency of results from FAERS and EV databases

Among the 22 pairs classified as having ‘high’ evidence of an association, uncertainty was lowest for rosiglitazone and ventricular arrhythmia (score=0.125) and highest for vildagliptin

and acute pancreatitis (score=0.625). This included the entire period also after first signals were raised (see table 2)

ANALYSIS OF HEALTHCARE DATA (PHARMACOEPIDEMOLOGY STUDIES) (WP4 &7)

This work was led by EMC with large input from *AEMPS, BWH, CMNS, PHARMO, RTI-HS, F-SIMG, UBATH, BIPS, UNIMIB*. The objectives of the work were:

the estimation of rates and relative risks for the outcomes of interest associated with non-insulin blood glucose lowering drugs (NIBGLD) as well as analysing their patterns of use, using electronic data from healthcare databases (DBs).

The tasks can be summarised in six main areas:

- development of a common protocol for drug utilization and comparative studies for the study of the association between cardio/cerebrovascular and pancreatic events (ten events of interest) and use of NIBGLD,
- mapping and benchmarking of all events (both outcomes and covariates),
- development of software for data linkage and Data-warehouse (remote research environment RRE) for standardized data elaboration and analysis,
- drug utilization studies (DUS),
- estimation of rates and relative risk of each outcome of interest and
- validation of outcomes.

In the original plan description and report of all these tasks were organized in five deliverables to be produced along the development of the WP4. To accommodate transition of key personnel at UBATH who was responsible for the DUS an additional deliverable (D4.6) was added to the set of original documents. This deliverable reports the final part of the DUS i.e., prescription level analysis that regards characteristics of subjects using NIBGLDs and channelling.

Protocol development

The common study protocol for the multinational database study was written and reported in D4.1. The deliverable consists of two parts: a protocol for the observational studies that will be performed to estimate the risk of each event of interest associated with T2DM drugs and to investigate dose and duration effects. A detailed description of methods to deal with confounding is provided in this part. The second part of D4.1 is the drug utilization protocol. Both protocols were submitted to ENCePP registry of studies at the European Medicines Agency and received an ENCePP seal. <http://www.encepp.eu/encepp/viewResource.htm?id=8326> and <http://www.encepp.eu/encepp/viewResource.htm?id=8323>.

Mapping: code mapping between different code systems and free text in the different languages of the DBs was conducted and harmonized. For each event (10 outcomes and more than 60 covariates) a clinical definition and a specific algorithm for each DB was generated. The harmonisation process comprises also the generation and comparison of age and gender specific incidence rates of each of the events, comparison of the distribution of codes. Figures and graphs for rates and code counts were produced using standardized software for data

elaboration and common scripts in a centralized environment (RRE) in order to ensure high standards of data management security and a uniform approach to the analysis. A detailed description of the whole process together with the algorithms and clinical definitions of outcomes and covariates and examples of the harmonization process is reported in D4.3. The definitions, terms and codes have been stored for re-use in the future.

Databases participating in SAFEGUARD are listed in table 3, the source population comprised 52 million subjects, a total of 287 million years of follow-up and 1,781,786 type II diabetes patients.

Table 4 Overview of participating databases in the pharmacoepidemiological studies

	Country	Type of data source	Period covered	Source population (millions)	Diagnosis terminology	Medication coding
GePaRD	Germany	Administrative	2003-2009	14.4	ICD10-GM	ATC
Regional DB Lombardy	Italy	Administrative	1999-2010	11.3	ICD9-CM	ATC
Regional DB Puglia	Italy	Administrative	2001-2010	4.8	ICD9-CM	ATC
Medicare	U.S.A.	Administrative	2006-2008	2.2	ICD9-CM	NDC
Pharmo	Netherlands	Record linkage	1998-2010	5.3	ICD9-CM	ATC
Health Search	Italy	Electronic	2000-2011	1.2	ICD9-CM and free text	ATC
IPCI	Netherlands	Medical Record	1999-2013	1.7	ICPC1 and free text	ATC
BIFAP	Spain	Electronic	2001-2011	3.7	ICPC1 and free text	ATC
CPRD	U.K.	Medical Record	1999-2011	7.5	READ	BNF/Multilex

Software Development for Data Linkage and Data Warehouse

A distributed network approach to the participating health care DBs with use of standardized and common software for the local elaboration of data in a common data model was applied (See figure).

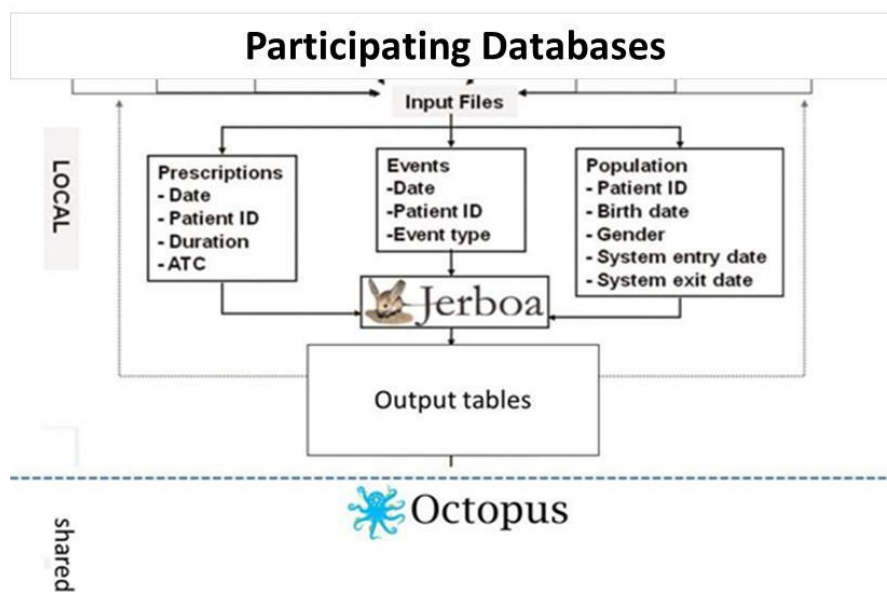


Figure 10 Common data model approach for data sharing as described in Trijiro et al. i

Jerboa, a JAVA based software was starting to be developed within the EU-ADR project (ICT-215847) and was adapted for SAFEGUARD. Jerboa aggregates, de-identifies and encrypts data producing a set of outputs useful for the analyses that are sent to a central repository for further evaluation and analysis. All analyses are performed using the specific Jerboa outputs produced for each study in a distributed fashion but by using a common remote research environment called Octopus, Octopus was built for ARITMO (FP7-HEALTH 241679) and re-utilized in SAFEGUARD (see figure 11). Databases custodians received a token and could share their data in this environment as well as work together on the analysis and pooling of results.

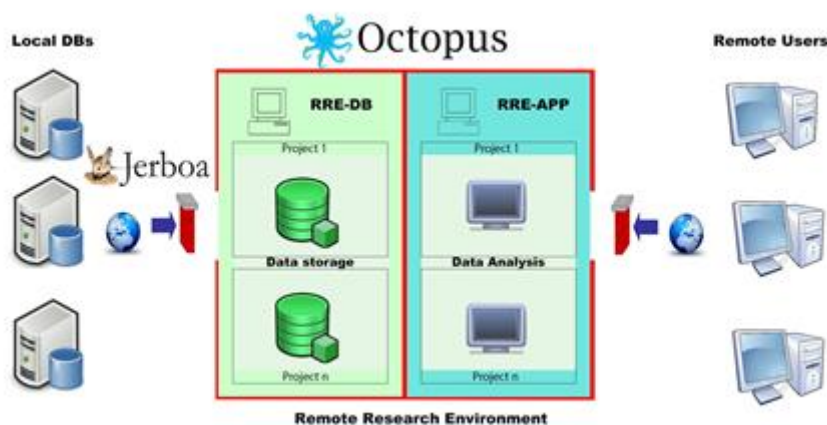


Figure 11: Octopus remote research environment for collaborative projects

Octopus allows for loading, retrieving, extracting, and transforming of the data. Each user has his/her own environment on the server containing all necessary analytical tools. Access to data is only granted if the user is part of the specific WP. Details on the security measures to ensure the high level of stored data protection as described in article 34 of the legislative decree 196/2003 and Directive 95/46/EC for processing of healthcare data as well as all details regarding Jerboa software, input and output files structure and several examples on these output files are reported in D4.3.

Drug Utilization Studies

All analyses were conducted using standardized data elaboration software and common scripts have been used to analyse all data in the centralized environment. This approach ensured high standards of data management and security and a uniform approach to the analysis. The data showed that newer drugs (incretin based treatments) were used in very limited amounts and mostly in USA, Spain and Italy, underlining the importance to use data from multiple countries. TZDs were mostly used in USA, fixed combinations were used frequently in Italy, but the basis of treatment in all countries were biguanides and sulfonylureas. Whereas treatment diversified upon introduction of newer classes, the percentage of time on biguanides increased.

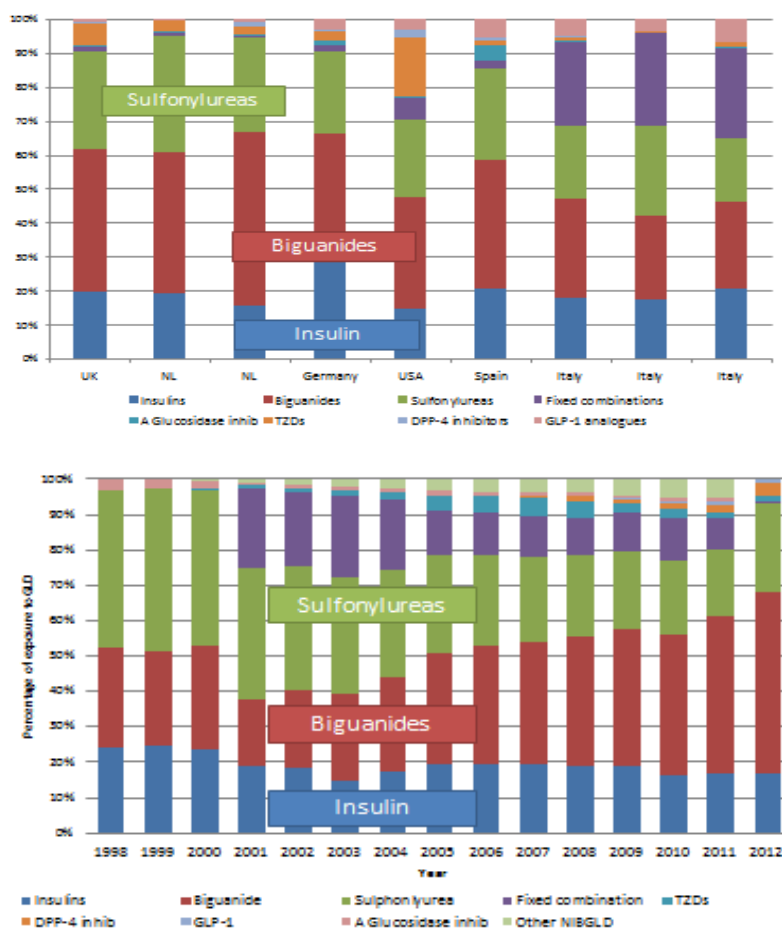


Figure 12 distribution of person time of exposure to different drugs in the different databases and over time
 Use of incretins increased over time with highest increases in sitagliptin (figure 13)

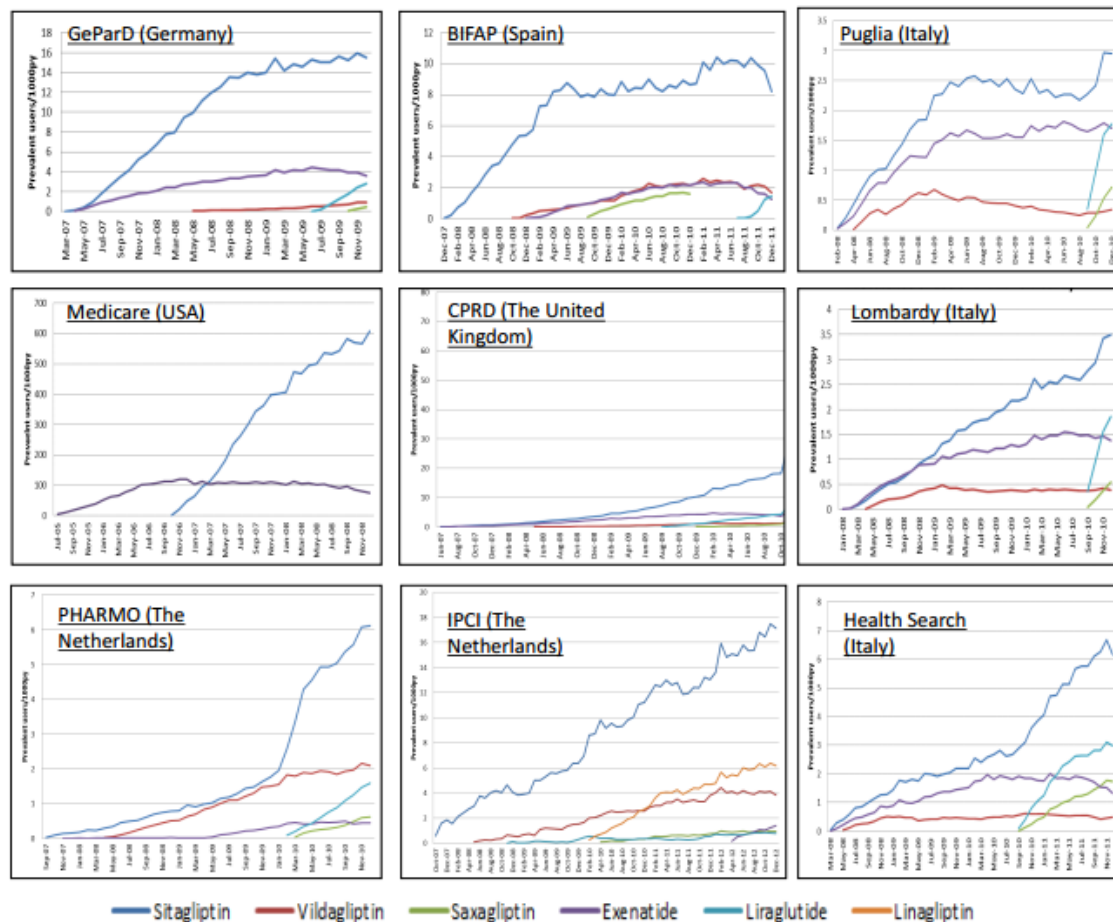


Figure 13 Use of incretins by database and time (y-axes differ)

Subjects starting GLP-1 therapy are younger than subjects who start using other NIBGLD. Metformin was the most used biguanide; glibenclamide, gliclazide and glimepiride are the sulfonylureas preferred in European databases except in the Netherlands where tolbutamide is preferred while glipizide is the preferred one in Medicare (USA). In GePaRD and the Italian DBs, pioglitazone is the preferred thiazolidinedione; regarding incretin-based therapies, sitagliptin is the preferred first DPP-4-inhibitor in all databases. Regarding GLP-1 receptor agonists, exenatide was preferred in BIFAP, CPRD, Medicare, and Puglia, while liraglutide was preferred in IPCI, Health Search, GePaRD, PHARMO and Lombardy. Biguanides are the most commonly used NIBGLD before starting any other group to treat hyperglycaemia, except for the new users of alpha glucosidase inhibitors in BIFAP, where sulfonylureas are the most common previous medication. We observed an increase in the number of previous GLD for those starting thiazolidinediones, meglitinides, DPP-4 inhibitors and GLP1 receptor agonists (compared to sulfonylureas and biguanides). This follows the recommendations considering these drugs are recommended as add-on therapies (2nd and 3rd line options). Biguanides is the group with less concomitant drugs, suggesting that it is mainly started in monotherapy, while others are used more in combination with other medications for hyperglycaemia; the most common concomitant GLD at the start of any other NIBGLD are biguanides and sulfonylureas, followed by thiazolidinediones that are more commonly used concomitantly with other GLDs in Medicare compared to other databases. Among comorbidities,

hypertension, obesity (ever) and hyperlipidaemia are the most common comorbidities observed in subject treated with NIBGLD. Drug utilization was described in D4.2 and D4.6.

Rates and Relative Risk Estimation in Databases

Background rates of the ten SAFEGUARD events (Myocardial Infarction, Heart Failure, Ventricular arrhythmia, Sudden cardiac death, Cerebrovascular, Hemorrhagic stroke, Ischemic stroke, Pancreatic events, Acute pancreatitis, Pancreas cancer, Bladder cancer and total mortality) were estimated in the T2DM population and in a population of subjects without T2DM diagnosis (see figure 14)

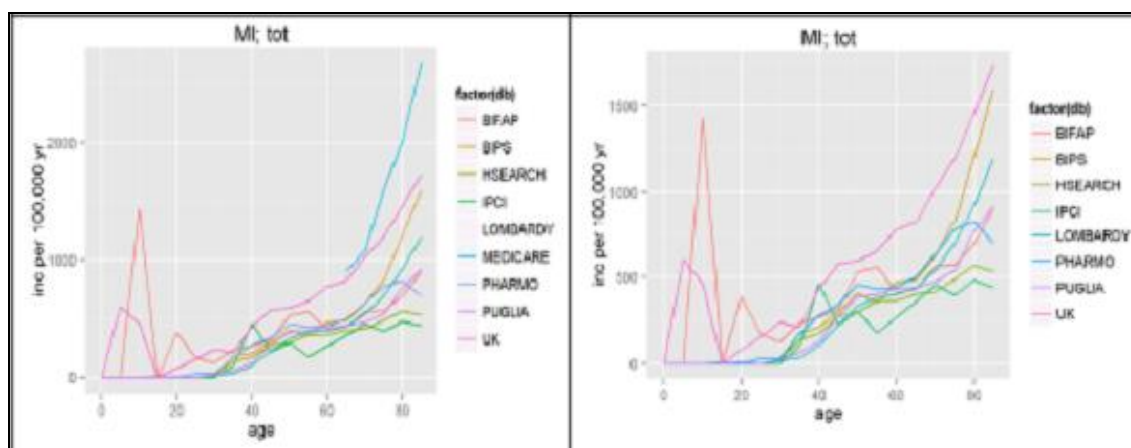


Figure 14 Incidence rates of myocardial infarction in T2DM patients, with (left) and without (right) US data

To assess the risk of each outcome of interest associated to NIBGLDs, nested case controls studies (for all outcomes except total mortality (TM)) and a cohort study (for TM) were performed. Controls were matched on database, gender, age and year of cohort entry. Details of the analyses are given in D4.5 that reports methods, settings, results and conclusions from the analyses performed in each DB but also the pooled estimates obtained applying the meta-analytic approach, a summary will be provided to the ENCePP website. Results are summarized in the integration tables below for each of the outcomes.

WP 7 assisted in the analysis and interpretation of the data: since different databases were involved in SAFEGUARD data aggregation and heterogeneity is a topic. Ways to address confounding, misclassification and pooling were described in D7.2 (Protocol for Advanced Statistical Analyses/Models: Description of statistical analyses plan, models and Jerboa output formats) and the results were reported in D7.4. Two methods for the adjustment of unmeasured confounders were applied to all exposure-outcome association estimates that were found statistically significant in database where some confounders are lacking. The results of the rule-out approach showed that smoking status, alcohol drinking and obesity (confounders not measured in the healthcare utilisation databases) couldn't completely explain the excess of risk observed concluding that the increased risk of the outcome might potentially be caused by the exposure. The results of the Montecarlo Sensitivity analysis showed that after the further adjustment for glycemic levels only the relationship between current use of rosiglitazone and risk of heart failure remain statistically significant suggesting the importance of adjusting the association estimate for this confounder. The instrumental variable approach considered a cohort design and was used to estimate the risk difference (RD) of myocardial infarction between users of DPP4 inhibitors (DPP4-i) and of sulphonylureas (SUs) used as add on therapy to metformin. The raw results showed that patients treated with

DPP4-i seem to have a risk of MI 0.00141 lower than patients treated with SUs although the RD is not significant. None of the potential confounder seem to be associated with MI risk except for age. After the adjustment for the unmeasured confounders through the instrumental variable approach, the RD for the exposure varied from -0.00141 to -0.01399. The results showed a substantial lack of effect of the IV approach. This analysis showed a non-significant risk difference of MI in patients using DPP4-i as second line treatment for diabetes compared to SUs.

Other statistical methods and study design for the adjustment of measured and unmeasured confounders were considered such as the use of propensity score and case-only designs. The results of the propensity score matching for TM are reported in deliverable 4.5 while the results of the case-crossover and case time-control were inconsistent respect to the results of the main analysis due to the too high random error related to the restriction of the sample to case only.

Regarding misclassification, the two proposed methods (regression calibration and SIMEX) were replaced by the Monte Carlo Sensitivity Analysis (MCSA) for misclassified categorical variables developed specifically for this project. The MCSA approach was implemented to assess the impact of the misclassification on the dose-response relationship between time spent with NIBGLDs available and onset of a hypothetical outcome when treatment duration is evaluated using the defined daily dose instead of the prescribed daily dose. Specifically, we defined several scenarios corresponding to different apparent risk ratio patterns assumed to be obtained in a hypothetical study. The results highlighted the complex effect of non-differential misclassification on the strength of the association between a categorical exposure and the considered outcome. In general, risk ratios may be biased towards or away from the null. Specifically, for the highest exposure category, it was noticed that apparent risk ratios always had the tendency to underestimate the true risk ratios, a general. Moreover, it was observed how uncertainty in misclassification-adjusted risk ratios might nontrivially depend on both the uncertainty in predictive values and the agreement between true and approximate exposure. However, uncertainty in adjusted risk ratios was higher for the latter, possibly owing to a greater discrepancy between true and proxy exposures.

Regarding the two proposed pooling approaches, they provided comparable results. Some associations were detected only by the meta-analytic approach such as current use metformin in combination with rosiglitazone and haemorrhagic stroke or sudden cardiac death, while others more frequently only by the individual data pooling. It has to be noticed that individual data pooling does not account for between database heterogeneity, however, in most cases the I² index, used to quantify the heterogeneity between databases, is very low suggesting that not considering this factor should not have compromised the results obtained from the individual pooling method except for specific situations. However, an individual data pooling approach allows studying a larger number of drug-event association compared to considering single databases. In fact, it is possible that the exposures reporting a number of exposed cases and controls lower than 5 in a single database (criteria used to exclude some exposures from the analyses) have been studied using this approach. Moreover, the estimates obtained are more precise than those of the meta-analytic approach, but since the individual pooling allow adjusting the estimated only for the covariates measured in all databases, they are potentially adjusted for a lower number of confounding factors than the meta-analytic estimates.

Cardiovascular events

Table 5 Meta-analytic and pooled estimates for myocardial infarction

Label	Fixed effect		Random effect		p-value	I ²	N	Individual pooling	
	OR	95% CI	OR	95% CI				OR	95% CI
Current use of Acarbose	0.95	(0.65-1.4)	0.95	(0.64-1.4)	0.38	1.73	4	1.00	(0.72-1.39)
Current use of Chlorpropamide	-	-	-	-	-	-	-	1.81	(0.67-4.90)
Current use of Exenatide	-	-	-	-	-	-	-	1.35	(0.70-2.61)
Current use of Glibenclamide	0.96	(0.84-1.09)	0.95	(0.82-1.1)	0.35	9.83	7	1.06	(0.94-1.19)
Current use of Glipizide	0.97	(0.9-1.05)	0.95	(0.85-1.06)	0.18	33.65	6	1.00	(0.93-1.07)
Current use of Glimepiride	0.97	(0.9-1.04)	0.97	(0.9-1.04)	0.64	0.00	8	1.03	(0.97-1.10)
Current use of Glipizide	1.02	(0.87-1.2)	0.99	(0.81-1.22)	0.34	9.93	4	1.10	(0.97-1.24)
Current use of Gliquidone	0.96	(0.59-1.55)	0.96	(0.59-1.55)	0.45	0.00	2	1.20	(0.79-1.83)
Current use of Metformin	0.83	(0.78-0.87)	0.83	(0.77-0.9)	0.06	45.77	9	0.82	(0.79-0.87)
Current use of Metformin and Exenatide	-	-	-	-	-	-	-	0.44	(0.22-0.88)
Current use of Metformin and Liraglutide	-	-	-	-	-	-	-	0.72	(0.39-1.32)
Current use of Metformin and Nateglinide	1.27	(0.67-2.41)	1.22	(0.47-3.17)	0.14	54.00	2	1.25	(0.72-2.19)
Current use of Metformin and Pioglitazone	0.85	(0.72-0.99)	0.85	(0.72-0.99)	0.82	0.00	6	0.81	(0.70-0.94)
Current use of Metformin and Repaglinide	0.97	(0.81-1.16)	0.97	(0.81-1.16)	0.94	0.00	7	1.08	(0.91-1.28)
Current use of Metformin and Rosiglitazone	0.82	(0.7-0.97)	0.82	(0.69-0.99)	0.37	7.39	7	0.73	(0.63-0.85)
Current use of Metformin and Saxagliptin	-	-	-	-	-	-	-	0.45	(0.19-1.04)
Current use of Metformin and Sitagliptin	0.78	(0.63-0.96)	0.76	(0.52-1.13)	0.03	62.41	5	0.79	(0.66-0.94)
Current use of Metformin and Vildagliptin	0.87	(0.55-1.38)	1.35	(0.26-6.99)	0.00	87.82	2	0.69	(0.48-1.00)
Current use of Miglitol	-	-	-	-	-	-	-	1.36	(0.56-3.26)
Current use of Nateglinide	-	-	-	-	-	-	-	1.40	(0.89-2.18)
Current use of Pioglitazone	0.98	(0.82-1.17)	0.97	(0.72-1.31)	0.12	48.77	4	0.97	(0.83-1.12)
Current use of Repaglinide	0.90	(0.8-1.02)	0.90	(0.8-1.02)	0.98	0.00	6	1.14	(1.01-1.28)
Current use of Rosiglitazone	1.29	(1.01-1.64)	1.29	(1.01-1.64)	0.55	0.00	4	1.32	(1.07-1.63)
Current use of Sitagliptin	1.29	(0.95-1.75)	1.18	(0.61-2.28)	0.02	74.42	3	1.23	(0.94-1.60)
Current use of Tolbutamide	1.05	(0.85-1.3)	1.05	(0.84-1.32)	0.31	3.78	2	1.02	(0.85-1.22)
Current use of any other NIBGLD	0.87	(0.81-0.94)	0.87	(0.81-0.94)	0.94	0.00	9	0.90	(0.84-0.97)
Past use of any NIBGLD	0.82	(0.78-0.86)	0.87	(0.77-0.99)	0.00	76.49	9	0.84	(0.80-0.88)
Recent use of any NIBGLD	0.95	(0.89-1.03)	0.98	(0.86-1.11)	0.04	51.00	9	0.96	(0.90-1.03)

This table shows that use of Rosiglitazone alone and repaglinide are associated with a significant increased risk of myocardial infarction, metformin and some metformin combinations reduced the risk.

Table 6 Meta-analytic and pooled estimates for heart failure

Label	Fixed effect		Random effect		p-value	I ²	N	Individual pooling	
	OR	95% CI	OR	95% CI				OR	95% CI
Current use of Acarbose	0.97	(0.65-1.43)	0.96	(0.52-1.75)	0.10	56.54	3	0.87	(0.64-1.19)
Current use of Chlorpropamide	-	-	-	-	-	-	-	1.63	(0.96-2.78)
Current use of Exenatide	-	-	-	-	-	-	-	1.11	(0.60-2.05)
Current use of Glibenclamide	0.82	(0.7-0.96)	0.82	(0.7-0.96)	0.68	0.00	7	0.95	(0.83-1.08)
Current use of Gliclazide	0.91	(0.84-1)	0.94	(0.79-1.13)	0.01	67.73	6	1.02	(0.95-1.10)
Current use of Glimepiride	0.90	(0.83-0.97)	0.87	(0.73-1.04)	0.00	72.90	8	1.00	(0.94-1.07)
Current use of Glipizide	1.24	(1.11-1.38)	1.24	(1.11-1.38)	0.40	0.00	4	1.22	(1.13-1.32)
Current use of Gliquidone	0.94	(0.6-1.48)	0.94	(0.6-1.48)	0.59	0.00	2	1.35	(0.94-1.96)
Current use of Metformin	0.85	(0.8-0.9)	0.85	(0.79-0.91)	0.18	29.71	9	0.85	(0.81-0.89)
Current use of Metformin and Acarbose	1.31	(0.6-2.87)	1.31	(0.6-2.87)	0.46	0.00	2	1.11	(0.65-1.92)
Current use of Metformin and Exenatide	-	-	-	-	-	-	-	0.92	(0.51-1.64)
Current use of Metformin and Liraglutide	-	-	-	-	-	-	-	0.99	(0.36-2.75)
Current use of Metformin and Nateglinide	-	-	-	-	-	-	-	1.44	(0.97-2.12)
Current use of Metformin and Pioglitazone	1.11	(0.97-1.27)	1.11	(0.97-1.27)	0.54	0.00	6	0.90	(0.80-1.01)
Current use of Metformin and Repaglinide	1.03	(0.83-1.27)	1.05	(0.8-1.39)	0.16	37.05	6	1.16	(0.96-1.39)
Current use of Metformin and Rosiglitazone	1.09	(0.95-1.26)	1.09	(0.95-1.26)	0.71	0.00	7	0.93	(0.82-1.05)
Current use of Metformin and Saxagliptin	-	-	-	-	-	-	-	0.97	(0.39-2.41)
Current use of Metformin and Sitagliptin	0.85	(0.63-1.15)	0.85	(0.63-1.15)	0.89	0.00	4	0.78	(0.6-1.00)
Current use of Metformin and Vildagliptin	1.09	(0.52-2.29)	1.05	(0.29-3.81)	0.08	66.76	2	0.76	(0.44-1.32)
Current use of Miglitol	-	-	-	-	-	-	-	0.72	(0.30-1.72)
Current use of Nateglinide	-	-	-	-	-	-	-	1.59	(1.20-2.11)
Current use of Pioglitazone	1.40	(1.24-1.58)	1.40	(1.24-1.58)	0.89	0.00	3	1.38	(1.26-1.52)
Current use of Repaglinide	0.97	(0.86-1.11)	0.97	(0.8-1.19)	0.09	47.08	6	1.42	(1.28-1.59)
Current use of Rosiglitazone	1.75	(1.5-2.03)	1.62	(1.11-2.37)	0.20	37.04	3	1.65	(1.45-1.86)
Current use of Sitagliptin	1.22	(0.93-1.62)	1.55	(0.89-2.68)	0.10	51.15	4	1.58	(1.26-1.99)
Current use of Tolbutamide	0.93	(0.73-1.18)	0.93	(0.73-1.18)	0.67	0.00	4	0.99	(0.82-1.20)
Current use of any other NIBGLD	1.18	(1.1-1.27)	1.11	(0.99-1.26)	0.06	47.26	9	1.21	(1.14-1.28)
Past use of any NIBGLD	0.96	(0.9-1.01)	1.03	(0.82-1.28)	0.00	91.64	9	0.91	(0.87-0.96)
Recent use of any NIBGLD	1.05	(0.96-1.13)	1.07	(0.85-1.34)	0.00	82.73	9	0.98	(0.91-1.05)

Current use of glipizide, pioglitazone, repaglinide, nateglinide, rosiglitazone and sitagliptin were associated with an increased risk of heart failure in the one stage pooling, this did not hold in the two stage pooling for repaglinide.

Table 7 Meta-analytic and pooled estimates for ventricular arrhythmia

Label	Fixed effect		Random effect		p-value	I ²	N	Individual pooling	
	OR	95% CI	OR	95% CI				OR	95% CI
Current use of Acarbose	-	-	-	-	-	-	-	2.37	(0.96-5.82)
Current use of Glibenclamide	1.21	(0.69-2.40)	1.21	(0.69-2.40)	0.97	0.00	2	1.62	(1.13-2.31)
Current use of Gliclazide	1.22	(0.90-1.67)	1.22	(0.90-1.67)	0.49	0.00	5	1.40	(1.10-1.77)
Current use of Glimepiride	0.95	(0.76-1.19)	0.95	(0.76-1.19)	0.52	0.00	6	1.22	(1.02-1.46)
Current use of Glipizide	-	-	-	-	-	-	-	1.70	(1.38-2.10)
Current use of Gliquidone	-	-	-	-	-	-	-	1.72	(0.69-4.31)
Current use of Metformin	1.04	(0.88-1.24)	1.04	(0.88-1.24)	0.73	0.00	7	1.03	(0.89-1.19)
Current use of Metformin and Acarbose	-	-	-	-	-	-	-	3.42	(1.09-10.70)
Current use of Metformin and Nateglinide	-	-	-	-	-	-	-	2.43	(0.84-7.02)
Current use of Metformin and Pioglitazone	1.04	(0.65-1.66)	1.43	(0.43-4.75)	0.09	64.50	2	0.67	(0.47-0.97)
Current use of Metformin and Repaglinide	1.58	(0.83-3.00)	1.58	(0.83-3.00)	0.92	0.00	3	1.68	(1.04-2.72)
Current use of Metformin and Rosiglitazone	-	-	-	-	-	-	-	0.80	(0.55-1.16)
Current use of Metformin and Sitagliptin	-	-	-	-	-	-	-	0.72	(0.36-1.42)
Current use of Nateglinide	-	-	-	-	-	-	-	1.61	(0.76-3.42)
Current use of Pioglitazone	-	-	-	-	-	-	-	1.19	(0.91-1.55)
Current use of Repaglinide	1.51	(1.03-2.21)	1.51	(1.03-2.21)	0.47	0.00	4	2.60	(1.96-3.45)
Current use of Rosiglitazone	-	-	-	-	-	-	-	0.95	(0.63-1.42)
Current use of Sitagliptin	-	-	-	-	-	-	-	1.59	(0.95-2.67)
Current use of Tolbutamide	-	-	-	-	-	-	-	1.02	(0.54-1.91)
Current use of any other NIBGLD	1.11	(0.90-1.36)	1.11	(0.90-1.36)	0.45	0.00	7	1.13	(0.95-1.35)
Past use of any NIBGLD	1.22	(1.03-1.44)	1.22	(1.03-1.44)	0.84	0.00	7	1.29	(1.13-1.48)
Recent use of any NIBGLD	1.40	(1.10-1.77)	1.40	(1.10-1.77)	0.98	0.00	7	1.51	(1.25-1.82)

Current monotherapy with glibenclamide, gliclazide, glimepiride, glipizide, repaglinide were associated with an increased risk of ventricular arrhythmia in a one stage pooling. The risk associated with repaglinide was strongest as monotherapy and in combination with metformin. This was also consistent in individual databases and two-stage pooling

Table 8 Meta-analytic and pooled estimates for sudden cardiac death

Label	Fixed effect		Random effect		p-value	I ²	N	Individual pooling	
	OR	95% CI	OR	95% CI				OR	95% CI
Current use of Glibenclamide	0.94	(0.59-1.49)	0.95	(0.56-1.59)	0.27	17.44	2	1.24	(0.80-1.93)
Current use of Gliclazide	1.07	(0.87-1.30)	0.98	(0.58-1.65)	0.02	82.67	2	1.08	(0.90-1.28)
Current use of Glimepiride	1.10	(0.86-1.42)	1.21	(0.71-2.07)	0.02	7.15	3	1.28	(1.02-1.60)
Current use of Glipizide	1.54	(1.08-2.20)	1.54	(1.08-2.20)	0.33	0.00	2	1.63	(1.27-2.09)
Current use of Metformin	0.93	(0.79-1.08)	0.93	(0.66-1.30)	0.02	75.61	3	0.91	(0.79-1.04)
Current use of Metformin and Pioglitazone	0.62	(0.37-1.03)	0.61	(0.32-1.17)	0.21	37.68	2	0.59	(0.39-0.89)
Current use of Metformin and Repaglinide	-	-	-	-	-	-	-	0.83	(0.43-1.59)
Current use of Metformin and Rosiglitazone	1.47	(1.00-2.17)	1.47	(1.00-2.17)	0.88	0.00	2	1.17	(0.83-1.65)
Current use of Metformin and Sitagliptin	1.20	(0.56-2.55)	1.20	(0.56-2.55)	0.44	0.00	2	0.94	(0.49-1.80)
Current use of Nateglinide	-	-	-	-	-	-	-	3.50	(1.69-7.28)
Current use of Pioglitazone	1.47	(0.95-2.27)	1.47	(0.95-2.27)	0.78	0.00	2	1.33	(0.96-1.85)
Current use of Repaglinide	1.12	(0.74-1.68)	1.17	(0.68-2.01)	0.26	21.23	2	1.95	(1.38-2.76)
Current use of Rosiglitazone	-	-	-	-	-	-	-	1.33	(0.81-2.19)
Current use of Sitagliptin	-	-	-	-	-	-	-	1.48	(0.66-3.31)
Current use of Tolbutamide	-	-	-	-	-	-	-	0.75	(0.29-1.94)
Current use of any other NIBGLD	0.83	(0.66-1.04)	0.83	(0.66-1.04)	0.40	0.00	3	0.88	(0.73-1.07)
Past use of any NIBGLD	1.81	(1.55-2.11)	1.80	(0.94-3.46)	0.00	93.90	3	1.86	(1.62-2.14)
Recent use of any NIBGLD	1.97	(1.59-2.43)	1.88	(1.26-2.80)	0.05	66.29	3	2.11	(1.74-2.56)

Current use of glimepiride, glipizide, nateglinide and repaglinide are associated with an increased risk of sudden cardiac death in a one stage pooling

Cerebrovascular events

Table 9 Meta-analytic and pooled estimates for ischemic stroke

Label	Fixed effect		Random effect		p-value	I ²	N	Individual pooling	
	OR	95% CI	OR	95% CI				OR	95% CI
Current use of Acarbose	0.92	(0.65-1.31)	0.92	(0.65-1.31)	0.66	0.00	5	0.88	(0.65-1.21)
Current use of Chlorpropamide	-	-	-	-	-	-	-	1.78	(0.76-4.16)
Current use of Exenatide	-	-	-	-	-	-	-	1.44	(0.69-3.01)
Current use of Glibenclamide	1.03	(0.9-1.17)	1.05	(0.85-1.3)	0.09	47.09	6	1.06	(0.94-1.19)
Current use of Gliclazide	0.95	(0.87-1.03)	0.96	(0.84-1.1)	0.09	48.10	6	0.98	(0.90-1.06)
Current use of Glimepiride	0.92	(0.85-0.99)	0.92	(0.85-0.99)	0.85	0.00	8	0.98	(0.92-1.05)
Current use of Glipizide	1.15	(0.99-1.34)	1.15	(0.99-1.34)	0.43	0.00	4	1.20	(1.06-1.35)
Current use of Gliquidone	0.87	(0.54-1.41)	0.89	(0.28-2.89)	0.01	83.18	2	1.08	(0.73-1.60)
Current use of Metformin	0.80	(0.75-0.84)	0.80	(0.75-0.84)	0.55	0.00	9	0.80	(0.76-0.85)
Current use of Metformin and Acarbose	-	-	-	-	-	-	-	0.94	(0.49-1.82)
Current use of Metformin and Exenatide	-	-	-	-	-	-	-	0.69	(0.32-1.48)
Current use of Metformin and Nateglinide	1.90	(0.96-3.74)	2.08	(0.8-5.44)	0.19	42.71	2	1.59	(0.91-2.79)
Current use of Metformin and Pioglitazone	0.68	(0.56-0.83)	0.68	(0.56-0.83)	0.42	0.00	5	0.61	(0.51-0.73)
Current use of Metformin and Repaglinide	1.12	(0.92-1.37)	1.12	(0.92-1.37)	0.63	0.00	6	1.22	(1.01-1.47)
Current use of Metformin and Rosiglitazone	0.75	(0.62-0.92)	0.75	(0.62-0.92)	0.63	0.00	5	0.65	(0.54-0.78)
Current use of Metformin and Saxagliptin	-	-	-	-	-	-	-	0.54	(0.23-1.29)
Current use of Metformin and Sitagliptin	0.75	(0.59-0.96)	0.75	(0.59-0.96)	0.86	0.00	4	0.69	(0.56-0.85)
Current use of Metformin and Vildagliptin	-	-	-	-	-	-	-	0.64	(0.43-0.95)
Current use of Nateglinide	-	-	-	-	-	-	-	1.13	(0.75-1.71)
Current use of Pioglitazone	0.81	(0.67-0.97)	0.79	(0.54-1.13)	0.10	45.51	6	0.84	(0.72-0.99)
Current use of Repaglinide	0.89	(0.78-1.01)	0.89	(0.78-1.01)	0.52	0.00	7	1.09	(0.97-1.24)
Current use of Rosiglitazone	0.88	(0.68-1.14)	1.01	(0.57-1.8)	0.06	65.20	3	0.88	(0.70-1.10)
Current use of Saxagliptin	-	-	-	-	-	-	-	2.34	(0.83-6.59)
Current use of Sitagliptin	0.84	(0.61-1.15)	1.00	(0.57-1.74)	0.06	59.48	4	0.88	(0.66-1.17)
Current use of Tolbutamide	0.99	(0.8-1.23)	1.08	(0.71-1.66)	0.14	53.79	2	0.94	(0.79-1.13)
Current use of Vildagliptin	-	-	-	-	-	-	-	1.14	(0.49-2.65)
Current use of any other NIBGLD	0.88	(0.81-0.95)	0.88	(0.8-0.97)	0.32	14.10	9	0.90	(0.83-0.98)
Past use of any NIBGLD	0.83	(0.78-0.88)	0.90	(0.76-1.06)	0.00	83.56	9	0.84	(0.80-0.89)
Recent use of any NIBGLD	0.97	(0.9-1.05)	1.03	(0.9-1.19)	0.01	58.47	9	0.97	(0.90-1.05)

Current use of glipizide monotherapy and metformin plus repaglinide were associated with an increased risk of ischemic stroke

Table 10 Meta-analytic and pooled estimates for haemorrhagic stroke

Label	Fixed effect		Random effect		p-value	I ²	N	Individual pooling	
	OR	95% CI	OR	95% CI				OR	95% CI
Current use of Acarbose	-	-	-	-	-	-	-	1.47	(0.73-2.95)
Current use of Glibenclamide	1.39	(0.95-2.02)	1.91	(0.77-4.75)	0.03	71.50	3	1.25	(0.92-1.71)
Current use of Gliclazide	0.97	(0.78-1.21)	0.97	(0.78-1.21)	0.61	0.00	6	0.96	(0.78-1.18)
Current use of Glimepiride	1.09	(0.9-1.32)	1.19	(0.92-1.55)	0.25	22.42	8	1.13	(0.95-1.34)
Current use of Glipizide	-	-	-	-	-	-	-	1.11	(0.79-1.56)
Current use of Metformin	0.98	(0.84-1.14)	1.09	(0.86-1.4)	0.06	47.74	8	0.98	(0.85-1.12)
Current use of Metformin and Pioglitazone	0.99	(0.51-1.93)	1.02	(0.4-2.62)	0.16	48.98	2	0.69	(0.43-1.09)
Current use of Metformin and Repaglinide	1.38	(0.78-2.45)	1.39	(0.77-2.49)	0.31	2.26	2	1.36	(0.86-2.15)
Current use of Metformin and Rosiglitazone	1.85	(1.04-3.29)	1.85	(1.04-3.29)	0.40	0.00	3	1.22	(0.79-1.88)
Current use of Metformin and Sitagliptin	-	-	-	-	-	-	-	0.83	(0.47-1.46)
Current use of Metformin and Vildagliptin	-	-	-	-	-	-	-	0.96	(0.35-2.64)
Current use of Pioglitazone	-	-	-	-	-	-	-	1.05	(0.70-1.58)
Current use of Repaglinide	1.37	(1.01-1.85)	2.12	(1.11-4.05)	0.02	62.41	6	1.68	(1.28-2.20)
Current use of Rosiglitazone	-	-	-	-	-	-	-	0.75	(0.37-1.54)
Current use of Sitagliptin	-	-	-	-	-	-	-	0.87	(0.37-2.04)
Current use of Tolbutamide	-	-	-	-	-	-	-	1.46	(0.92-2.31)
Current use of any other NIBGLD	1.00	(0.82-1.22)	1.00	(0.82-1.22)	0.66	0.00	8	0.88	(0.72-1.09)
Past use of any NIBGLD	1.17	(1.02-1.34)	1.26	(1.03-1.56)	0.19	30.14	8	1.22	(1.07-1.38)
Recent use of any NIBGLD	1.15	(0.94-1.42)	1.32	(0.94-1.85)	0.08	44.05	8	1.15	(0.95-1.39)

Current use of repaglinide monotherapy was associated with an increased risk of hemorrhagic stroke

Pancreatic events

Table 11 Meta-analytic and pooled estimates for acute pancreatitis

Label	Fixed effect		Random effect		p-value	I ²	N	Individual pooling	
	OR	95% CI	OR	95% CI				OR	95% CI
Current use of Acarbose	-	-	-	-	-	-	-	0.80	(0.37-1.74)
Current use of Glibenclamide	1.17	(0.8-1.69)	1.16	(0.68-1.97)	0.34	9.70	4	1.14	(0.83-1.57)
Current use of Glimepiride	0.99	(0.78-1.25)	0.99	(0.78-1.25)	0.98	0.00	6	1.01	(0.81-1.25)
Current use of Glimepiride	1.02	(0.84-1.24)	1.02	(0.84-1.24)	0.88	0.00	6	1.04	(0.87-1.24)
Current use of Glipizide	-	-	-	-	-	-	-	1.49	(1.14-1.95)
Current use of Metformin	0.84	(0.73-0.96)	0.84	(0.73-0.96)	0.77	0.00	8	0.88	(0.77-1.00)
Current use of Metformin and Liraglutide	-	-	-	-	-	-	-	1.03	(0.38-2.74)
Current use of Metformin and Pioglitazone	0.98	(0.66-1.46)	0.98	(0.66-1.46)	0.64	0.00	4	0.96	(0.68-1.35)
Current use of Metformin and Repaglinide	1.23	(0.74-2.05)	1.23	(0.74-2.05)	0.52	0.00	3	1.16	(0.77-1.73)
Current use of Metformin and Rosiglitazone	1.32	(0.84-2.09)	1.32	(0.84-2.09)	0.39	0.00	2	1.03	(0.71-1.49)
Current use of Metformin and Sitagliptin	-	-	-	-	-	-	-	0.73	(0.46-1.16)
Current use of Metformin and Vildagliptin	-	-	-	-	-	-	-	1.17	(0.55-2.47)
Current use of Nateglinide	-	-	-	-	-	-	-	1.79	(0.80-4.00)
Current use of Pioglitazone	-	-	-	-	-	-	-	1.27	(0.93-1.73)
Current use of Repaglinide	0.88	(0.59-1.31)	0.88	(0.59-1.31)	0.73	0.00	3	0.93	(0.67-1.28)
Current use of Rosiglitazone	-	-	-	-	-	-	-	1.11	(0.67-1.86)
Current use of Sitagliptin	1.29	(0.64-2.58)	1.29	(0.64-2.58)	0.57	0.00	2	1.53	(0.88-2.64)
Current use of Tolbutamide	-	-	-	-	-	-	-	1.19	(0.67-2.11)
Current use of any other NIBGLD	1.01	(0.85-1.2)	1.01	(0.85-1.2)	0.83	0.00	8	1.12	(0.94-1.34)
Past use of any NIBGLD	0.93	(0.81-1.07)	0.93	(0.8-1.09)	0.10	41.79	8	0.97	(0.85-1.10)
Recent use of any NIBGLD	1.1	(0.9-1.33)	1.1	(0.88-1.36)	0.23	25.83	8	1.14	(0.96-1.36)

Current monotherapy with glipizide is associated with an increased risk of acute pancreatitis

Validation of Outcomes

Validation of events was conducted only in selected databases (BIFAP and IPCI) where review of electronic clinical records and/or letter is possible. In order to have more detailed information from each DB, a table with the list of specific information necessary to perform validation studies was circulated among all partners. A common protocol was developed and used for the validation process: these protocols have been used by assessors to classify each case as definite case, probable case, doubtful case and 'no case' together with the set of decision criteria used in these algorithms. The common protocols were developed by a working group at EMC supported by colleagues from BIFAP, HSD and RTI-HS. These have been circulated among participants in WP4. From both DBs involved in the validation, a random sample of 50 incident cases per outcome was selected. The positive predictive value (PPV) was calculated as the proportion of true positives (definite/probable) divided by the total number of evaluated cases together with the 95%CI of the PPV. This process provided an insight regarding the extent of misclassification and allowed for analytic approaches to address it (e.g., regression calibration). The results of this analysis were reported in D4.5. Overall, IS had the lowest PPV probably due by case definition (that includes unspecific stroke codes that

represent a high proportion of cases included). When validation is restricted to those cases identified as specific ischaemic stroke the PPV increased to 85.7%.

MECHANISTIC STUDIES (WP6)

Research partners collaborating in WP6 were VUA/VUMC and CUNI. The objectives of the mechanistic studies were:

- To detail the effects of incretin-based therapies, both GLP-1 receptor agonists and DPP-4 inhibitors, on the cardiovascular (CV) system and the kidney in humans.
- To study the mechanisms underlying the effects of incretin-based therapies on the CV system and the kidney in humans.
- To study the effects on the digestive system, including the gut, pancreas, liver and gall bladder in humans.

During October 2011 to September 2015, the two partners (VUMC and CUNI) designed and performed 4 randomized clinical trials. This comprised literature studies, discussions with experts in the field, designing and writing study protocols, performing administrative tasks, writing standard operating procedures, designing patient information folders and case report forms, familiarizing/training with the used methodology/techniques, following dedicated courses, arranging the necessary approvals of the scientific review boards, ethics review boards, and state agencies, recruiting patients, screening and including patients, performing the test procedures, clinical follow-up during the studies, and all matters involving data management, statistics and writing the reports. Throughout this process, there was frequent contact between VUMC and CUNI to align the protocols and methods as best as possible.

Completing the studies (as described below and in D6.1) was a major achievement for both VUMC and CUNI, given the complexity and grandiosity of their design. A plethora of gold-standard and in-depth physiology tests were conducted, to obtain results with the highest possible accuracy. However, given that many of these tests were not used in clinical practice, they had to be set-up and validated. Moreover, including over 40 subjects per center for experimental studies comprising 12-weeks of treatment with at least 6 testing days per patient required tremendous effort which is not frequently done.

However, during these extensive and complex studies, both study sites experienced several unforeseen challenges that were mitigated excellently and the final results were produced. VUMC included 60 patients, and CUNI 42 patients. We feel that the slightly lower power has no major effect on the results, since the observed effect sizes were so small that we would have needed more than the calculated 15 subjects per treatment-group.

After consulting many experts in the field of cardiovascular, renal and gastrointestinal medicine, a draft protocol was developed (deliverable D6.1). Because of several practical, logistical and regulatory differences between the two study sites, it was decided - after extensive discussion - not to perform identical studies. Instead, we decided to perform complementary studies, while care was taken to align the study protocols as much as possible. Subsequently, both partners arranged the necessary approval(s) and study drugs, and started the experimental part of the randomized trials.

At VUMC Amsterdam, two double-blind randomised placebo-controlled trials were performed in patients with type 2 diabetes: 1) an acute-infusion study with the GLP-1RA exenatide or placebo; and 2) 12 weeks of treatment with the GLP-1RA liraglutide, the DPP-4I sitagliptin, or matching placebos. At CUNI Prague, two open-label randomised trials were performed in patients with type 2 diabetes: 1) an acute study with subcutaneous injection of exenatide or placebo; and 2) 12 weeks of treatment with the GLP-1RA exenatide, the DPP-4I linagliptin, or the sulphonylurea gliclazide MR. At both study sites, measurements were performed prior to and after treatment to assess the drug-induced changes in endpoints of interest.

Because of unanticipated delays and difficulties with patient recruitment (described above), we were not able to present acute data of GLP-1 receptor agonists on cardiovascular function in patients with type 2 diabetes for D6.2. After discussion with the Steering Committee, it was decided to include data of the pilot-study performed at VUMC. Here, we demonstrated in 6 healthy overweight volunteers, that acute infusion of the GLP-1 receptor agonist exenatide had no significant effect on any of the measured cardiovascular parameters, including systemic haemodynamics, cardiac autonomic nervous system balance, cardiac function, vascular stiffness and endothelial function.

After almost 2 years of full-time recruiting patients with type 2 diabetes and performing experiments, both study sites were able to produce reliable data for deliverables, papers and presentations. At VUMC, 60 patients were included. Because of drop-outs, 57 patients were available for the acute study, and 55 patients for the 12-week study. At CUNI, 42 patients were included and available for the acute study. Because of drop-outs, 40 patients were available for the 12-week study.

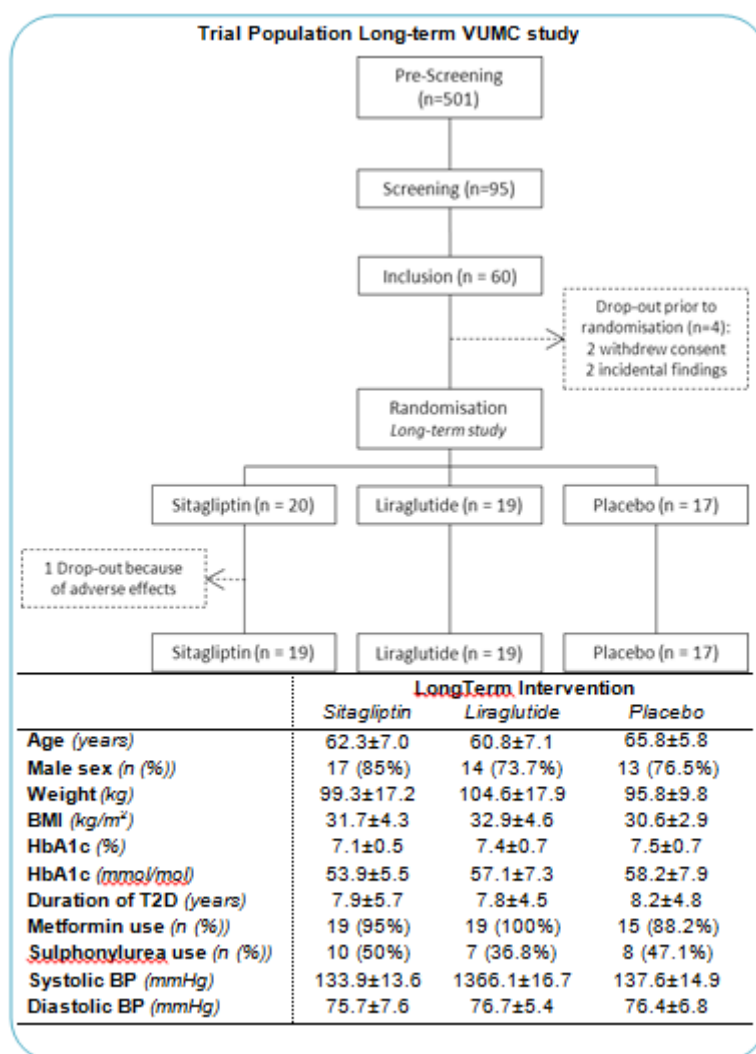


Figure 15 Trial population long term study VUMC

Cardiovascular measurements (D6.3) included blood pressure (measured using automated oscillometric techniques), systemic haemodynamics (beat-to-beat finger blood pressure techniques), heart rate variability, vascular stiffness (pulse wave analysis / pulse wave velocity), parameters of atherosclerosis (vascular ultrasound), cardiac function (cardiac ultrasonography) and microvascular function (measured by LASER Doppler fluxmetry and capillary videomicroscopy). The GLP-1 receptor agonists liraglutide and exenatide significantly increased heart rate. In the acute setting, this was associated with increased blood pressure, while in the long-term blood pressure tended to decrease. No clear effect on autonomic nervous system, large vessels, or microcirculation was observed with any GLP-1RA or DPP-I. Similarly, no clear, clinically relevant effect on cardiac morphology and function could be seen.

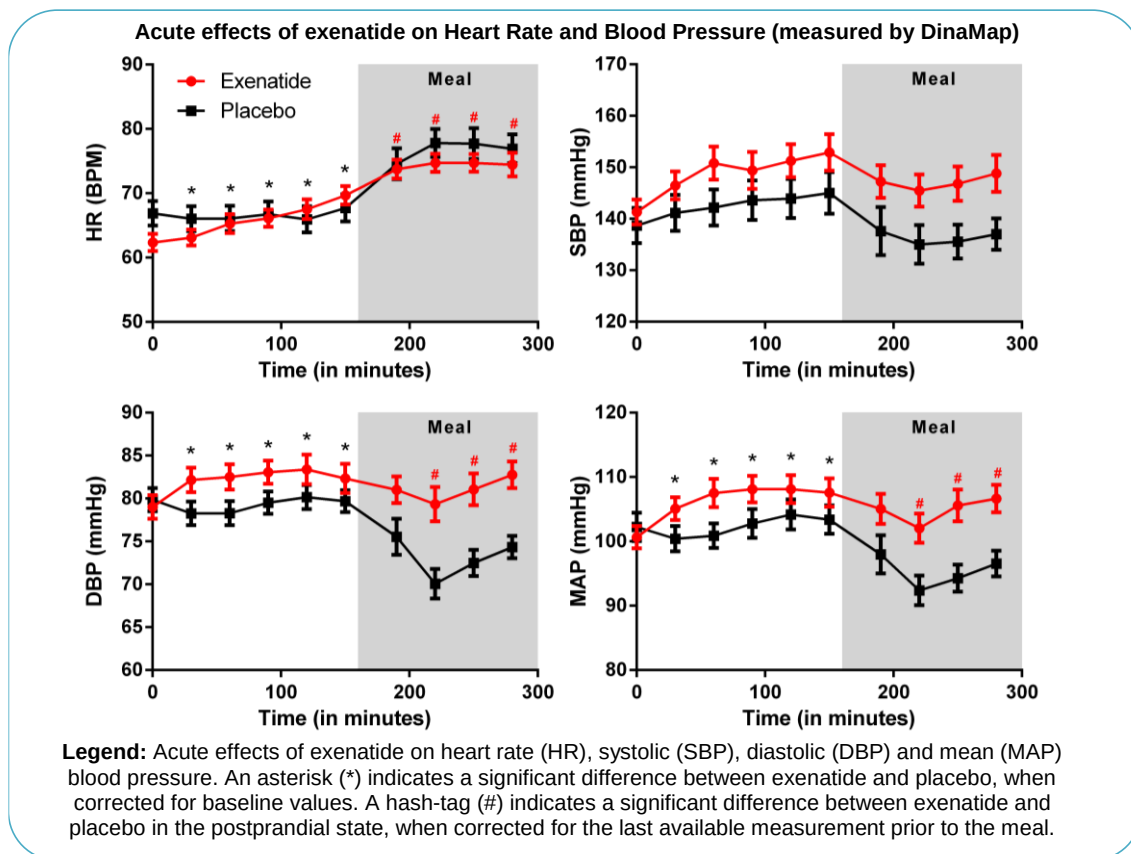


Figure 16 Example of WP 6 study output

Renal measurements (D6.4) included glomerular filtration rate (GFR; inulin and creatinine clearance techniques), effective renal plasma flow (ERPF; para-aminohippuric acid clearance technique). Tubular function was assessed by measuring urinary sodium, potassium and urea excretion. Urinary markers of renal damage (albumin-creatinine ratio, neutrophil gelatinase-associated lipocalin and kidney injury molecule-1) were determined. Filtration fraction and effective renal vascular resistance were calculated. Acute intravenous exenatide had no effect on renal haemodynamics, while increasing tubular excretion of sodium and potassium. In contrast, 12-week treatment with GLP-1 receptor agonists liraglutide and exenatide, or the DPP-4 inhibitor sitagliptin does not affect renal physiology in obese type 2 diabetes patients with normal renal function and low-grade albuminuria, while the DPP-4 inhibitor linagliptin slightly increased glomerular filtration rate.

Gastrointestinal measurements (D6.5) included plasma lipase and amylase levels, exocrine pancreatic enzyme secretion (faecal elastase-1 and chymotrypsin), pancreatic digestive function (¹³C-Mixed Triglycerides breath test), pancreatic volume (MRI-scan), pancreatic bicarbonate secretion (secretin-enhanced magnetic resonance cholangiopancreatography), and pancreatic/ductal morphology (MRI and MRCP), gallbladder emptying (ultrasound techniques), gastric emptying (acetaminophen absorption test) and hepatic fat content (MRI-techniques). The DPP-4 inhibitor sitagliptin, in contrast to liraglutide, exenatide and linagliptin, increased plasma pancreatic amylase secretion. However, none of the used agents induced changes in pancreatic exocrine secretion, digestive function or anatomy. Moreover, these

agents did not affect gallbladder or gastric emptying, and did not change hepatic enzyme secretion.

Combined, the results as presented in D6.3 to D6.5, including the effects of 2 separate GLP-1 receptor agonists (i.e. exenatide and liraglutide) and DPP-4 inhibitors (i.e. sitagliptin and linagliptin), are novel, timely and needed. Moreover, these results add to the data generated by the other WPs within SAFEGUARD.

- Pancreatitis: We demonstrate that, despite increases in pancreatic enzyme levels, no changes occur in exocrine physiology or anatomy. While a small-sized study in a small number of patients, there were no signs demonstrating pancreatic adverse effects.
- Heart rate acceleration: The increase in heart rate with GLP-1 receptor agonists does not appear to be caused by chronic increases in sympathetic activity. Moreover, heart rate variability (which is inversely associated with mortality) does not change. Based on these mechanistic data, there is no evidence of harm. In contrast, there is even a reduction in blood pressure with GLP-1 receptor agonists.
- Heart failure: The studied DPP-4 inhibitors had no evident cardiovascular effect, which supports the findings that sitagliptin and linagliptin have no effect on heart failure.
- Renal failure: None of the agents affected renal function in a negative manner. However, the natriuresis which occurred with acute GLP-1 receptor agonist intervention could potentially, in combination with other factors which reduce circulating volume, lead to pre-renal failure.

INTEGRATION OF EVIDENCE (WP7)

Knowledge integration is the process of combining evidence coming from different and independent sources into a coherent structure. In SAFEGUARD we used Dempster-Shafer model for integration of independent sources of evidence. To perform the integration, first of all, it is necessary to identify some hypotheses (basic hypotheses) of interest and then to harmonize the meaning of each hypothesis among sources. The basic hypotheses should reflect the level of association between each drug and each outcome (low, medium, high). A mass function, that is a measure of reliability of a hypothesis, is defined for each hypothesis in order to construct the combined probability assignment. Combination of the information from the difference sources of information was done using a specific rule available from literature. Both belief and plausibility functions, that define the uncertainty of each specific hypothesis, need to be calculated. Heterogeneity among different sources also needs to be taken into account in order to evaluate the strength of evidence obtained from each source in the proper way. The final product is a 'traffic-light' that is a graphic representation of the results obtained from the Dempster-Shafer theory. The following hypotheses were used for all sources of evidence (i.e., WP3, WP4 and WP5):

- H1 = low belief that there is an 'association' (green light)
- H2 = medium belief that there is an 'association' (yellow light)
- H3 = high belief that there is an 'association' (red light)
- H1UH2UH3 = defined as the complete uncertainty on the existence of 'association' (grey light)

For the individual packages the criteria are listed below.

Table 12 Criteria for starting hypothesis in analysis of spontaneous reporting databases (WP3)

STARTING HYPOTHESIS FOR 'ASSOCIATION'	CRITERIA	TRAFFIC LIGHT
High (H3)	Disproportionality detected in at least 4 of the 8 analyses including at least one analysis that used the narrow case definition AND the diabetes drugs only as the comparator	
Intermediate (H2)	Disproportionality detected in at least 1 of the 8 analysis but not meeting RED criteria	
Low (H1)	No disproportionality detected in any of the 8 analysis	
Inconclusive (H1UH2UH3)	No reports for the drug-outcome in either database	

In work package 4 the following cut off values were used based on the random effects meta-analysis

For cardiovascular outcomes

- Green light = $OR \leq 1$
- Yellow light = $1 < OR < 1.5$
- Red light = $OR \geq 1.5$
- Grey light = uncertainty

For pancreatic outcomes and BC

- Green light = $OR \leq 1.5$
- Yellow light = $1.5 < OR < 3.0$
- Red light = $OR \geq 3.0$

In work package 5 the following criteria were used.

Table 13 Criteria for Classification of Risk from Results of Meta-Analyses of Randomized Controlled Trials

OUTCOMES	GREY: INCONCLUSIVE (INSUFFICIENT OR NO EVIDENCE AVAILABLE)	GREEN: LOW RISK	YELLOW: INTERMEDIATE RISK	RED: HIGH RISK
AMI, Stroke, HF	Number of studies <2	Upper bound of 95%CI <1.3	Upper bound of 95%CI ≥ 1.3 OR lower bound of the 95%CI ≤ 1.8	Lower bound of 95%CI > 1.8
Bladder cancer, Acute Pancreatitis, Pancreatic	Number of studies <2	Upper bound of 95%CI	Upper bound of 95%CI ≥ 1.5 OR lower bound of 95%CI	Lower bound of

Cancer		<1.5	≤3.0	95%CI >3.0
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Table 14 Criteria for Classification of Risk from Results of Meta-Analyses of Observational Studies

OUTCOMES	INCONCLUSIVE: INSUFFICIENT OR NO EVIDENCE AVAILABLE	LOW RISK	INTERMEDIATE RISK	HIGH RISK
AMI, Stroke, HF	Number of studies <3	Number of studies ≥ 3 Pooled OR ≤ 1	Number of studies ≥ 3 Pooled OR 1 -1.5	Number of studies ≥ 3 Pooled OR > 1.5
Acute Pancreatitis, Pancreatic Cancer	Number of studies <1	Number of studies ≥ 1 Pooled RR ≤ 1.5	Number of studies ≥ 1 Pooled RR 1.5-3.0	Number of studies ≥ 1 Pooled RR > 3.0

Based on equal weights of WP4 and 4 evidence it is clear that rosiglitazone shows a high belief that there is an 'association' with all cardiovascular outcomes. Instead, GLP-1 receptor agonists (exenatide and liraglutide) and some DPP-4 inhibitors (alogliptin, sitagliptin, saxagliptin) show a high risk for acute pancreatitis but not for the cardiovascular outcomes. Effect of alpha-glucosidase inhibitors depend on the specific active ingredient, although none of them shows a high risk: an intermediate risk of acute pancreatitis and low risk for all cardiovascular outcomes was observed for acarbose; on the other hand, miglitol and voglibose pose a low risk for acute pancreatitis but at intermediate risk for one cardiovascular outcome (MI and IS respectively). The only drug showing a low risk for all outcomes is pramlintide. No conclusions can be inferred for acetohexamide, carbutamide, gyclopyramide or tolazamide. Intermediate risk of HF, MI and SCD can be seen for metformin; the effect of sulfonylureas on cardiovascular outcomes depends on the specific active ingredient. In general, sulfonylureas as sub-classified into the first (carbutamide, acetohexamide, chlorpropamide, tolbutamide) and second (glipizide, gliclazide, glibenclamide, gliquidone, glyclopyramide, glimepiride) generation.

Results from WP5 show that, when the information is available, the level of risk of cardiovascular outcomes (MI, HF and stroke) is intermediate or low for rosiglitazone when compared with metformin and sulfonylureas in the observational studies; the association between these drugs and AP was studied as a class in the RCTs and also per drug in the observational studies but the results obtained were discordant probably because of the different comparator used in the studies. DPP-4 inhibitors and GLP-1 receptor agonists have been studied only through RCTs for the cardiovascular outcomes while also observational studies have been used for the analysis of the risk of AP. For this outcome, the risk is classified as low by the observational studies while intermediate by the RCTs.

In summary, a high risk of cardiovascular outcomes in users of thiazolidinediones, in particular rosiglitazone, arise from the DS analysis while a high risk of AP is detected for DPP-4 and GLP-2 drugs, while from the results of WP5 and only through RCTs studies an intermediate evidence of risk of AP for DPP-4 and GLP-1. Risk of sulfonylureas depends on the specific active ingredient.

Table 15 shows the results of a potential run on the integration giving equal weights to spontaneous reports and odds ratios. Weights may be varied, increasing weight of the

observational studies does not impact a lot. For regulatory purpose traffic lights will be combined from all sources and put together without weighting.

Table 15: Traffic lights based on Dempster-Shafer analysis of spontaneous reports and met-analysis of pharmacoepidemiological studies

Dempster-Shafer traffic-lights	OUTCOMES						
DRUG	AP	HF	HS	IS	MI	SCD	VA
Acarbose	●	●	●	●	●	●	●
Acetohexamide	●	●	●	●	●	●	●
Alogliptin	●	●	●	●	●	●	●
Benfluorex	●	●	●	●	●	●	●
Carbutamide	●	●	●	●	●	●	●
Chlorpropamide	●	●	●	●	●	●	●
Exenatide	●	●	●	●	●	●	●
Glibenclamide	●	●	●	●	●	●	●
Gliclazide	●	●	●	●	●	●	●
Glimepiride	●	●	●	●	●	●	●
Glipizide	●	●	●	●	●	●	●
Gliquidone	●	●	●	●	●	●	●
Gyclopyramide	●	●	●	●	●	●	●
Linagliptin	●	●	●	●	●	●	●
Liraglutide	●	●	●	●	●	●	●
Metformin	● ●	●	●	●	●	●	●
Metformin and Acarbose		●					
Metformin and Nateglinide				●	●		
Metformin and Pioglitazone	●	●	●	●	●	●	●
Metformin and Repaglinide	●	●	●	●	●		●

	OUTCOMES						
DRUG	AP	HF	HS	IS	MI	SCD	VA
Metformin and Rosiglitazone	●	●	●	●	●	●	
Metformin and Sitagliptin		●		●	●	●	
Metformin and Vildagliptin		●			●		
Miglitol	●	●	●	●	●	●	●
Mitiglinide	●	●	●	●	●	●	●
Nateglinide	●	●	●	●	●	●	●
Pioglitazone	●	●	●	●	●	●	●
Pramlintide	●	●	●	●	●	●	●
Repaglinide	●	●	●	●	●	●	●
Rosiglitazone	●	●	●	●	●	●	●
Saxagliptin	●	●	●	●	●	●	●
Sitagliptin	●	●	●	●	●	●	●
Tolazamide	●	●	●	●	●	●	●
Tolbutamide	●	●	●	●	●	●	●
Vildagliptin	●	●	●	●	●	●	●
Vioglibose	●	●	●	●	●	●	●
Other NIBGLD	●	●	●	●	●	●	●
Past use	●	●	●	●	●	●	●
Recent use	●	●	●	●	●	●	●

2. POTENTIAL IMPACT, MAIN DISSEMINATION ACTIVITIES AND EXPLOITATION OF RESULTS

2.1 IMPACT

Regarding the project's impact, the SAFEGUARD project addressed the topic published by the EC *HEALTH-2011-4.2-2: Adverse drug reaction research*. SAFEGUARD has specifically been devoted to assess and further quantify and understand the cardio/cerebrovascular and pancreatic safety of blood glucose lowering agents, in particular the TZDs and the novel incretin-based drugs and amylin analogues in T2DM patients. It should be stressed that this topic was promoted by the European Medicines Agency (EMA), thus acknowledging the importance and public health impact. A clear example of the impact reached by the SAFEGUARD project is the intense communication and collaboration with the EMA and the pharmacovigilance risk assessment committee (PRAC), which is using SAFEGUARD generated information into its decision-making process and consults SAFEGUARD experts regularly. Results of the project were discussed at the informal PRAC meeting in March 2016, which generated a lot of discussion both on the scientific content as well as on the sustainability of the platform after the project phase.

2.2 DISSEMINATION ACTIVITIES

The SAFEGUARD partners have participated in many scientific events (conferences, meetings, workshops and posters) which represents the highest share of dissemination activities (44.4%). Some of the events in which members of the SAFEGUARD consortium have participated are listed below:

- Annual Meeting of the German Society of Epidemiology (DEGpi), September 2013
- 7th Congress of the Italian Society of Medical Statistics and Clinical Epidemiology (SISMEC), September 2013
- European meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), November 2013
- Digestive Disease Week (DDW), May 2014
- 35th Annual Conference of the International Society for Clinical Biostatistics (ISCB), August 2014
- 50th meeting of the European Association for the Study of Diabetes (EASD), November 2014
- Meeting of the North European Young Diabetologists meeting, May 2015
- 75th meeting of the American Diabetes Association (ADA), June 2015
- 15th annual meeting of the International Society of Pharmacovigilance (ISOP), October 2015
- CARING & SAFEGUARD symposium for regulators (October 2016, Utrecht)
- Informal PRAC meeting: Utrecht March 2016

In the International Society of Pharmacoepidemiology the project has been increasingly present on an annual basis. Beyond that, it is important to highlight that SAFEGUARD organised a symposium on September 14th 2014 in the framework of the 50th EASD Annual Meeting (Vienna, 15-19 September 2014) with the title "*Safety of novel diabetes drugs from the SAFEGUARD project. In memoriam: Prof. Diamant*".

Due to the relevance in the field, most dissemination efforts have targeted the Annual International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE). The International Society for Pharmacoepidemiology (ISPE) which organises the ICPE Conference is an international organization dedicated to advancing the health of the public by providing a forum for the open exchange of scientific information and for the development of policy, education, and advocacy for the field of pharmacoepidemiology, including such areas as pharmacovigilance, drug utilization research, comparative effectiveness research, and therapeutic risk management. During the lifespan of the project, four editions of the ICPE conference have taken place where the consortium has presented 16 abstracts for consideration:

- 28th ICPE, Barcelona, August 2012
- 29th ICPE, Montreal, August 2013
- 30th ICPE, Taipei, October 2014
- 31st ICPE, Boston, August, 2015

Additional abstracts have been prepared for the 32nd ICPE in Dublin

In order to keep track of the different activities carried out, every 6 months partners have been asked to report dissemination activities planned or done in the period. Only those activities that effectively reflect on the project dissemination are taken into account.

2.3 OUTREACH TO ADDITIONAL AUDIENCES AND OTHER INITIATIVES

The Communication Plan identified a number of relevant audiences for the project, towards which the communication efforts should be primarily targeted. These encompassed: i) Regulatory authorities (EMA, National Regulatory Agencies); ii) International Societies; iii) Clinicians (general practitioners and specialists); iv) Patient organizations; v) Pharmaceutical companies and international branch organisations; vi) Funding agencies; vii) Researchers in pharmacovigilance and pharmacoepidemiology; and viii) general public.

An intense communication channel was established with the European Medicines Agency (EMA) as a primary target audience of the project. It should be reminded that the 7th Framework Programme Call in which SAFEGUARD was awarded was requested by the EMA. During a first teleconference with the EMA (November 2013) the project and its first results were presented and the need for establishing a communication policy between SAFEGUARD and EMA became apparent. In the context of this framework, the EMA and the SAFEGUARD Consortium agreed to share information according to the following set of principles:

- The SAFEGUARD Consortium would send to EMA pre-publication manuscripts which are relevant to regulators, i.e. those with findings of the meta-analysis and the new studies. The timing of this communication will be after the manuscripts are accepted in peer reviewed journals. Sharing the manuscript's content at this stage provides an additional quality hallmark of the information shared. When the SAFEGUARD consortium considers that a publication has a potential for high public health impact, it would inform the EMA earlier than at acceptance of manuscript for publication (e.g. upon provisional acceptance). All shared information would be explicitly labelled as "confidential", to make sure the information is not disclosed.
- In order to prevent embargo/confidentiality issues in the case of the shared pre-publication manuscripts, the EMA would provide a letter for journal editors (annexed to this document as annex I) stating its interest in the manuscripts for regulatory purposes,

so that the SAFEGUARD Consortium can share the EMA's request with the journal editors.

- In case the SAFEGUARD project data and results would be used for regulatory action and communication, EMA would inform the SAFEGUARD Coordinator with an embargo date prior to engaging in any action. The reason for this is to allow the SAFEGUARD partners to coordinate internally a unified response in case there are specific reactions. For the same reason, the SAFEGUARD Consortium would like to know which parties the EMA has informed of any potential public health issues based on SAFEGUARD results. The EMA stated that this information flow cannot be guaranteed from the side of the member states because, under the current legislative framework, they are not legally obliged to previously inform about regulatory actions to the EMA. It was also clarified that this disclosure of information would be usually done approximately two days in advance.
- In order to avoid multiple communication channels, EMA would be responsible for liaising with the Pharmacovigilance Working Party, national competent authorities and other regulatory authorities.
- Additionally, SAFEGUARD Consortium would provide regular updates on the project progress to the EMA (i.e. yearly).
- Finally, in order to ensure efficient communication between EMA and the SAFEGUARD Consortium, one contact person from each organization was identified to centralise all contacts:
 - From EMA: Kevin Blake
 - From SAFEGUARD: Miriam Sturkenboom

Pursuant to the collaboration framework, an ad-hoc meeting was been organised on February 5th 2014 with EMA in order to update on the progress of the project

2.4 COMMUNICATION TOOLS

The project developed several tools for dissemination purposes, containing up-to-date information and adapted to the project needs and audiences.

PROJECT LOGO

Figure below shows the final logo version selected, after voting within the consortium.



The SAFEGUARD project logo is inspired by a “sugar cube” icon, which liaises with the study of Diabetes Mellitus, and the inclusion of a pill in one of the cubes to relate with the treatment studies. The project acronym is divided into two parts, “SAFE” to relate with the drug safety analysis and “GUARD” to highlight the focus of the studies towards the improvement of treatments and health. The colour code, which uses orange and blue, can be linked as well to alert and security. Finally, the full title of the project is added to distinguish the acronym from those of other already existing products, services or projects with same label. The logo has been consistently used during the whole project life in the presentations delivered, posters, and other communications and media.

PRESS RELEASE

A first press release was produced on December 2011, posted on the website and distributed to relevant audiences at the European level. Following the Consortium policy for press releases, several partners adapted the text to their local language and country's specifics, adding more information about their respective institutions and their role in the project, in order to make it more appealing for the local media. The press release was distributed to several media, which resulted in various news items, and articles published of different impact.

FLYER

A project flyer was developed in August 2012 and consisted on a presentation of information that displays SAFEGUARD key relevant points at a glance (see Annex I), with non-confidential information about the Project, including its objectives, some general technical details, partners and contact information.

The flyer was distributed by partners alongside the press release, but also several events such as the different editions of the International Society for Pharmacoepidemiology (ICPE), the EASD, or other key events where the project has been presented.

POSTER/POWER POINT TEMPLATE

In order to maximize the visual impact of the project and to help building a project's "brand image", several templates were created for the Consortium to use. Although most of them can be classified as internal (used within the Consortium), some tools were created with external use:

- Power point with basic information about the project. This has been updated during the project life and made available to the private area of the website.
- Poster.

VIDEO

A promotional video was also produced by CommHERE for HorizonHealth.eu (internet portal promoting EC research) describing the project overview and objectives. The video has a duration of 2:54 minutes, was uploaded in the project's website and is available on YouTube's HorizonHealth space (https://youtu.be/yAF_HwTlexw).

PROJECT WEBSITE

A project webpage was launched in November 2011, including also a partner-only, password-protected private area (set up on February 2012) for allowing information exchange and knowledge management within the consortium, containing all the minutes of the meetings, the presentations, the deliverables, working documents, etc.

The website was designed to support the project's general dissemination activities, becoming the prime access site for comprehensive information about the project and registered in the following domains: www.safeguard-diabetes.org and www.safeguard-diabetes.eu.

2.5 EXPLOITATION OF RESULTS

The primary results of the SAFEGUARD project are the integrated evidence to allow for better regulatory and clinical decision making and the infrastructure established that may be used to look at other drugs. The plan is that the SAFEGUARD generated infrastructure and decision models will be adopted by regulatory agencies and clinicians. A proof of success of the project

results uptake is clearly on the regulatory side, where EMA is waiting for final SAFEGUARD results to incorporate them in their decision making processes. This makes the project special, as it is not just a research project, with the target to set up a collaborative network for doing research, it actually needs to deliver state of the art results, that can be utilized directly, without peer review.

Some of the outputs created by SAFEGUARD are already being implemented and improved in the IMI JU funded EMIF (European Medical Information Framework) and ADVANCE (in the vaccine area), and used also by the EU-ADR Alliance, the post-project exploitation route of the EU-ADR project. Examples of those outputs include the terminology mapping results, methodology for conducting the literature review analyses (both on clinical trials and on observational studies), the tools for pooling data from different electronic healthcare records databases, the secure repository for data storage and analysis and the advanced statistical methods applied for the results analysis.

Besides the individual results generated during the project, SAFEGUARD has significantly progressed in the development of a platform that would allow for rapid epidemiological studies since the cohort will be defined, disease and drug terminologies will be mapped, and harmonization will have been achieved. This platform may be used to address newly occurring safety issues, which are likely to occur since very little is yet known about the novel incretin-based therapies.

This platform can and should be further utilized beyond the project scope and duration, and for this reason discussions have already been engaged with the European Medicines Agency (face-to-face meetings in November 2013 and February 2014, and a planned meeting by mid-2016 for presenting the final results and agree on next steps), although the lack of funding is currently an issue. The pharmaceutical industry also has expressed interest in utilizing the potential and capabilities of this platform, which is being explored to be integrated as part of the EU-ADR Alliance framework, although further conversations with the network of experts around it are still required.

2.6 ADDRESS OF THE PROJECT PUBLIC WEBSITE AND RELEVANT CONTACT DETAILS

- **Project coordinator:** Prof. Miriam CJM Sturkenboom, Erasmus Universitair Medisch Centrum Rotterdam
- **Project manager:** Ángel Honrado, Synapse Research Management Partners

Contact details: www.safeguard-diabetes.org

List of Partners

1. Erasmus Universitair Medisch Centrum Rotterdam (Netherlands) - Coordinator
2. Synapse Research Management Partners S.L. (Spain)
3. PHARMO Institute N.V. (Netherlands)
4. Fondazioni Scientifica SIMG-ONLUS (Italy)
5. University of Bath (United Kingdom)

6. Agencia Española de Medicamentos y Productos Sanitarios (Spain)
7. Drug Safety Research Trust (United Kingdom)
8. Univerzita Karlova v Praze (Czech Republic)
9. Stichting VU-VUMC (Netherlands)
10. The Brigham and Women's Hospital, Harvard Medical School (United States)
11. University of Milano-Bicocca (Italy)
12. Universitaet Bremen (Germany)
13. RTI Health Solutions (United States)
14. BIPS Institut für Epidemiologie und Präventionsforschung GmbH (Germany)

¹ Trifiro² G, Coloma PM, Rijnbeek PR, Romio S, Mosseveld B, Weibel D, Bonhoeffer J, Schuemie M, van der Lei J, Sturkenboom M. Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how? J Intern Med. 2014 Jun;275(6):551-61