SEVENTH FRAMEWORK PROGRAMME

SAFEGUARD

SAFETY EVALUATION OF ADVERSE REACTIONS IN DIABETES

Safety Evaluation of Adverse Reactions in Diabetes

HEALTH-282521

Executive Summary Report on Rates and Relative Risks by Individual Drug

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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 1 *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 Medical Record	2000-2011	1.2	ICD9-CM and free text	ATC
IPCI	Netherlands	Electronic Medical Record	1999-2013	1.7	ICPC1 and free text	ATC
BIFAP	Spain	Electronic Medical Record	2001-2011	3.7	ICPC1 and free text	ATC
CPRD	U.K.	Electronic 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).

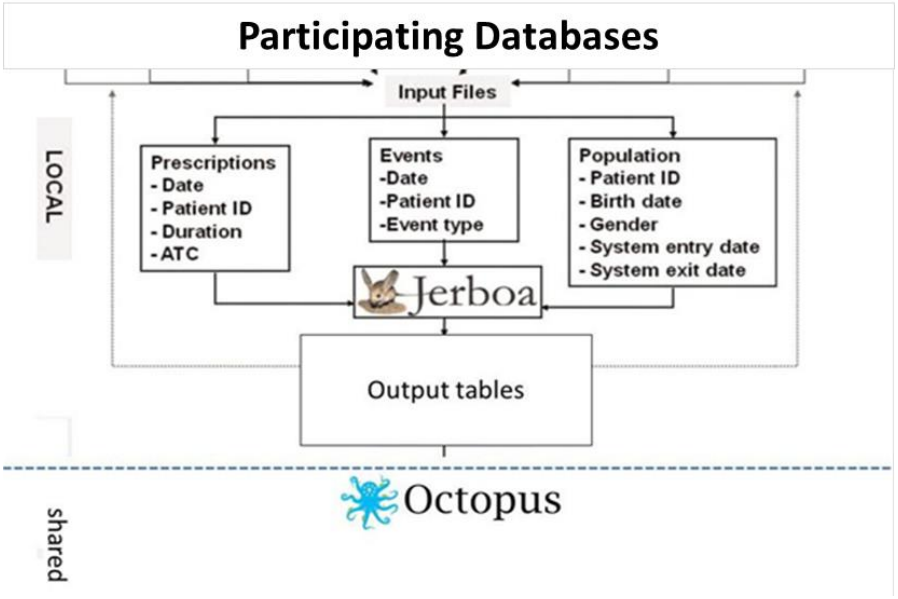

Figure 1 *Common data model approach for data sharing as described in Trifiro et al.i*

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.

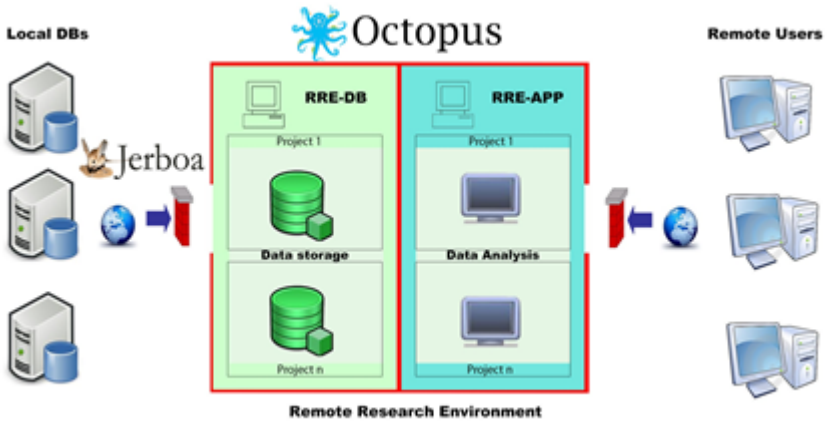

Figure 2: *Octopus remote research environment for collaborative projects*

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 the 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.

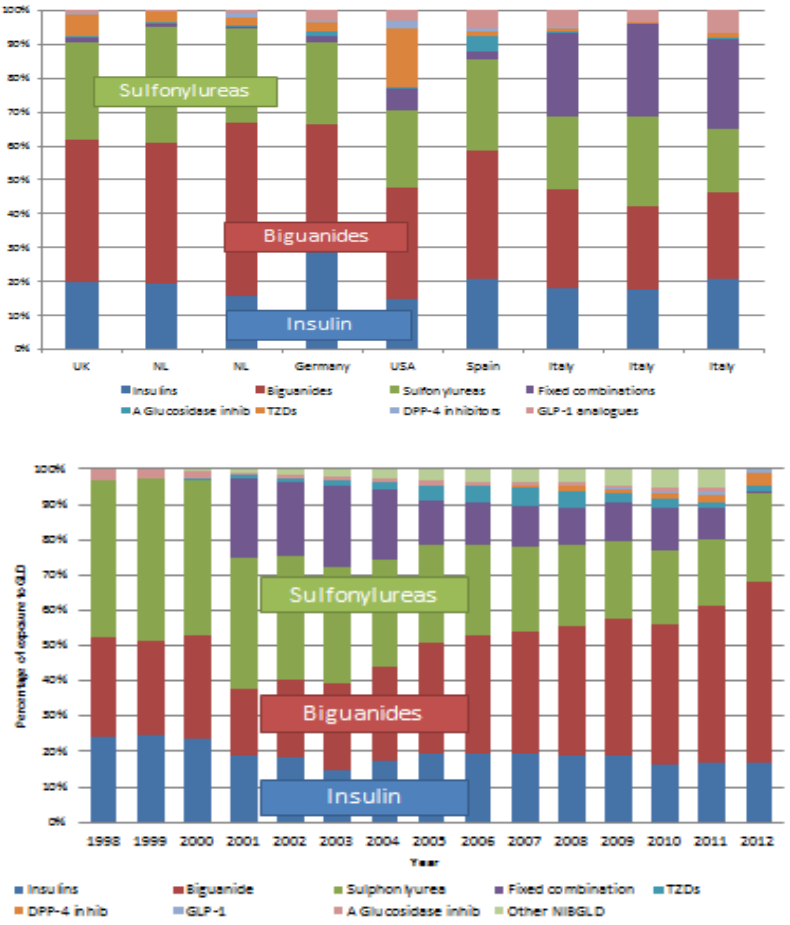

Figure 3 *distribution of person time of exposure to different drugs in the different databases and over time*

Use of incretins increased over time with highest increases in sitagliptin (figure 13)

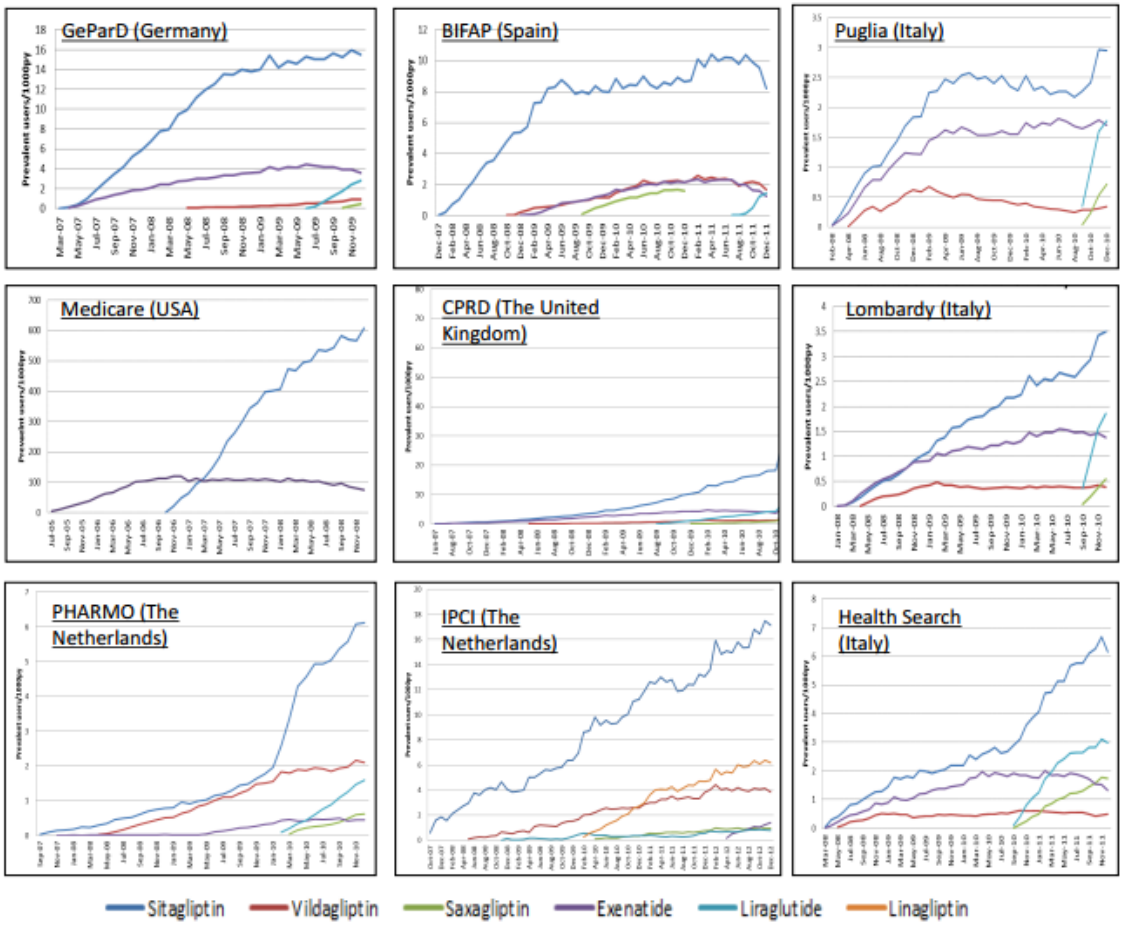

Figure 4 *Use of incretins by database and time (y-axes differ)*

Subjects starting GLP-1 therapy are younger that subjects who start using other NIGBLD. 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)

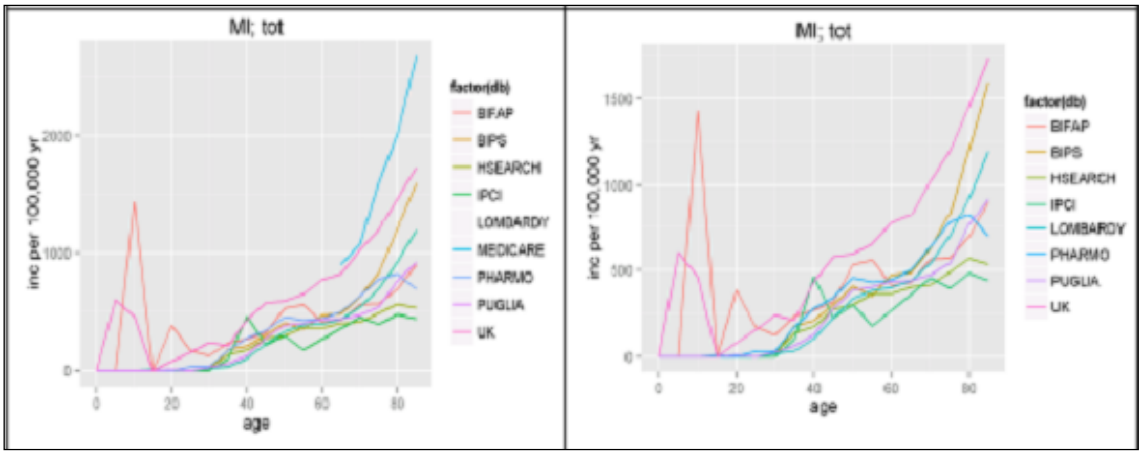

Figure 5 *Incidence rates of myocardial infarction in T2DM patients, with (left) and without (right) US data*

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 a 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 2 *Meta-analytic and pooled estimates for myocardial infarction*

	Fixed effect		Random effect					Individual pooling	
Label	OR	95% CI	OR	95% CI	p-value	I^2	N	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 Gliclazide	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 3 *Meta-analytic and pooled estimates for heart failure*

	Fixed effect		Random effect					Individual pooling	
Label	**OR**	**95% CI**	**OR**	**95% CI**	**p-value**	**I^2**	**N**	**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 4 *Meta-analytic and pooled estimates for ventricular arrhythmia*

	Fixed effect		Random effect					Individual pooling	
Label	OR	95% CI	OR	95% CI	p-value	I^2	N	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 5 *Meta-analytic and pooled estimates for sudden cardiac death*

	Fixed effect		Random effect					Individual pooling	
Label	OR	95% CI	OR	95% CI	p-value	I^2	N	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 6 *Meta-analytic and pooled estimates for ischemic stroke*

	Fixed effect		Random effect					Individual pooling	
Label	OR	95% CI	OR	95% CI	p-value	I^2	N	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 7 *Meta-analytic and pooled estimates for haemorrhagic stroke*

Label	Fixed effect		Random effect					Individual pooling	
	OR	95% CI	OR	95% CI	p-value	I^2	N	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 8 *Meta-analytic and pooled estimates for acute pancreatitis*

Label	Fixed effect		Random effect					Individual pooling	
	OR	95% CI	OR	95% CI	p-value	I^2	N	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 Gliclazide	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%.

[i] 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