Final Report Summary - ARITMO (Arrhythmogenic potential of drugs)

Executive Summary:

The ability of some compounds to prolong the QT interval of the electrocardiogram and to precipitate torsade de pointes (TdP, a potentially fatal arrhythmia) has caused several regulatory interventions: a number of drugs were withdrawn from the market, whereas others were restricted in use. Specific guidelines have been implemented to detect QT liability of new compounds as early as possible. However there is increasing evidence showing that an increase in the QT interval does not necessarily lead to TdP which further increased the regulatory and clinical difficulties, intrinsically due to the fact that TdP is a serious, albeit rare event.
The ARITMO project assessed the arrhythmogenic potential of antipsychotics, antihistamines and anti-infectives (588 individual compounds). This was done for each drug by systematically investigating pharmacokinetics and dynamics (hERG affinity, the most important mechanism of drug-induced TdP) from literature, experimental and in silico data, and by estimating the effect of the drug on the QT interval (literature), risk of Torsade de Pointes (Pharmacovigilance, field studies), QT prolongation (pharmacovigilance and field studies), as well as ventricular arrhythmia (VA) or sudden cardiac death (SCD) (epidemiological studies & pharmacovigilance). Patient related factors that may influence arrhythmogenicity were investigated by an attempt to find new ECG parameters that would predict TdP, and genetic analyses. All new ARITMO drug related evidence was aggregated in an overall score that was presenting the level of evidence of arrhythmogenic risk based on a Dempster Shafer model. This was compared to the knowledge we have on hERG affinity, QT prolongation and VA/SCD risk from published studies.

The project has yielded a wide variety of data based on the work that was done in each of the workpackages.

Drug related information: a database with pharmacokinetic parameters of all drugs, a databases with the cardiac safety profile (in silico) of 413 ARITMO drugs listing hERG, Nav, Cav pIC 50 values, a sheet with the number of case reports and other data to evaluate causality assessment (traditional approach) and new pharmacovigilance score based on case reports from the French, German, UK, and Italian national spontaneous reporting databases as well as the AERS (the FDA archive) and EUDRAVIGILANCE (the EMA archive) international databases. From these pharmacovigilance analyses new signals were identified as well as a ranking of drugs based on their arrhythmogenic risk. Overall, 167 ARITMO drugs had pharmacovigilance data (i.e. they received a pharmacovigilance score), drugs with highest scores were oxatomide, rupatadine (antihistamines) ziprasidone, pimozide, thioridazine (antipsychotics, all included in AZCERT lists) plus halofantrine (antiprotozoal). The association between ARITMO and non-ARITMO drugs and severe symptomatic confirmed QT prolongation was studied using existing field studies in the UK, Netherlands and Germany, as well as medical record databases. The risk of ventricular arrhythmia could be studied for 38 antibiotics, 15 antihistamines and 19 antipsychotics. The studies on VA were conducted using data from 7 different health care databases in 5 countries, whereas the association with SCD was studied in two databases. Literature on hERG affinity, clinical studies on QT prolongation and observational studies on VA or SCD was systematically reviewed and abstracted for 220 selected ARITMO drug, this subset was created based on frequency of use and other relevant parameters. The literature review data were integrated into different levels of evidence and contrasted with the derived integrated data in the ARITMO project on hERG affinity, pharmacovigilance and epidemiological risk. For each drug, these three independent pieces of information were integrated into an overall ARITMO score using the Dempster Shafer (DS) model and compared with the literature data. Evidence integration was achieved for 450 drugs: among these, 79 had all the three different sources of information quoted above. In addition, a comparison between literature review and DS assessment could be provided for 205 drugs: 26 antihistamines, 36 antipsychotics and 143 anti-infective drugs. Among antihistamines, for 16 drugs new evidence emerged from ARITMO, for 3 drugs ARITMO confirmed literature evidence and for 7 drugs ARITMO refined the information. Fexofenadine, cetirizine and levocetirizine belong to low risk category (green traffic light). Among antipsychotics, for 20 drugs there was no data in literature and ARITMO
provided new evidence, for 5 drugs ARITMO confirms literature data (notably, for thioridazine, mesoridazine, droperidol and risperidone high arrhythmogenic risk has been confirmed) and for 11 drugs ARITMO refines the evidence. Among the anti-infective drugs, for 122 drugs no information was retrieved from literature and ARITMO could provide additional data on risk. From the DS analysis emerged that anti-infective drugs mainly belong to low risk categories (i.e. green or green-orange). In addition, different aminoglycosides, azole antifungals, antivirals (protease inhibitors) and anti-malarials were classified as high arrhythmogenic risk drugs (i.e. red traffic light).

Patient related information: For ECG parameters a pipeline was developed for paper-to-digital ECG conversion, to allow for automated measurement of short-term QT variability. The ECGs from TdP cases were analysed, changes in QT interval were observed towards the event, no new parameters could be identified. Candidate genes were identified based on in silico predictions done in ARITMO.

We conclude that the ARITMO consortium has developed a workflow that has proven to yield comprehensive and multifaceted information on the arrhythmogenic potential of many drugs by exploiting and integrating existing data sources. This information can be used for clinical and regulatory decision making. The consortium advocates that the accumulated information should be made available to the different stakeholders and that the workflow is maintained to investigate the arrhythmogenic potential of other drugs much faster.

Project Context and Objectives:

Cardiac ventricular arrhythmia as a side effect of anti-arrhythmic and non-antiarrhythmic drugs has become a major pharmacological safety concern for the pharmaceutical industry and the health regulatory authorities1,2. Among drug-induced arrhythmias, Torsade de Pointes (TdP) is by far the most important and worrisome.

Electrophysiology of heart rhythm

The rhythm of the heart is controlled by a balance of ions flowing into and out of individual cardiac cells. Most of this ionic traffic flows through membrane-spanning proteins known as voltage-dependent ion channels. The three most important types of channels governing electrical activity in the human heart are those that carry Na+, Ca2+, and K+, respectively. When they work in concert, the activity of these ion channels gives rise to the shape and duration of the action potential on the cellular level and to the electrocardiogram (ECG) measured clinically. The influx of Na+ and Ca2+ into heart cells, through their respective channels, produces excitation and contraction of the myocardium. Activation of K+ channels allows for the efflux of this ion out of cardiac cells. Several types of voltage-dependent K+ channels exist in the human myocardium, and their activity promotes repolarization of the heart, termination of the action potential, and an end to the ECG waveform24.

Figure 1: Action potential and ion in-outflow

Torsade de Pointes and risk factors
Torsade de Pointes is a polymorphic ventricular tachycardia, if it occurs it may lead to syncope, seizure, ventricular fibrillation and sudden death. The most important risk factor for TdP is prolongation of the QT interval, which can be congenital but is mostly drug-induced. Other risk factors are: hypokalaemia, heart failure, myocardial infarction, diabetes mellitus and bradycardia. Prolongation of the QT interval may result in early after depolarizations (EAD), which in turn may induce re-entry and thereby provoke Torsade de Pointes and fatal ventricular fibrillation leading to sudden cardiac death. Although QTc (QT interval corrected for the heart rate) prolongation is almost always present in cases with TdP and in itself has been directly associated with sudden cardiac death in epidemiological studies, QTc prolongation itself is not a perfect predictive marker of TdP risk. Many persons have QTc prolongation and will not develop TdP. Moreover, there is no consensus on the magnitude of prolongation raising concern, although the threshold on the extent of prolongation for regulatory purposes is a mean increase of 10 ms. Some drugs prolong the QTc interval, but appear devoid of torsadogenic effects (e.g. verapamil), whereas others seem not to be associated with a significant QTc prolongation, but are still considered to be associated with cardiac arrhythmias. It is to be expected that both drug as well as person based risk factors may interact to cause TdP.

QTc prolongation and mechanisms

The vast majority of drugs associated with QTc prolongation are thought to act by reducing the IKr current in the heart. This IKr current is conducted by tetrameric pores with the individual subunits encoded by the human ether-a-go-go-related gene (hERG or now termed KCNH2). Blockade of hERG K+ channels has been studied mostly and is widely regarded as the predominant cause of drug-induced QT prolongation. Due to the role of hERG in causing QTc prolongation and potentially TdP and the availability of in vitro methods to model hERG binding, a common first step of screening drugs for potential torsadogenic effects is to look at hERG affinity.

Unfortunately hERG binding does not predict TdP perfectly. Terfenadine is a potent IKr blocker, but usually does not prolong the QTc interval because it is readily transformed into a metabolite with no QT liability. In any case, because of the possible occurrence of drug interactions diseases that inhibit metabolism and due to the existence of alternatives, its use has been restricted. It is therefore likely that other drug and patient related factors/variables (and not only IKr blockade) are involved in provoking or preventing Torsade de Pointes. These actions may be either direct (by blunting early after depolarizations) or indirect (by blunting the prolongation of the action potential). Moreover, TdP may be mediated by other ion channels such as the Ca2+ or Na+ channels. In addition, the assessment of the net arrhythmic effects should also comprise pharmacokinetic aspects including metabolism since a very low baseline pro-arrhythmic effects may become clinically important in case of drug interactions leading to higher than expected plasma levels.

Regulatory actions

In the 1980s, large case series of TdP were accumulated, which showed the overwhelming
preponderance of non-antiarrhythmic drug therapy to cause TdP. Risk estimates range in the order of 1-8% for quinidine and sotalol, and similar rates have also been recorded for ibutilide and dofetilide18. Non-antiarrhythmic drugs that have been associated with TdP and sudden death include antipsychotics7,19,20, antihistamines (especially diphenhydramine and astemizole)18,21, anti-infectives (macrolides, quinolones, imidazole antifungals) and gastrointestinal drugs (cisapride and domperidone)22, but incidence with non-antiarrhythmic drugs (whenever available) is less common (1-5 per 100,000)5,23. This long and growing list of non-antiarrhythmic drugs linked to TdP has contributed to the unjustified view that QT prolongation is usually an effect of a whole therapeutic class, whereas, in many cases, it is displayed only by specific compounds within a given class. Rarely however, all drugs in the entire class are investigated. In ARITMO, we look at all drugs in 3 main classes: anti-histamines, anti-infectives and anti-psychotics.

In recent years, a number of blockbuster antipsychotic, antihistaminic, gastrointestinal and anti-infective drugs (e.g. thioridazine, astemizole, cisapride, grepafloxacin)3 have been withdrawn from the market because of reports of Torsade de Pointes (TdP) and sudden death or cardiac death (SD or SCD), and several others were restricted in use (e.g. terfenadine, haloperidol, sertindole). This has resulted in health concerns for patients as well as billions of dollars of lost revenues for the pharmaceutical industry4. The relative rarity of drug-induced TdP in non-antiarrhythmic drugs5 and our imperfect prediction of risk for a given individual, make this a particularly vexing problem for clinicians.

Several attempts have been made to list the drugs that are associated with QTc prolongation and cardiac arrhythmias1,10-12. Although these lists provide some ranking, the absolute and relative risks of TdP and sudden death for the listed drugs are mostly unknown as most are based on case reports and incomplete evidence.

In the absence of complete explanatory factors but the link with QTc prolongation, regulatory agencies have taken several measures to reduce the risk of licensing potentially torsadogenic drugs by implementing guidelines (ICH S7B and ICH E14) for the early identification of TdP. This involves a battery of preclinical and clinical tests (in vitro and in vivo models of a delayed cardiac ventricular repolarization, or QTc interval prolongation, as surrogate biomarkers of TdP risk6). However the link between the primary abnormalities such as hERG channel inhibition and TdP or sudden death is a complex one, as it is modulated by a number of factors. The low specificity (i.e. the chances to label as negative those drugs carrying no risk) of the current in vitro test battery leads to many false positive screens, which may cause many potentially valuable drugs to be terminated during non-clinical or clinical development28,29. Some attempts were made to associate in vitro measures with clinical measures or spontaneous reports of ventricular arrhythmia or sudden death but a systematic comprehensive assessment that includes epidemiological studies as well was still lacking11,30. Since apparently not all TdP can be predicted accurately by either hERG blockade or QTc prolongation, it is likely that other genetic and environmental risk factors may affect or modify the association between QTc-prolongation, TdP and sudden death. In ARITMO we tried to integrate all factors.

Genetics and drug-induced long QT syndrome, TdP or cardiac arrest

Until the start of ARITMO, the search for sequence variants contributing to sudden death (SD) risk was
restricted to several candidate genes known for their role in arrhythmogenesis. Yet, the relatively small size of existing sudden death collections and etiologic heterogeneity limit the statistical power to detect causal variants. Therefore, initial attention has focused on quantitative sudden death risk factors available in large cohorts, such as QT prolongation. Approximately 35% of the variation in QT interval duration in unselected community-based samples is heritable\textsuperscript{32,33}. Hundreds of mutations in 10 genes linked to the long-QT syndrome have been identified\textsuperscript{34}. Mutations in three genes, each encoding a cardiac ion channel that is important for ventricular repolarization, account for the vast majority of cases; the resulting subtypes are called LQT1 (loss of function mutations in KCNQ1), LQT2 (loss of function mutations in KCNH2 or HERG) and LQT3 (mutations that disrupt the cardiac sodium channel SCN5A). Other mutations associated with long-QT are LQT5-9\textsuperscript{34,35} Most reported mutations are in coding regions, although non-coding mutations and ‘private’ (family bases) mutations have been seen\textsuperscript{34}. The prevalence of mutations is at least 1 per 2000 persons, however most remain asymptomatic during life\textsuperscript{34}. More recently the NOS1AP gene was reproducibly associated with QT interval variation in several large population samples\textsuperscript{36,37}. The interaction between LQT mutations or NOS1AP variants and drug-induced symptomatic QT prolongation is largely unknown due to the rarity of the event and the lack of large case series. The identification of common variants that modify risk of drug-induced arrhythmia would be exciting from a clinical perspective.

Genetic variation is now well-recognized as one source of variable response to drug therapy including variable susceptibility to adverse drug reactions. An association study utilising a candidate SNP chip array was utilised in cases of drug induced TDP and controls that were either from the general population or patients challenged with a QT prolonging drug without evidence for drug-induced long QT syndrome (DiLQTS). It identified the uncommon missense variant D85N in the KCNE1 gene, the beta subunit of the IKs current and implicated in congenital LQTS, as being more prevalent (8.6% vs 2.9% vs 1.8%).\textsuperscript{3} In addition, Sanger sequencing studies have identified rare likely disease causing genetic variants in ion channel genes associated with LQTS in approximately 10% of cases. \textsuperscript{1;2}

With the current next generation sequencing technology, it has been possible to sequence larger numbers of cardiac ion channel function genes in less time despite the computational difficulties involved in data analysis. One recent study evaluated the frequency of rare non-synonymous variants in genes contributing to the maintenance of heart rhythm in cases of diLQTS using targeted capture coupled to next-generation sequencing.\textsuperscript{4} In their cohort, 11 of 31 DiLQTS subjects (36%) carried a novel missense mutation in genes with known congenital arrhythmia associations or with a known LQTS mutation. In the 26 Caucasian subjects, 23% carried a highly conserved rare variant predicted to be deleterious to protein function in these genes compared with only 2-4% in public databases. The authors concluded that the rare variation in genes responsible for congenital arrhythmia syndromes is frequent in diLQTS and their findings demonstrate that diLQTS is a pharmacogenomic syndrome predisposed by rare genetic variants.\textsuperscript{4}

The overall goal of the ARITMO project was to analyse the arrhythmic potential of drugs in the following classes of study drugs, all included the EC FP7 call: antipsychotics (ATC N05A), anti-infectives (J), and H1-antihistamines (ATC R06), globally and in specific subgroups (age, co-morbidity, genetically).

The specific objectives were:
1) To predict QT liability and TdP propensity for study drugs via in silico modelling.
2) To annotate relevant pharmacokinetic parameters of the study drugs.
3) To review the published pre-clinical in vitro and in vivo evidence for the study drugs.
4) To review the occurrence and extent of QTc prolongation from published clinical trials and the risk of ventricular fibrillation, TdP and sudden death from published epidemiological studies or large simple trials on study drugs.
5) To assess the reporting rate and relative risk (disproportionality) of QTc prolongation, TdP, ventricular fibrillation and sudden death from regional and international pharmacovigilance databases.
6) To assess the rate and relative risk of symptomatic QTc prolongation, TdP, ventricular arrhythmia and sudden death during use of study drugs.
7) To assess effect modification by concomitant drug use, co-morbidities, and genetic factors for drug induced symptomatic QTc prolongation, ventricular fibrillation and sudden death.
9) To further explore the relationship between new electrophysiological parameters and arrhythmias.

All objectives were addressed through the workplan that split the work over various areas of expertise, whereas it was integrated in the ‘integration’ work package.

Project Results:

1.3.1 Source documents

The multifaceted workplan for ARITMO was started by creating source documents that described:

1) The ARITMO study drugs
2) The ARITMO outcome definitions
3) The ARITMO covariates

These list were followed by all workpackages.

The ARITMO drug list

ARITMO aimed to analyse the proarrhythmic potential of the following classes of medications: antipsychotics, anti-infectives and H1-antihistamines. To this aim, a list of all drugs to be investigated was created according to ATC classification by considering: (1) all V level ATC codes in the classes J (anti-infectives for systemic use, except for vaccines), N05A (antipsycotics, except for lithium (N05AN)), P01 (antiprotoszoals) and R06A (antihistamines for systemic use); (2) V level ATC codes of molecules belonging to the aforementioned pharmacological groups, but included in other ATC classes, provided that they can have systemic effects (e.g. A02BD which corresponds to combinations of antibacterials used in the treatment of peptic ulcer). This list has been named as “the broad ARITMO drug list”. The broad ARITMO drug list contains multiple ATC codes for the same active substances, as some active substances have different ATC codes, based on different indications for use; - drugs that are currently no longer or seldom used in Europe (e.g. astemizole and thioridazine, which, however, can be interesting to study as well). Overall, the broad ARITMO drug list includes 588 different ATC codes (V level),
corresponding to 485 active substances. This broad list was taken into account in the activities of all the Work Packages except for WP6 (Literature review) and docking of molecules (WP 7). The narrow ARITMO drug list comprising 220 drugs has been prepared using various criteria based on frequency of use and publications or thorough QT studies. The drug lists are available on the ARITMO website.

The ARITMO outcomes

The cardiologists and epidemiologists defined the ARITMO outcome list, which was used across all of the workpackages (figure 1). Since the different workpackages use different type of data, that may be coded with different terminologies. D5.1 describes the mapping of the terminologies for the outcomes using the Unified Medical Language System. This approach offered the opportunity to provide consortium with a shared semantic basis for the creation of queries, to be adapted to the heterogeneity of different databases.

ARITMO covariates

As covariates of interest, we identified all the potential risk factors of QT prolongation, Torsade de pointes, ventricular fibrillation and sudden cardiac death. As there is a common pathway leading from QT prolongation to sudden cardiac death we did not distinguish at this stage the risk factors for individual study outcomes. Apart from the risk factors of QT prolongation and related cardiac arrhythmias, we identified also the main indication for use of the different study drugs. A source document with disease and drugs that were considered as covariates in the observational studies in WP 4 & 5 is available on the ARITMO website (source documents).

Figure 3: ARITMO outcomes

1.3.2 A platform for collaborative work

The analyses on healthcare data, epidemiological data and pharmacovigilance data was performed in a distributed fashion by using a common Remote Research Environment (RRE) which is located at EMC. The RRE allows for loading, retrieving, extracting, and transforming of the data. The security measures taken for the Remote Research Environment (RRE) 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.

The RRE consist of two servers, a database server (RRE-DB) located at the Department of Medical Informatics of EMC and an application server (RRE-APP) located in the demilitarized zone (DMZ) of EMC hosted at the Rotterdam Internet Exchange (R-iX) (see fig 4). RRE-DB is placed in a locked server room and was not directly connected to the RRE-APP server in de DMZ. Furthermore, there is a firewall that isolates RRE-DB from the Local Area Network (LAN). The RRE-APP server is secured by the EMC firewall and will not have any direct connections to the LAN of the hosting institute. ARITMO data are accessible for partners on the RRE for the coming years and data will be archived after publications of the papers. The exact details are described in the RRE security document that was part of the WP 1 deliverables. All partners signed confidentiality agreements.
1.3.3 Newly generated data for ARITMO drugs: drug related factors

1.3.3.1 Pharmacodynamic data: hERG, NaV, CaV target interactions

As explained above, the earliest indicator used to assess torsadogenic risk is usually based on the hERG pIC50 value. However other ion channels are important as well and there is evidence of cases of ventricular arrhythmia arising from pharmacological blockade of ion channels different from hERG: particularly susceptible are I (fast sodium channel, Nav1.5) and INaCaL (the L-type calcium channel, Cav1.2). Blockade of these channels will lead to anomalies in the action potential raising the risk of arrhythmic episodes. Accordingly it has been suggested that multi-channel effects must be considered when evaluating arrhythmic risk (see figure 5). WP 7 provided a cardiac safety profile (including hERG, Nav and Cav channel information) for the ARITMO drugs.

Figure 5: Schematic description of Cav1.2 Nav1.5 and hERG channels block and the related anomalies of cardiac action potential, ECG and types of arrhythmias

Using several strategies a database containing in vitro compound-target interactions and in silico predictions thereof have been compiled for the ARITMO drugs. Three targets with established impact on the cardiac profile were selected to set up the risk profile, hERG, Nav1.5 and Cav1.2. Data on target interactions were retrieved and described in D7.2 following

Experimental data: AstraZeneca extraction of internal in vitro assay data resulted in 35 reported pIC50s for hERG and 78 reported classification values. For Nav1.5 26 pIC50s were reported and 69 binary responses and finally for Cav1.2 3 cases with pIC50 values and 35 binary. This was complemented with the public data extraction approach performed by FIMIM, 60 pIC50 hERG values were obtained.

3D QSAR modelling (figure 6) was used for the ARITMO drugs. The hERG blocking activity of most of the drugs (172 out of 218) belonging to the narrow ARITMO list was predicted using the 3D QSAR equation derived from the newly developed CoMFA model.

In silico target profiling could be used to predict 36 drugs in the hERG model, 10 Cav1.2 and one for Nav1.5.

Machine learning based QSAR models available from AstraZeneca on hERG, CaV, NaV

An excel sheet with the different pIC50 values is available for the ARITMO drugs (CSPD_v5.xls)

Figure 6: 3D QSAR modelling

1.3.3.2 Pharmacokinetic data for ARITMO drugs

The ability of compounds to inhibit hERG potassium currents in recombinant cell systems has been
extensively used in the early assessment of compounds likely to prolong the QT interval. The close
correlation between free plasma concentrations associated with QT prolongation in both dog and man and
the concentration associated with inhibition of the hERG channel in vitro have been demonstrated for
terfenadine, terodiline and cisapride. An analysis of available data relating to QT prolongation
demonstrated the dependence of QT prolongation on free plasma concentrations and lent support to the
application of a 30-fold safety multiple between therapeutic activity and concentration causing QT
prolongation. This can be further refined by the incorporation of a pharmacokinetic component to provide
greater assurance that clinical exposure at proposed therapeutic doses will not approach free plasma
concentrations expected to cause this adverse pharmacology. For ARITMO AstraZeneca has searched
several databases containing published PK data. The results show that we currently have at least one PK
parameter for 76% of the drugs and a fairly complete set of PK parameters for 60% of the ARITMO drugs.
The results show that for the drugs for which we have data we generally have a lot of replicate measures.
However a complete set of the core PK parameters for a drug (i.e. Cmax, Clearance, Tmax, Plasma
Protein Binding and Bioavailability) is not that common. For 150 compounds we could provide the full
profile of the above parameters, and for another 150 one parameter were lacking. Data were made
available in an excel sheet (D7.1)

1.3.3.3 Pharmacovigilance data for ARITMO drugs

The WP3 approach (Pharmacovigilance) posed the basis to create a report on the methods, opportunities
and limitations for monitoring of QT and TdP liability of drugs marketed in the European Union. This
method can also be adopted by regulators to periodically monitor and prioritize potential signals arising
from spontaneous reporting systems, especially for newly marketed drugs.

Spontaneous reports of drug-event combinations are collected by drug companies and at a regional,
national and international level through different databases. Each European country collects its own
reports in a national spontaneous reporting database, although also international archives gather reports
originating from different countries. Among international archives, the Eudravigilance database (European
Union Drug Regulating Authorities Pharmacovigilance) is held by the European Medicines Agency and
collects/exchanges electronically ADRs coming from national regulatory authorities, marketing
authorization holders and sponsors of interventional clinical trials and non-interventional studies in Europe.
The Uppsala Monitoring Centre in Sweden is responsible for the worldwide gathering of all serious ADRs
received by regulatory authorities and companies. The FDA Adverse Event Reporting System (FAERS)
collects ADRs from the US as well as rare/severe events from Europe and offers public access to raw data
from 2004.

Two different approaches were used for providing the required data for each ARITMO drug while using the
multiple resources: a traditional approach and a novel approach.

A traditional approach of disproportionality analyses was taken for the EUDRAVIGILANCE (EV) and
FAERS databases using stringent case definitions (TdP or QT prolongation), an easily replicable score
was created giving one point to each of the following criteria 1) number of cases for TdP/QT (&gt; 3
cases); 2) number of cases for TdP/QT abnormalities without drugs listed by AZCERT (&gt; 3 cases); 3)
significance of the Reporting Odds Ratio (ROR, 95%CI&gt;1) for TdP/QT when using all other drugs as
reference; 4) significance of the Reporting Odds Ratio (ROR) for VA/SCD, in both EUDRAVIGILANCE as well as FAERS.

Among the 588 ARITMO drugs with an ATC code (i.e. the original full ARITMO drug list used in the search strategy), 148 drugs fulfilled at least one criterium. Notably, only olanzapine fulfilled all the criteria in FAERS and EV, thus it was the only agent reaching the maximum score of 8/8. Seven agents resulted in a score of 7/8: clozapine, haloperidol, quetiapine and ziprasidone are included in AZCERT lists and, therefore are positive controls, whereas fluphenazine, levomepromazine, and zuclopenthixol are not labelled by AZCERT and, therefore can be considered as potential emerging signals deserving case-by-case evaluation. Twelve compounds reached a score of 6/8: amantadine, amisulpride, aripiprazole, azithromycin, ceftazidime, chlorpromazine, clarithromycin, moxifloxacin, posaconazole, prothypendyl, risperidone and rupatadine: aripiprazole, ceftazidime, posaconazole, prothypendyl and rupatadine are not included in AZCERT lists and, therefore, could be considered as potential emerging signals deserving case-by-case evaluation.

Fifteen agents reached a score of 5/8, of which the following could be potential emerging signals: asenapine, bromperidol, ceftriaxone, chlorprothixene, dexchlorpheniramine, fexofenadine, linezolid, metronidazole, promazine, saquinavir. The list of scores is available in deliverable D 3.3.

Novel approach. A new ARITMO Pharmacovigilance Score was developed that goes beyond the current standard and that allows for integration of evidence from multiple sources (see figures 7 and 8).

<table>
<thead>
<tr>
<th>Criterium Description</th>
<th>Threshold Value</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. cases of groups I and II 3 or more cases</td>
<td>Number of cases per 1000 reports</td>
<td>0,7</td>
</tr>
<tr>
<td>2. cases of groups I and II without concomitant drugs listed in AZCERT I or II 3 or more cases</td>
<td>Number of cases per 1000 reports</td>
<td>0,95</td>
</tr>
<tr>
<td>3. cases of groups I and II without concomitant cardio-vascular drugs 3 or more cases</td>
<td>Number of cases per 1000 reports</td>
<td>0,95</td>
</tr>
<tr>
<td>4. ROR for groups I and II (complete database) Significant ROR (i.e. Lower Limit 95%CI&gt;1) and 3 or more cases</td>
<td>Lower Limit 95%CI value</td>
<td>0,5</td>
</tr>
<tr>
<td>5. ROR for groups III and IV (complete database) Significant ROR (i.e. Lower Limit 95%CI&gt;1) and 3 or more cases</td>
<td>Lower Limit 95%CI value</td>
<td>0,2</td>
</tr>
<tr>
<td>6. ROR for groups I and II of the pharmacological class* Significant ROR (i.e. Lower Limit 95%CI&gt;1) and 3 or more cases</td>
<td>Lower Limit 95%CI value</td>
<td>0,5</td>
</tr>
<tr>
<td>7. ROR for groups III and IV of the pharmacological class* Significant ROR (i.e. Lower Limit 95%CI&gt;1) and 3 or more cases</td>
<td>Lower Limit 95%CI value</td>
<td>0,1</td>
</tr>
<tr>
<td>8. ROR for groups I and II within pharmacological class** Significant ROR (i.e. Lower Limit 95%CI&gt;1) and 3 or more cases</td>
<td>Lower Limit 95%CI value</td>
<td>0,7</td>
</tr>
<tr>
<td>9. ROR for groups III and IV within pharmacological class** Significant ROR (i.e. Lower Limit 95%CI&gt;1) and 3 or more cases</td>
<td>Lower Limit 95%CI value</td>
<td>0,4</td>
</tr>
<tr>
<td>10. ROR for groups I and II within pharmacological subclass*** Significant ROR (i.e. Lower Limit 95%CI&gt;1) and 3 or more cases</td>
<td>Lower Limit 95%CI value</td>
<td>0,8</td>
</tr>
<tr>
<td>11. ROR for groups III and IV within pharmacological subclass*** Significant ROR (i.e. Lower Limit 95%CI&gt;1) and 3 or more cases</td>
<td>Lower Limit 95%CI value</td>
<td>0,8</td>
</tr>
</tbody>
</table>
Figure 7: description of criteria used to calculate the pharmacovigilance score, with relevant thresholds, the value used in the calculation and coefficient used to weight each criterium (obtained through a consensus approach among WP3 partners). The full description of criteria and relevant information was provided in a dedicated Deliverable (D3.3).

Figure 8: approach for novel pharmacovigilance score (left) and the number of drugs for which a novel PhV score could be calculated.

The score was calculated by integrating evidence from 5 databases, and figure 8 shows that the combination of those databases allows for information on many more drugs than what would have been possible from a single source. A score for a drug could only be calculated if there were at least 3 case reports in each of the databases. Overall, 157 drugs received in integrated score and a value of uncertainty (i.e. a qualitative measure of the score that was calculated by using data on drug consumption, time on the market and consistency among the different scores considered in couple). Use of the novel PhV score allowed for graphical display of the score across the classes (figure 9). Notably, there are inter and intra-class differences in the distribution of the scores: for instance, nine antipsychotics received a score higher than moxifloxacin (the drug with the highest score among antibacterials). Among antipsychotics, the score spans from 0.915 (ziprasidone) to 0.018 (clotiapine). Oxatomide received the highest maximum score (=1), but with high degree of uncertainty (0.867) followed by rupatadine (score=0.935; uncertainty=0.636) and ziprasidone (0.915; 0.572).

Figure 9: Distribution of PhV score (y-axis) for the different drug classes

Key message from pharmacovigilance

- Pharmacovigilance Score and uncertainty were calculated for 157 drugs.
- All 5 SRS databases have significantly contributed in the assignment of the score, as demonstrated by the fact that there are some drugs that received a given score only from one source.
- There are inter and intra-class differences in the distribution of the score that may allow provisional risk ranking.
- For WP8 integration, 240 drugs were categorized. Please remember that, for WP8 purpose, we also identified low risk drugs, i.e. those without a pharmacovigilance score because less than 3 cases in all databases were reported, but with an uncertainty calculated (both drug utilization data and time on the market available).
- High risk category (h3 in WP8): 38 drugs with a Pharmacovigilance score ≥ 0.363 (0.363 represents the median value of the score for drugs in AZCERT lists 1, 2 and 3) were prioritized.
- Of these, 20 drugs could be potential novel signals (i.e. because they were previously unknown for this risk based on the information obtained from the AZCERT lists): 10 antipsychotics, 4 antihistamines, 2 antiprotozoals, 2 antifungals, 2 antivirals.
- For the remaining 18 drugs, the signal was confirmed (already listed by AZCERT) or strengthened (possible refinement of the AZCERT lists).
- Added value of the Pharmacovigilance Score (calculation of the uncertainty and increased positive
predictive value as compared to traditional disproportionality approach): detection of tiapride and oxatomide, drugs which already had provisional evidence of pro-arrhythmic risk.

1.3.3.4 Associations between (a) symptomatic QT prolongation and ARITMO drugs

In order to assess the risk of symptomatic and severe asymptomatic QTc prolongation for the ARITMO drugs a large case control study was conducted in a population from 4 European countries. QTc prolongation or TdP are not easy to measure in many of the health care databases since there are no ICD-9 or ICD-10 codes coding for these conditions. The study was therefore piggy backed on existing field studies: the Berlin Case-Control Surveillance Study (Germany), the Rotterdam Cohort Study (Netherlands), the Bologna Cohort Study (Italy), the Amsterdam Resuscitation Studies (Netherlands) and on three electronic medical record databases (HSD [Italy], IPCI [Netherlands], and THIN [UK]) providing information on QTc prolongation or TdP in free-text fields available in these databases.

A matched case-control design was chosen to analyse the data. Two different case definitions were established to which the different data sources contributed to different extent depending on their data availability: Case definition 1 was based on ECG-confirmed cases with moderate or severe QTc prolongation with clinical symptoms including TdP and VF, or severe QTc prolongation without clinical symptoms. Case definition 2 included patients with evidence of QTc prolongation as found via free-text search in the electronic healthcare databases or QTc prolongation comparing two standardised subsequent ECG readings. Controls were ascertained from the same data source and matched by age and sex. Exposure to the ARITMO drugs (anti-infectives, antihistamines and antipsychotics) as well as to all other drugs was analysed. In an initial approach, three different ATC levels were evaluated for the ARITMO drugs: the therapeutic group (ATC level 2), the pharmacological subgroup (ATC level 3) and the single substance (ATC level 5). As these analyses suffered from limited study power for case definition 1, but also from instable statistical models for case definition 2, another approach was chosen presented here. In this second approach, drugs were grouped according to their indication and by their known or assumed potential to cause QTc prolongation or TdP. Drugs were identified from the Arizona Cert List (http://crediblemeds.org). We also consulted the drug database of the German "arznei-telegramm" (http://www.arznei-telegramm.de/db/01pin.php3) searching for drugs reportedly associated with the adverse events "QT prolongation" and "torsade de pointes". For all these analyses, as confounders, cardiologic and other comorbidities were taken into account. For case definitions 1 and 2, regression models were fitted regarding the different exposure definitions. First, univariate conditional logistic regressions were conducted for each drug group/substance to provide an unadjusted risk estimate for comparison. Second, the odds ratio (OR) for current use (i.e. on the index date) relative to non-use was estimated for each drug group and each single substance using multivariate conditional logistic regression while adjusting in one analysis for potential confounders except other drugs ("single drug assessment") and in another analysis additionally for all other significant drugs ("joint drug assessment"). All comorbidities or comorbidity groups were forced into the model. To reduce the number of parameters and to exclude too rare medication exposures, only drugs that were observed in at least three cases at the index date for case definition 1 or 2 combined and that showed an elevated risk in the single drug assessment were considered to be of interest for the main analysis of the joint drug assessment.

Table 1 shows the number of cases per case group and datasource.
Table 1: Cases by datasource in the case control study on ARITMO drugs & QTc prolongation

<table>
<thead>
<tr>
<th>Case definition Event</th>
<th>Total</th>
<th>ARREST</th>
<th>BOLOGNA</th>
<th>FAKOS</th>
<th>HSD</th>
<th>IPCI</th>
<th>ROTTERDAM</th>
<th>THIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case definition 1</td>
<td>N=899</td>
<td>N=6</td>
<td>N=16</td>
<td>N=59</td>
<td>N=411</td>
<td>N=288</td>
<td>N=24</td>
<td></td>
</tr>
<tr>
<td>N=356 Long QT with TdP</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Long QT with VF</td>
<td>11</td>
<td>6</td>
<td>-</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Long QT with Syncope</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Severe long QT w/o symptoms</td>
<td>311</td>
<td>-</td>
<td>3</td>
<td>20</td>
<td>-</td>
<td>288</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Case definition 2</td>
<td>N=543</td>
<td>Delta QTc &gt; 50ms</td>
<td>13</td>
<td>-</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Found in free-text</td>
<td>530</td>
<td>-</td>
<td>95</td>
<td>411</td>
<td>-</td>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although case definition 1 included 356 cases and case definition 2 included 546 cases, very few cases and controls were exposed to any of the ARITMO drugs or to any of the other drugs potentially causing QTc prolongation and therefore did not contribute to the analyses.

Table 2: Association between ARITMO drugs and symptomatic & non-symptomatic QTc prolongation with respect to case definition 1

<table>
<thead>
<tr>
<th>ATC-level 5 + lumped drug groups</th>
<th>ARITMO and other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only significant drugs (pseudo-univariate) in the model POOLED (all contributing data sources)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable Frequency of Unadj.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR Adj. OR Cases Controls Exp. Unexp. Exp. Unexp.</td>
</tr>
</tbody>
</table>

| Amiodarone - C01BD01 | 26 330 1 961 26 24.991 [ 2.09,299.3]* |
| Domperidone - A03FA03 | 2 354 1 961 2 1.26E6 [ 0.00 . ] |
| Flecainide - C01BC04 | 5 351 3 959 1.667 3.658 [ 0.39,34.00] |
| Ondansetron - A04AA01 | 3 353 2 960 2.85 1.752 [ 0.11,27.37] |
| Sotalol - C07AA07 | 13 343 9 953 5.428 12.893 [ 2.05,80.91]* |
| ** Intestinal antiinfectives ** | 2 354 1 961 14.65 7.759 [ 0.03 2089] |
| ** Agents acting on the renin-angiotensin system ** | 20 336 19 943 2.087 1.502 [ 0.44 5.07] |
We dispensed with pooling of case definitions 1 and 2, since the major number of cases for case definition 1 came from the Rotterdam cohort for which we had very limited confounder information. Table 2 shows the results for case definition 1 for the joint drug assessment. Significantly elevated risks of a-symptomatic and symptomatic QTc prolongation were not observed for any of the ARITMO drugs. Among the non-ARITMO drugs, the known QTc-prolonging and arrhythmogenic potential of amiodarone and sotalol was confirmed.

The analysis regarding case definition 2 revealed increased risks for the antipsychotics quetiapine and thioridazine. Thioridazine is listed as drug with known TdP list on the Arizona Cert list. Among the newer antipsychotic drugs, quetiapine appears to prolong the QTc interval to the most marked extent. Severe QTc interval prolongation under quetiapine has been described to range between 3.1% and 7.8% (Wenzel-Seifert, K.; Wittmann, M.; Haen, E. QTc prolongation by psychotropic drugs and the risk of Torsade de Pointes. Dtsch. Arztebl. Int. 2011, 108, 687-693). Among anti-infective drugs, a significantly increased risk was observed for the fluoroquinolones moxifloxacin, norfloxacin and ciprofloxacin. Based on the HERG inhibition in in-vitro studies, the potency of the fluoroquinolones in terms of QT-interval prolongation has the following rank order: sparfloxacin &gt; grepafloxacin &gt; moxifloxacin &gt; gatifloxacin &gt; levofloxacin &gt; ciprofloxacin &gt; ofloxacin (Briasoulis, A.; Agarwal, V.; Pierce, W.J. QT prolongation and torsade de pointes induced by fluoroquinolones: infrequent side effects from commonly used medications. Cardiology 2011, 120, 103-110). Our results indicate that even fluoroquinolones with lower HERG affinity may be associated with an increased risk of QTc prolongation. Norfloxacin is a very old drug and there is not much information available on its QT prolonging potential. There was no increased risk observed for any drug of the group of antihistamines.

The results of the analysis for case definition 2 also confirmed the known arrythomogenic risks of the antiarrythmic drugs amiodarone, flecainide, disopyramide and sotalol. All these drugs are listed as drugs with known TdP risk on the Arizona Cert list. Among the other non-ARITMO drugs, other single drug substances with significantly increased risks included domperidone and ondansetron. Both drugs are also
listed as drugs with known TdP risk on the Arizona Cert list. There was no increased risk observed for any other single drug substance. The increased risk observed for some lumped drug groups are not interpretable and therefore cannot provide relevant signals. Often drugs from many different drug classes were combined in these groups in order to reduce the number of covariables in the statistical model, given the limited number of cases. Drugs grouped for obstructive airway diseases thus e.g. include β1- and β2-sympathomimetic drugs, inhaled glucocorticoids, anticholinergic drugs and theophylline. Among the comorbidities, we observed quite expectedly increased risks for arrhythmias and electrolyte imbalances. We further observed an increased risk also for cancer diseases.

Table 3: Association between ARITMO drugs and symptomatic & non-symptomatic QTc prolongation with respect to case definition 2

Case definition 2
ATC-level 5 + lumped drug groups
ARITMO and other drugs. Only significant drugs (pseudo-univariate) in the model POOLED (all contributing data sources)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine - N05AH02</td>
<td>1 542 7 52058 14.74 6.935</td>
<td>[0.71,67.45]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol - N05AD01</td>
<td>3 540 61 52004 4.815 2.191</td>
<td>[0.54 8.86]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine - N05AH04</td>
<td>3 540 31 52034 9.602 8.408</td>
<td>[2.47,28.58]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioridazine - N05AC02</td>
<td>1 542 3 52062 30.23 32.261</td>
<td>[2.95,352.8]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin - J01MA02</td>
<td>3 540 34 52031 8.817 5.062</td>
<td>[1.45,17.71]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin - J01MA14</td>
<td>1 542 2 52063 49.84 23.777</td>
<td>[1.58,356.8]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norfloxacin - J01MA06</td>
<td>3 540 28 52037 10.8 9.404</td>
<td>[2.72,32.50]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine - R06AD02</td>
<td>1 542 35 52030 2.861 1.899</td>
<td>[0.25,14.42]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone - C01BD01</td>
<td>15 528 164 51901 9.344 7.584</td>
<td>[4.13,13.93]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram - N06AB04</td>
<td>8 535 297 51768 2.508 2.015</td>
<td>[0.93 4.39]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyramide - C01BA03</td>
<td>2 541 4 52061 50 50.116</td>
<td>[9.10,275.9]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domperidone - A03FA03</td>
<td>3 540 76 51989 3.938 3.466</td>
<td>[1.05,11.40]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram - N06AB10</td>
<td>2 541 32 52033 6.587 3.811</td>
<td>[0.78,18.56]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide - C01BC04</td>
<td>10 533 146 51919 7.036 4.700</td>
<td>[2.37,9.31]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron - A04AA01</td>
<td>9 534 7 52058 19.79 22.335</td>
<td>[1.97,252.9]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol - C07AA07</td>
<td>39 504 642 51423 6.883 6.148</td>
<td>[4.29 8.81]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen - L02BA01</td>
<td>1 542 20 52045 5.113 1.636</td>
<td>[0.13,19.87]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*** Anti-parkinson drugs *** 3 540 41 52024 6.924 5.662 [1.54,20.85]*
*** Beta-lactam antibacterials *** 8 535 183 51882 3.953 2.840 [1.31 6.14]*
*** Intestinal antiinfectives *** 4 539 100 51965 3.388 3.089 [1.07 8.91]*
*** Sulfonamides and trimethoprim *** 2 541 74 51991 2.717 2.557 [0.61,10.80]
*** Tetracyclines *** 6 537 127 51938 4.787 4.518 [1.94,10.53]*
*** Agents acting on the renin-angiotensin system *** 23 520 992 51073 2.365 1.256 [0.67 2.35]
*** Antithrombotics *** 15 528 571 51494 2.699 0.948 [0.45 2.00]
1.3.3.5 Associations between VA, SCD and ARITMO drugs

Retrospective, population-based, multi-database, nested case-control studies in cohorts of users of the drug class were conducted to assess in a large population from 5 European Countries the risk of VA and SCD associated with current use of individual ARITMO drugs. These studies were registered as ENCePP studies. Different drug class and outcome-specific case-control sets were created at the site of the database custodian using dedicated standardized software, known as Jerboa©, which was originally developed in the EU-ADR project. All data were analysed and pooled on a remote research environment that is managed by Erasmus University Medical Center and analysed in a distributed fashion with all database custodians through secured remote access (see figure 10).

Figure 10: Distributed database approach utilizing common input files, standardized Jerboa scripts and the OCTOPUS remote research environment

Using these data drug utilization studies, incidence rate studies of VA and SCD and association studies were conducted. Drug utilization data were delivered in D5.4 and have resulted in several abstracts,
papers and presentations. Figure 11 shows the incidence of VA after the harmonization of events. During a period ranging from 1997 to 2010 we identified overall 31,353 cases of VA (age standardized incidence rate: 0.2 per 1000 person years) from seven healthcare databases (AARHUS [Denmark], GEPARD [Germany], Health-Search/Thales (HSD) and Emilia-Romagna Regional Database (ERD) [Italy], PHARMO and IPCI [Netherlands], and THIN [UK]), covering a total population of around 27 million individuals and 150 million person years of follow-up time and 33,607 cases of SCD (age standardized incidence rate: 1.4 per 1000 person-years) from two healthcare databases (IPCI & Aarhus).

For each individual drug class and outcome, a cohort of incident users of that drug class during a period ranging from 1997 to 2010 was identified in each database. Within this cohort all cases of VA and SCD were identified using harmonized and validated DB-specific codes based on diagnostic codes and free-text search. Up to 100 controls were then drawn from the same source population and matched to each case by index date, sex, age and database.

Exposure to study drugs was categorized into mutually exclusive groups of current (if exposure was at the index-date and/or in a carry-over period of either 7 or 30 days, depending on the drug class), recent (if exposure period ended between 7 (or 30) and 90 days before the index date), past (if the exposure period ended between 90 and 365 days before the index date), and non-use (if there was no exposure within 365 days prior to index date). Estimates were calculated only for drugs with at least 3 exposed cases to avoid instable estimates. For each drug class the odds ratio (OR) for current use for individual medications relative to non-use was estimated using multivariate conditional logistic regression while adjusting for recent and past use and for potential confounders. Since infections/fever is a risk factor for VA we also estimated the effect for antibiotics against current use of amoxicillin in a sensitivity analysis. In the final models we included as confounders all the known strong risk factors of VA (pre-defined) plus other weaker risk factors of VA based on modeling. Risk estimates were reported for each database separately. Data pooling was done by using a meta-analysis of single database estimates, as well as by pooling all data together (unweighted).

Antibiotics

Ventricular arrhythmia

Overall, in the pooled analysis the risk of VA could be explored for 38 antibiotics (as individual ATC codes), separately. Current use of the most frequently used penicillins (in ranked order, phenoxymethylpenicillin, amoxicillin with enzyme inhibitor, amoxicillin, pivmecillinam and pivampicillin), cephalosporins (ceftriaxone, cefpodoxime and cefaclor) and macrolides (azithromycin, clarithromycin, roxithromycin and erythromycin) showed a statistically significant increase in the risk of VA as compared with non-use, while no increased risk was documented for any of the fluoroquinolones (ciprofloxacin, levofloxacin, norfloxacin and moxifloxacin) and tetracyclines. However, in comparison to non-use, higher risk of VA (OR=3.6; 95%CI: 1.4-9.3) was reported for moxifloxacin in one database (ERD). In general, these findings were confirmed in the meta-analyses of single database risk estimates. When using current use of amoxicillin as comparator, only ceftriaxone was associated with a statistically significant increased
risk of VA (OR= 4.1; 95% CI: 1.7 - 9.9). Sensitivity analyses confirmed the robustness of the main findings. Current use of azithromycin versus non-use resulted in an OR of 1.9 (95% CI: 1.3 - 2.7) when using pooled data from the seven databases; however, no increase in the risk was observed when current use of amoxicillin was used as comparator (OR=1.1; 95% CI: 0.7 - 1.9).

Sudden cardiac death

Overall, the risk of SCD could be explored for 19 antibiotics in AARHUS and 1 in IPCI (as individual ATC codes). In AARHUS, the vast majority of antibiotics (including penicillins, cephalosporins, aminoglycosides, macrolides and fluoroquinolones), with some heterogeneity across different compounds, were also associated with increased risk of SCD as compared to non-use, confounding by indication may not be totally dealt with in these analyses. Interestingly, azithromycin was not associated with an increased risk of SCD (OR= 1.1; 95%CI: 0.8-1.5) as compared to non-use.

In IPCI current use of amoxicillin plus clavulanic acid was not associated with statistically significant increased risk of SCD as compared to non-use.

Anti-histamines

Ventricular arrhythmia

The risk of VA could be explored for 15 different anti-histamines. Only current use of cyclizine (OR= 5.2; 95% CI: 3.2 – 7.6) showed a statistically significant increase in the risk of VA as compared to non-use. Looking at database-specific estimates, the increased risk for cyclizine could be documented only in THIN.

Removal of carry-over from the current use risk window changed the results slightly: a statistically significant increase in the risk of VA was documented now also for clemastine, whereas the risk estimate for cyclizine increased. No dose effects were observed. Interestingly, loratadine was associated with a protective effect towards VA as compared to none use (OR=0.6; 95% CI: 0.4-0.9). This finding was confirmed in the meta-analysis of single database estimates.

When using cetirizine as comparator to take away potential confounding by indication, the statistically significant increase in the risk for VA was retained for cyclizine (OR= 6.3; 95% CI: 3.6 - 11.0). The risk of VA seems to be lower with longer duration of cyclizine treatment as compared to short-term use of that drug (&lt;30 days).

Sudden cardiac death

Overall, the risk of SCD could be explored only in AARHUS for 9 antihistamines (as individual ATC codes). A statistically significant increased risk of SCD was observed for promethazine (OR= 5.1; 95% CI:1.8 - 14.8) and cetirizine (OR= 1.4; 95% CI:1.2 – 1.5).

Antipsychotics
Ventricular arrhythmia

Overall, in the pooled analysis the risk of VA could be estimated for 17 antipsychotics, and, of these, 4 were atypical antipsychotics (olanzapine, quetiapine, risperidone, and amisulpride). Current use of haloperidol (OR: 2.0; 95%CI: 1.4 - 3.0) showed a statistically significantly increased risk of VA as compared to non-use. No increased risk of VA could be observed for any of the atypical antipsychotics, neither in the pooled analysis nor in the meta-analysis of database-specific estimates. The main findings were observed also in the sensitivity analyses. After removing the carry-over period, an increased risk of VA was seen also for thioridazine (OR: 2.6; 95%CI: 1.3 - 5.3). For the drugs with an increased risk, a trend towards a lower risk for medium/long term use versus short term use was observed.

Sudden cardiac death

Overall, the risk of SCD could be explored for 20 antipsychotics in AARHUS and 1 in IPCI. In AARHUS, in addition to haloperidol, a statistically significant increased risk of SCD was observed for levomepromazine, chlorpromazine, chlorprothixene, zuclophenthixol, risperidone, olanzapine, melperone and penfluridol.

Antimycotics

Ventricular arrhythmia

Overall, in the pooled analysis the risk of VA could be estimated for 7 antimycotics. Among drugs with enough exposure for measuring risk estimates, no antimycotic drug was found to be associated with VA. As regards fluconazole, an association with VA was reported only in Aarhus (OR=2.4; 95% CI: 1.1-5.1).

Sudden cardiac death

The risk of SCD could be explored only in AARHUS for 7 antimycotics (as individual ATC codes). In ranked order, nystatin, ketoconazole, fluconazole and itraconazole were associated with a statistically significant increased risk of SCD as compared to non-use of any antimycotic. A protective effect was reported for terbinafine.

Antiprotozoals

Ventricular arrhythmia

Overall, in the pooled analysis the risk of VA could be estimated for 4 antiprotozoals. Among drugs with enough exposure, no antiprotozoal drug was found to be associated with VA.

Sudden cardiac death

The risk of SCD could be explored in AARHUS only for 3 anti-protozoals. Current use of metronidazole (OR= 2.7; 95%CI: 2.2 - 3.3) was associated with a significantly increased risk of SCD as compared to non-use.
Antivirals

Ventricular arrhythmia

Overall, in the pooled analysis the risk of VA could be estimated only for 3 antivirals (acyclovir, amantadine and valaciclovir). Current use of these drugs did not show any statistically significant association with the outcome.

Sudden cardiac death

The risk of SCD could be explored only in AARHUS for 2 antivirals (acyclovir and valaciclovir). Current use of these drugs did not show any statistically significant association with SCD.

1.3.4 ARITMO Literature review of drug related factors

The objective of the ARITMO literature review is to identify, assess and summarise the existing evidence from the published literature for the arrhythmogenic potential of selected, marketed drugs within three therapeutic classes: antihistamines, antipsychotics and anti-infective agents.

Evidence from published preclinical, clinical and observational studies was collected using a systematic (Cochrane-style) approach involving a comprehensive search of the published literature and selection of relevant publications according to pre-defined eligibility criteria. This was done for all drugs on the ARITMO short list. These methods have been fully described in Deliverables 6.1 and 6.2. Deliverable 6.3 provides a description of the analysis of the evidence for each drug of interest and is accompanied by a Microsoft Access databases that provides evidence ‘profiles’ for each drug that summarises the quantitative evidence of arrhythmogenic potential.

Inclusion criteria for the different types of evidence were:

- Preclinical
  - hERG/IKr assays providing IC50 only
- Clinical trials
  - Placebo-controlled TQT & ECG studies, RCTs reporting QTc data
- Observational studies
  - Comparative cohort/case control studies reporting estimates for VA/SCD

In total, 245 eligible publications were selected for review (figure 12). This included: 84 studies in which data on hERG or IKr channel block were provided, 145 randomised, placebo-controlled clinical trial studies providing one or more risk estimate relating to QTc prolongation and 16 observational studies providing one or more risk estimates relating to ventricular arrhythmia or sudden cardiac death.

Figure 12: Literature review process
Figure 13 shows the distribution of the types of evidence by drug class. Of the 67 studies identified for antihistamines, 29 (43%), 35 (52%) and 3 (4%) were found for hERG/IKr, clinical trials and observational studies respectively. The corresponding proportions for the 112 studies identified for anti-infectives were 37 (33%), 66 (59%) and 9 (8%); and for the 90 studies identified for antipsychotics were 35 (39%), 49 (54%) and 6 (7%). Clinical trial evidence represented the highest proportion of eligible studies for all three drug classes with a relatively low proportion of observational studies.

Figure 13: Type of studies by drug class

In order to standardize the interpretation of results for the different types of outcome measures generated by the studies in the literature review, results were classified into 4 categories, coded according to a ‘traffic light’ system:

‘Significant’ is defined by the perceived practical or clinical importance of the results rather than statistical significance. The criteria for clinical importance are based on pragmatic selection of pre-defined arbitrary thresholds. Table 3 shows the criteria used to define each of the 4 categories across the different outcomes reported.

Table 3: Criteria for interpretation of quantitative data from WP6 (literature review)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No evidence available</th>
</tr>
</thead>
<tbody>
<tr>
<td>'0'</td>
<td>No evidence of significant risk</td>
</tr>
<tr>
<td>'1'</td>
<td>Evidence for significant risk inconclusive</td>
</tr>
<tr>
<td>'2'</td>
<td>Evidence of significant risk</td>
</tr>
<tr>
<td>'3'</td>
<td>Dichotomous outcomes* [Relative Risk, Odds Ratio or Incidence Rate Ratio]</td>
</tr>
<tr>
<td></td>
<td>(VA, SCD, QTc prolongation) No studies Upper limit of 95% CI &lt;2 or zero events 95% CI spans 2 Lower limit of 95% CI &gt;2</td>
</tr>
<tr>
<td>Continuous outcomes*</td>
<td></td>
</tr>
<tr>
<td>(milliseconds)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(MD in dQTc, ddQTc) No studies Mean effect &lt;5 msec or upper bound &lt;10 msec Mean effect 5-20 msec Mean effect &gt;20 msec or upper bound &gt;30 msec</td>
</tr>
<tr>
<td>hERG (margin) No studies Central margin &gt;30 Central margin spans 30 Central margin &lt;30</td>
<td></td>
</tr>
<tr>
<td>VA: Ventricular arrhythmia; SCD: Sudden Cardiac Death; CI: Confidence interval; MD: Mean difference in delta QTc; ddQTc: placebo subtracted delta QTc * The full description of dichotomous and continuous outcomes is provided in Deliverable 6.3.</td>
<td></td>
</tr>
</tbody>
</table>

As described in Deliverable 6.3 the hERG safety margin was calculated from the published IC50 divided by the peak plasma concentration (Cmax) that was retrieved for each drug from the pharmacokinetics database on the ARITMO drugs in the ARITMO project (WP7). This approach of categorisation of quantitative results does not, however, provide any indication of the quality of the evidence which, of course, may be highly variable across different studies, different outcomes and across different drugs. A strategy was therefore also developed to provide a means of summarising the quality of evidence from the
Interpretation of Quality of Evidence in the Literature Review

For each outcome, five ‘uncertainty factors’ were identified that were considered to have a bearing on the interpretation of the quantitative results. The body of evidence for each drug was assessed according to each of these five factors and given a pre-defined score of 0.2 for each one that applied (equal weighting assumed). Table 4 shows the criteria that were used to allocate uncertainty factors. An overall ‘uncertainty score’ was computed from the sum of these individual factors (from 0-1) and presented alongside the quantitative results to assist interpretation.

Table 4: Criteria for assessment of level of uncertainty in evidence

<table>
<thead>
<tr>
<th>Uncertainty Factor</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>hERG Data</td>
<td>Clinical Data1</td>
</tr>
<tr>
<td>Volume</td>
<td>If only one study available</td>
</tr>
<tr>
<td>Precision</td>
<td>If central range not precise enough to dichotomize between red and green categories</td>
</tr>
<tr>
<td>Consistency</td>
<td>If full range of data highly variable, e.g. IC50 or Cmax varies by an order of magnitude or if there were clear outliers in the dataset.</td>
</tr>
<tr>
<td>Validity</td>
<td>If most studies did not involve use of positive or negative control compounds</td>
</tr>
<tr>
<td>Representativeness</td>
<td>If studies use only one, less useful test condition e.g. only uses high potassium levels or only tests at room temperature.</td>
</tr>
</tbody>
</table>

1 From either experimental or observational studies.

2 Note that for the clinical evidence, ‘validity’ is measured according to the overall risk of bias or methodological weakness from the quality assessments of individual studies that were performed using the Cochrane Collaboration Tool or Newcastle Ottawa Scale and are detailed in Deliverable 6.2.

Overall Summary of Evidence from Literature review

In order to provide a simple summary that incorporates both quantitative and qualitative results an overall evidence categorisation was adopted and was based on consideration of all of the available evidence. An overall colour banding was then assigned according to the criteria in Table 5.

Table 5: Overall Classification of Evidence about Arrhythmogenic risk for Each Drug

A quality control check was carried out to ensure data accuracy. Two reviewers, independently, assessed the data. The overall conclusion statements and the uncertainty for hERG data have been completed, whereas the cross-check on clinical and observational studies was carried out on a sample of data.
Among the 28 antihistamines that were reviewed (Table 6), most drugs had grey level of evidence (n=17), one was green (fexofenadine), one is red (terfenadine) and for 9 drugs there was uncertainty in the available evidence.

Table 6. Output of the Literature Review for Antihistamines

<table>
<thead>
<tr>
<th>Year of marketing</th>
<th>Drug</th>
<th>hERG 1</th>
<th>Clinical trials 2</th>
<th>Observational 3</th>
<th>Conclusion 4 5 VA SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1946</td>
<td>diphenhydramine</td>
<td>0,4</td>
<td>Insufficient</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1951</td>
<td>promethazine</td>
<td>0,6</td>
<td>Insufficient</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1963</td>
<td>chlorphenamine</td>
<td>0,4</td>
<td>Insufficient</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1980</td>
<td>ketotifen</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1983</td>
<td>astemizole</td>
<td>0,2</td>
<td>0,6</td>
<td>0,2</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1984</td>
<td>mequitazine</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1992</td>
<td>clemastine</td>
<td>0,6</td>
<td>0,2</td>
<td></td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1993</td>
<td>loratadine</td>
<td>0,4</td>
<td>0,6</td>
<td>0,4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1993</td>
<td>terfenadine</td>
<td>0,2</td>
<td>0,8</td>
<td>0,4</td>
<td>Some evidence of significant risk</td>
</tr>
<tr>
<td>1994</td>
<td>acrivastine</td>
<td>0,6</td>
<td>Insufficient</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1995</td>
<td>cetirizine</td>
<td>0,2</td>
<td>0,6</td>
<td>0,4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1996</td>
<td>fexofenadine</td>
<td>0,8</td>
<td>0,2</td>
<td></td>
<td>No evidence of significant risk</td>
</tr>
<tr>
<td>1997</td>
<td>mizolastine</td>
<td>0,8</td>
<td>0,6</td>
<td></td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>2001</td>
<td>desloratadine</td>
<td>0,6</td>
<td>0,4</td>
<td>0,4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>2001</td>
<td>ebastine</td>
<td>0,6</td>
<td>0,2</td>
<td>0,6</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>2001</td>
<td>levocetirizine</td>
<td>0,6</td>
<td>0,8</td>
<td>0,4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>2005</td>
<td>cyclizine</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>2005</td>
<td>oxatomide</td>
<td>0,6</td>
<td>Insufficient</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>2008</td>
<td>rupatadine</td>
<td>0,8</td>
<td>0,8</td>
<td>0,6</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>2009</td>
<td>alimemazine</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>Unknown</td>
<td>cyproheptadine</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>Unknown</td>
<td>depropiene</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>Unknown</td>
<td>dexchlorpheniramine</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>Unknown</td>
<td>dimetindene</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>Unknown</td>
<td>mebhydrolin</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>Unknown</td>
<td>meclozine</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>Unknown</td>
<td>oxomemazine</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>Unknown</td>
<td>thiazinam</td>
<td></td>
<td>No evidence</td>
<td></td>
<td>No evidence available</td>
</tr>
</tbody>
</table>

1= undefined QTc prolongation; 2= mild or moderate QTc prolongation; 3= difference in mean delta QTc for drug and placebo; 4= placebo-adjusted delta QTc; 5= severe QTc prolongation; VA: ventricular Arrhythmia; SCD: Sudden Cardiac Death.

ANTIPSYCHOTICS
Among the 37 antipsychotics that were reviewed (Table 7), most drugs had grey level of evidence (n=20), 4 were red (thioridazine, mesoridazine, droperidol and risperidone) and for 13 drugs there was uncertainty in the available evidence.

Table 7. Output of the Literature Review for Antipsychotics

<table>
<thead>
<tr>
<th>Year of marketing</th>
<th>Drug</th>
<th>hERG</th>
<th>Clinical Obs</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1956</td>
<td>prochlorperazine</td>
<td>0.4</td>
<td>Insufficient evidence available</td>
<td></td>
</tr>
<tr>
<td>1956</td>
<td>promazine</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>1957</td>
<td>chlorpromazine</td>
<td>0.4</td>
<td>0.6 0.4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1957</td>
<td>perphenazine</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1958</td>
<td>perazine</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>1959</td>
<td>chlorprothixene</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>1959</td>
<td>fluphenazine</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1959</td>
<td>levomepromazine</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>1962</td>
<td>thioridazine</td>
<td>0.2</td>
<td>0.6 0.4 0.6 0.4</td>
<td>Some evidence of significant risk</td>
</tr>
<tr>
<td>1966</td>
<td>mesoridazine</td>
<td>0.2</td>
<td>0.6 0.4 0.6 0.4</td>
<td>Some evidence of significant risk</td>
</tr>
<tr>
<td>1966</td>
<td>periciazine</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>1967</td>
<td>haloperidol</td>
<td>0.2</td>
<td>0.6 0.4 0.2 0.2 0.6</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1970</td>
<td>pipamperone</td>
<td>0.6</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1980</td>
<td>melperone</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>tiapride</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>flupentixol</td>
<td>0.6</td>
<td>0.4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1984</td>
<td>pimozide</td>
<td>0.4</td>
<td>0.6</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1984</td>
<td>sulpiride</td>
<td>0.4</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1984</td>
<td>zuclopenthixol</td>
<td>0.4</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1985</td>
<td>levosulpiride</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>droperidol</td>
<td>0.4</td>
<td>0.2 0.2 0.4 0.2 0.4</td>
<td>Some evidence of significant risk</td>
</tr>
<tr>
<td>1989</td>
<td>clozapine</td>
<td>0.2</td>
<td>0.4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1993</td>
<td>amisulpride</td>
<td>0.4</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1993</td>
<td>risperidone</td>
<td>0.4</td>
<td>0.8 0.4 0.4 0.4 0.4</td>
<td>Some evidence of significant risk</td>
</tr>
<tr>
<td>1996</td>
<td>olanzapine</td>
<td>0.4</td>
<td>0.4 0.6 0.4 0.4 0.4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1996</td>
<td>sertindole</td>
<td>0.6</td>
<td>0.4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1997</td>
<td>quetiapine</td>
<td>0.8</td>
<td>0.6 0.4 0.4 0.2 0.4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1998</td>
<td>penfluridol</td>
<td>0.2</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>2001</td>
<td>ziprasidone</td>
<td>0.4</td>
<td>0.4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>2002</td>
<td>aripiprazole</td>
<td>0.4</td>
<td>0.2 0.2 0.4 0.2</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>2002</td>
<td>clotiapine</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>bromperidol</td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>paliperidone</td>
<td>0.2</td>
<td>0.2 0.4 0.2 0.4 0.2</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>2009</td>
<td>asenapine</td>
<td>0.6</td>
<td>0.4 0.6 0.2</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>Unknown fluspirilene</td>
<td></td>
<td></td>
<td>No evidence available</td>
<td></td>
</tr>
</tbody>
</table>
Unknown mosapramine No evidence available
Unknown prothipendyl No evidence available
1= undefined QTc prolongation; 2= mild or moderate QTc prolongation; 3= difference in mean delta QTc for drug and placebo; 4= placebo-adjusted delta QTc; 5= severe QTc prolongation; VA: ventricular Arrhythmia; SCD: Sudden Cardiac Death.

ANTI-INFECTIVES

Among the 154 anti-infectives that were reviewed (Table 8), most drugs had grey level of evidence (n=132) and for 22 drugs there was uncertainty in the available evidence.

Table 8. Output of the Literature Review for Anti-infectives

<table>
<thead>
<tr>
<th>Year of marketing</th>
<th>Drug</th>
<th>hERG</th>
<th>Clinical Obs</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>sulfadiazine</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1949</td>
<td>chloroquine</td>
<td>0,8</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1949</td>
<td>meglumine antimonate</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1952</td>
<td>pyrimethamine</td>
<td>0,4</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1953</td>
<td>tetracycline</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1955</td>
<td>hydroxychloroquine</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1958</td>
<td>nitrofurantoin</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1963</td>
<td>metronidazole</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1964</td>
<td>erythromycin</td>
<td>0,2</td>
<td>0,8 0,6 0,4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1964</td>
<td>vancomycin</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1965</td>
<td>ampicillin</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1966</td>
<td>amphotericin B</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1967</td>
<td>doxycycline</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1967</td>
<td>ethambutol</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1970</td>
<td>clindamycin</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1971</td>
<td>cefalexin</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1971</td>
<td>flucytosine</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1971</td>
<td>minocycline</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1971</td>
<td>pyrazinamide</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1973</td>
<td>cefazolin</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1974</td>
<td>amoxicillin</td>
<td>0,4</td>
<td>0,4</td>
<td>Uncertainty in existing evidence</td>
</tr>
<tr>
<td>1974</td>
<td>miconazole</td>
<td>0,6</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1977</td>
<td>pivmecillinam</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1978</td>
<td>cefamandole</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1978</td>
<td>sulfamethoxazole</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1979</td>
<td>colistin</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1979</td>
<td>cotrimoxazole</td>
<td>0,4</td>
<td></td>
<td>Insufficient evidence available</td>
</tr>
<tr>
<td>1979</td>
<td>dapsone</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
<tr>
<td>1980</td>
<td>gentamicin</td>
<td></td>
<td></td>
<td>No evidence available</td>
</tr>
</tbody>
</table>
1981 amikacin No evidence available
1981 ketoconazole 0 0,6 0,6 Uncertainty in existing evidence
1981 piperacillin No evidence available
1982 aciclovir No evidence available
1982 dicloxacillin No evidence available
1982 nystatin No evidence available
1982 trimethoprim 0,4 Insufficient evidence available
1983 cefotaxime No evidence available
1983 cefuroxime No evidence available
1983 inosine pranobex No evidence available
1983 isoniazid No evidence available
1983 pipemidic acid No evidence available
1984 co-amoxiclav No evidence available
1984 pentamidine 0,4 0,4 0,6 Uncertainty in existing evidence
1984 tobramycin No evidence available
1985 ceftazidime No evidence available
1985 phenoxymethylpenicillin No evidence available
1985 ribavirin No evidence available
1986 amantadine 0,4 Insufficient evidence available
1986 aztreonam No evidence available
1986 norfloxacin No evidence available
1986 sulbactam No evidence available
1986 ciprofloxacin 0,6 0,6 0,6 0,6 Uncertainty in existing evidence
1987 zidovudine No evidence available
1988 clindamycin No evidence available
1988 halofantrine 0,4 Insufficient evidence available
1989 cefixime No evidence available
1989 ganciclovir No evidence available
1989 mefloquine 0,2 0,8 Uncertainty in existing evidence
1989 rifampicin 0,8 Insufficient evidence available
1989 roxithromycin 0,6 Insufficient evidence available
1989 teicoplanin No evidence available
1990 fluconazole 0,6 0,4 Uncertainty in existing evidence
1990 ofloxacin 0,8 Insufficient evidence available
1991 clarithromycin 0,4 0,6 0,6 0,2 Uncertainty in existing evidence
1991 didanosine No evidence available
1991 fosfomycin No evidence available
1992 azithromycin 0,8 Insufficient evidence available
1993 tazobactam No evidence available
1994 famciclovir No evidence available
27 of 65
1994 quinine No evidence available
1994 stavudine No evidence available
1995 ceftibuten No evidence available
1995 lamivudine No evidence available
1995 saquinavir 0,8 Insufficient evidence available
1996 atovaquone No evidence available
1996 cefepime No evidence available
1996 fosfomycin No evidence available
1996 indinavir No evidence available
1996 levofloxacin 0,4 0,4 0,6 0,6 0,4 Uncertainty in existing evidence
1996 meropenem No evidence available
1996 nevirapine 0,4 Insufficient evidence available
1996 ritonavir 0,8 0,4 0,2 0,4 Uncertainty in existing evidence
1996 terbinafine 0,6 Insufficient evidence available
1997 cefaclor No evidence available
1997 nelfinavir 0,8 0,4 0,4 0,6 Uncertainty in existing evidence
1997 paromomycin No evidence available
1998 abacavir No evidence available
1998 benzylpenicillin No evidence available
1998 efavirenz 0,4 Insufficient evidence available
1998 valaciclovir No evidence available
1999 artemether No evidence available
1999 flucloxacillin No evidence available
1999 lumefantrine (with artemether) No evidence available
1999 moxifloxacin 0,2 0,6 0,6 0,6 Uncertainty in existing evidence
1999 oseltamivir 0,6 Insufficient evidence available
1999 zanamivir No evidence available
2000 brivudine No evidence available
2000 griseofulvin No evidence available
2000 linezolid No evidence available
2001 caspofungin No evidence available
2001 lopinavir 0,8 0,4 Uncertainty in existing evidence
2001 netilmicin No evidence available
2001 valganciclovir No evidence available
2002 adeovir No evidence available
2002 cefpodoxime No evidence available
2002 tenofovir No evidence available
2002 voriconazole 0,6 Insufficient evidence available
2003 atazanavir 0,4 Insufficient evidence available
2003 enfuvirtide No evidence available
2003 fosamprenavir No evidence available
2003 gemifloxacin 0,6 Insufficient evidence available
2004 emtricitabine No evidence available
2004 prulifloxacin 0,6 0,4 Uncertainty in existing evidence
The ultimate objective of the ARITMO integration model was to actually translate results from the ARITMO project into useful recommendations for clinicians and regulators (see figure 14).
From a population perspective, drug characteristics were assessed through the following approaches:

1) Systematic reviews and syntheses of information from pre-clinical information, clinical trials and observational studies on a selected list of ARITMO drugs that are frequently used (WP6).
2) Assessment of pharmacovigilance data for all ARITMO drugs (WP3);
3) Design and conduct of multi-country studies in currently available health care databases in the UK, Netherlands, Denmark, Germany and Italy for all ARITMO drugs (WP4 & 5)
4) In silico predictions of QT liability and proarrhythmic potential of drugs using various approaches (pharmacophoric, target profiling and molecular modelling) (WP7)

From an individual perspective, patient characteristics were identified through:

1) Novel markers for Torsade de Pointes on ECGs (WP7)
2) Genetic factors that can modify drug risk (WP7)

Figure 14: ARITMO model for data integration

The main results from WP 3 (pharmacovigilance), WP 5 (database studies) and 7 (hERG affinity) were integrated in a Dempster Shafer (DS) model (WP8) the output of which was a traffic light. The literature review in WP also resulted in a traffic light, with different interpretation and value; it was not about the level or risk but the level of evidence of risk.

The DS model allows combing evidence from heterogeneous and independent sources using expert judgment. Basically, it combines the “evidential weight” (also known as hypotheses) originated from WP3, 5 and 7 into a “combined mass”. The drug risk category is defined by considering the hypothesis with the highest value of the mass, provided that it is ≥0.300. In other circumstances, a grey category (representing uncertainty) is assigned.

Combination of the two results from the two traffic light systems (WP6-literature review and WP8-DS evidence integration) may lead to different scenarios:

THEORETICAL SCENARIO 1:

No evidence from literature review (WP6), and some evidence in Dempster Shafer analysis (WP8) which is based on data from pharmacovigilance (WP3), pharmacoepidemiology (WP5) or hERG affinity (WP7).

THEORETICAL SCENARIO 2:

Evidence from literature review (WP6), and consistent traffic lights from Dempster Shafer analysis (WP8) which is based on data from pharmacovigilance (WP3), pharmacoepidemiology (WP5) or hERG affinity (WP7)

THEORETICAL SCENARIO 3:
Uncertainty in evidence from literature review (WP6), and green or red traffic lights from Dempster Shafer analysis (WP8) which is based on data from pharmacovigilance (WP3), pharmacoepidemiology (WP5) or hERG affinity data (WP7).

THEORETICAL SCENARIO 4:

Evidence from literature review (WP6), and inconsistent traffic lights from Dempster Shafer analysis (WP8) which is based on data from pharmacovigilance (WP3), pharmacoepidemiology (WP5) or hERG affinity (WP7). This theoretical example never occurred in ARITMO

FOR CLINICIANS: the overall traffic light system results may be very informative to guide the choice of therapy in patients susceptible of arrhythmia (e.g. because of the presence of multiple risk factors, which may be modifiable or not). We developed the following proposal (Figure 15)

FOR REGULATORS: the most important use of ARITMO results may be the identification of newly available evidence from the ARITMO model, i.e. ARITMO provides new data (evidence of high or low risk) that did not arise from the literature (i.e. grey area due to missing information). An algorithm could be developed (beyond the ARITMO project) with the aim of supporting EMA in revising information reported in the summary of product characteristics, in particular in sections 4.3 (contraindications), 4.4 (warnings and precautions) and 4.8 (side effects).

KEY RESULTS

Notably, the DS model was applied only if at least 2 WPs provided data. After merging data from the three WPs, 450 drugs had data from at least 2 WPs (among WP3, WP5 or WP7) and were processed by the DS approach for evidence integration. Please note that, in the following tables, an asterisk in the DS column indicates that all 3 WPs provided hypotheses.

Comparison with the literature
For 205 drugs, out of 450, a comparison between WP6 (literature review, which was performed on the ARITMO narrow drug list) and DS assessment is provided: 26 antihistamines (15 with asterisk), 36 antipsychotics (16 with asterisk) and 143 anti-infectives (44 with asterisk).

Antihistamines

Among antihistamines, 16 drugs fulfill scenario 1 (new evidence emerged from ARITMO DS), 3 drugs fulfill scenario 2 (ARITMO DS confirmed literature evidence: notably, for terfenadine, red light has been confirmed, and for fexofenadine, green light has been confirmed) and 7 fulfill scenario 3 (refinement of intermediate score to high or low risk category). Fexofenadine, cetirizine and levocetirizine belong to low risk category (green light).

N° ATC_V Drug literature DS Scenario
1 R06AA02 diphenhydramine

2 R06AA04 clemastine *

3 R06AB02 dexchlorpheniramine *

4 R06AB03 dimetindene *

5 R06AB04 chlorphenamine *

6 R06AD01 alimemazine

7 R06AD02 promethazine *

8 R06AD07 mequitazine

9 R06AD08 oxomemazine

10 R06AE03 cyclizine *

11 R06AE05 meclozine

12 R06AE06 oxatomide

13 R06AE07 cetirizine *

14 R06AE09 levocetirizine *

15 R06AX02 cyproheptadine
Among antipsychotics, 20 drugs fulfill scenario 1, 5 drugs fulfill scenario 2 (notably, for thioridazine, mesoridazine, droperidol and risperidone red light has been confirmed) and 11 fulfill scenario 3. Most benzamides resulted in low risk categories: sulpiride, tiapride and levosulpiride in the green group, whereas amisulpride in the green-orange group.

N° ATC_V Drug literature DS Scenario
1 N05AA01 chlorpromazine
<table>
<thead>
<tr>
<th>Code</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>N05AA02</td>
<td>levomepromazine</td>
</tr>
<tr>
<td>N05AA03</td>
<td>promazine</td>
</tr>
<tr>
<td>N05AB02</td>
<td>fluphenazine</td>
</tr>
<tr>
<td>N05AB03</td>
<td>perphenazine</td>
</tr>
<tr>
<td>N05AB04</td>
<td>prochlorperazine</td>
</tr>
<tr>
<td>N05AB10</td>
<td>perazine</td>
</tr>
<tr>
<td>N05AC01</td>
<td>periciazine</td>
</tr>
<tr>
<td>N05AC02</td>
<td>thioridazine</td>
</tr>
<tr>
<td>N05AC03</td>
<td>mesoridazine</td>
</tr>
<tr>
<td>N05AD01</td>
<td>haloperidol</td>
</tr>
<tr>
<td>N05AD03</td>
<td>melperone</td>
</tr>
<tr>
<td>N05AD05</td>
<td>pipamperone</td>
</tr>
<tr>
<td>N05AD06</td>
<td>bromperidol</td>
</tr>
<tr>
<td>N05AD08</td>
<td>droperidol</td>
</tr>
</tbody>
</table>

* Indicates a specific medication.
16 N05AE04 ziprasidone
3
17 N05AF01 flupentixol
* 3
18 N05AF03 chlorprothixene
* 1
19 N05AF05 zuclopenthixol
* 1
20 N05AG01 fluspirilene
1
21 N05AG02 pimozide
3
22 N05AG03 penfluridol
1
23 N05AH02 clozapine
3
24 N05AH03 olanzapine
* 2
25 N05AH04 quetiapine
* 3
26 N05AH05 asenapine
3
27 N05AH06 clotiapine
1
28 N05AL01 sulpiride
* 1
29 N05AL03 tiapride
1
30 N05AL05 amisulpride
*
Among anti-infectives, 122 drugs fulfill scenario 1, 4 drugs fulfill scenario 2 and 16 fulfill scenario 3. In comparison with the other ARITMO drug classes, in most cases literature did not provide definite evidence (from WP6 emerged 142 drugs, of which only 19 belonged to orange class and all remaining drugs to grey class). Notably, from DS analysis emerged that anti-infectives mainly belong to low risk categories (i.e. green or green-orange). By contrast, different aminoglycosides, azole antifungals, antivirals (protease inhibitors) and antimalarials were classified as high risk drugs (red traffic light). Only for telithromycin, DS analysis did not provide a definite category as compared to the literature (orange traffic light).

<table>
<thead>
<tr>
<th>N°</th>
<th>ATC_V</th>
<th>Drug</th>
<th>literature</th>
<th>DS</th>
<th>Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>J01AA02</td>
<td>doxycycline</td>
<td>*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>J01AA07</td>
<td>tetracycline</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>J01AA08</td>
<td>minocycline</td>
<td>*</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>J01AA12</td>
<td>tigecycline</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>J01CA01</td>
<td>ampicillin</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>J01CA02 pivampicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>J01CA04 amoxicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>J01CA08 pivmecillinam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>J01CA12 piperacillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>J01CE01 benzylpenicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>J01CE02 phenoxyimethylpenicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>J01CE05 pheneticillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>J01CF01 dicloxacillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>J01CF05 flucloxacillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>J01CG01 sulbactam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>J01CG02 tazobactam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>J01DB01 cefalexin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>J01DB04 cefazolin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>J01DC02 cefuroxime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

37 of 65
20 J01DC03 cefamandole

1
21 J01DC04 cefaclor
*  
1
22 J01DD01 cefotaxime

1
23 J01DD02 ceftazidime

1
24 J01DD04 ceftriaxone
*  
1
25 J01DD08 cefixime
*  
1
26 J01DD13 cefpodoxime
*  
1
27 J01DD14 ceftibuten

1
28 J01DE01 cefepime

1
29 J01DF01 aztreonam

1
30 J01DH02 meropenem

1
31 J01DH04 doripenem

3
32 J01EA01 trimethoprim
*  
1
33 J01EB02 sulfamethizole
*  
1
34 J01EC01 sulfamethoxazole

38 of 65
<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>J01EC02</td>
<td>sulfadiazine</td>
</tr>
<tr>
<td>J01FA01</td>
<td>erythromycin</td>
</tr>
<tr>
<td>J01FA02</td>
<td>spiramycin</td>
</tr>
<tr>
<td>J01FA06</td>
<td>roxithromycin</td>
</tr>
<tr>
<td>J01FA09</td>
<td>clarithromycin</td>
</tr>
<tr>
<td>J01FA10</td>
<td>azithromycin</td>
</tr>
<tr>
<td>J01FA15</td>
<td>telithromycin</td>
</tr>
<tr>
<td>J01FF01</td>
<td>clindamycin</td>
</tr>
<tr>
<td>J01GB01</td>
<td>tobramycin</td>
</tr>
<tr>
<td>J01GB03</td>
<td>gentamicin</td>
</tr>
<tr>
<td>J01GB06</td>
<td>amikacin</td>
</tr>
<tr>
<td>J01GB07</td>
<td>netilmicin</td>
</tr>
<tr>
<td>J01MA01</td>
<td>ofloxacin</td>
</tr>
<tr>
<td>J01MA02</td>
<td>ciprofloxacin</td>
</tr>
<tr>
<td>J01MA06</td>
<td>norfloxacin</td>
</tr>
</tbody>
</table>
50 J01MA11 grepafloxacin

51 J01MA12 levofloxacin

52 J01MA14 moxifloxacin

53 J01MA15 gemifloxacin

54 J01MA17 prulifloxacin

55 J01MB04 pipemidic acid

56 J01XA01 vancomycin

57 J01XA02 teicoplanin

58 J01XA03 telavancin

59 J01XB01 colistin

60 J01XD01 metronidazole

61 J01XD02 tinidazole

62 J01XE01 nitrofurantoin

63 J01XX01 fosfomycin
64 J01XX08 linezolid
1
65 A07AA11 rifaximin
*
1
66 J02AA01 amphotericin B
1
67 J02AB01 miconazole
*
1
68 J02AB02 ketoconazole
3
69 J02AC01 fluconazole
*
3
70 J02AC02 itraconazole
*
1
71 J02AC03 voriconazole
1
72 J02AC04 posaconazole
1
73 J02AX01 flucytosine
1
74 J02AX04 caspofungin
1
75 J02AX05 micafungin
1
76 A07AA02 nystatin
*
1
77 N04BB01 amantadine
*
1
78 D01AA08 griseofulvin
1 79 D01AE15 terbinafine
* 1
80 G01AF02 clotrimazole
* 1
81 G01AF05 econazole

1
82 G01AF08 tioconazole

1
83 G01AF07 isoconazole

1
84 G01AF12 fenticonazole

1
85 G01AF15 butoconazole

1
85 G01AF17 oxiconazole

1
86 J04AB02 rifampicin

1
87 J04AB03 rifamycin

1
88 J04AB04 rifabutin

1
89 J04AD01 protionamide

1
90 J04AD03 ethionamide

1
91 J04AK01 pyrazinamide

1
92 J04AK02 ethambutol
<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>J04BA02</td>
<td>dapsone</td>
</tr>
<tr>
<td>J05AB01</td>
<td>aciclovir</td>
</tr>
<tr>
<td></td>
<td>*</td>
</tr>
<tr>
<td>J05AB04</td>
<td>ribavirin</td>
</tr>
<tr>
<td>J05AB06</td>
<td>ganciclovir</td>
</tr>
<tr>
<td>J05AB09</td>
<td>famciclovir</td>
</tr>
<tr>
<td>J05AB11</td>
<td>valaciclovir</td>
</tr>
<tr>
<td></td>
<td>*</td>
</tr>
<tr>
<td>J05AB14</td>
<td>valganciclovir</td>
</tr>
<tr>
<td>J05AB15</td>
<td>brivudine</td>
</tr>
<tr>
<td>J05AD01</td>
<td>foscarnet</td>
</tr>
<tr>
<td>J05AE01</td>
<td>saquinavir</td>
</tr>
<tr>
<td>J05AE02</td>
<td>indinavir</td>
</tr>
<tr>
<td>J05AE03</td>
<td>ritonavir</td>
</tr>
<tr>
<td>J05AE04</td>
<td>nelfinavir</td>
</tr>
<tr>
<td>J05AE06</td>
<td>lopinavir</td>
</tr>
</tbody>
</table>
107 J05AE07 fosamprenavir

1

108 J05AE08 atazanavir

2

109 J05AE09 tipranavir

1

110 J05AF01 zidovudine

1

111 J05AF02 didanosine

1

112 J05AF04 stavudine

1

113 J05AF05 lamivudine

1

114 J05AF06 abacavir

1

115 J05AF08 adefovir

1

116 J05AF09 emtricitabine

1

117 J05AG01 nevirapine

1

118 J05AG03 efavirenz

1

119 J05AG04 etravirine

3

120 J05AH01 zanamivir

1

121 J05AH02 oseltamivir
122 J05AX02 lysozyme

123 J05AX05 inosine pranobex

124 J05AX07 enfuvirtide

125 J05AX08 raltegravir

126 P01AA01 broxyquinoline

127 P01AA02 clioquinol

128 P01AB01 metronidazole

129 P01AB04 azanidazole

130 P01AX06 atovaquone

131 P01BA01 chloroquine

132 P01BA02 hydroxychloroquine

133 P01BA03 primaquine

134 P01BB01 proguanil

135 P01BC01 quinine

136 P01BC02 mefloquine
Additional results from DS

The following tables provided the DS output for drugs not investigated by the literature review (WP6). In fact, the literature search strategy was performed by considering a reduced number of compounds (i.e. the narrow ARITMO drug list) as compared to broad ARITMO drug list. Both lists are available as a source document in the project website (www.aritmo-project.org).

Among antihistamines, 18 received red, 9 received red-orange classification, 2 classified as orange, only 1 is green classification (epinastine), whereas 2 drugs did not have sufficient data to provide a traffic light classification (grey area).

Also in case of antipsychotics, most drugs (17) belong to red class, 3 received red-orange classification, only 1 is orange and 2 are green-orange (benzamides: sultopride and veralipride). Only 1 ARITMO drug remains in the grey area and only one carries an asterisk (see above for definition).

By contrast, most anti-infectives listed below are categorized into lower risk classes: 54 out of 189 are green (29%), 99 green-orange (52%) and 5 orange. Sixteen received red-orange classification and only 6 resulted as red. The remaining 9 are grey and only 3 carry an asterisk.

Antihistamines
N° ATC_V Drug Literature DS
1 R06AA01 bromazine -
2 R06AA06 chlorphenoxamine -
3 R06AA07 diphenylpyraline -
4 R06AA08 carboxamine -
5 R06AA09 Doxylamine -
6 R06AB01 brompheniramine -
7 R06AB05 pheniramine -
8 R06AB06 dexamphiramine -
9 R06AB07 talastine -
10 R06AC01 mepyramine -
11 R06AC02 histapyrrodine -
12 R06AC03 chloropyramine -
13 R06AC04 tripelennamine -
14 R06AC05 methapyrilene -
15 R06AC06 thonzylamine -
16 R06AD03 thiethylperazine -
17 R06AD04 methdilazine -
18 R06AD05 hydroxyethylpromethazine -
19 R06AD09 isothipendyl -
20 R06AE01 buclizine -
21 R06AE04 chlorcyclizine -
22 R06AX01 bamipine -
23 R06AX03 thenalidine -
R06AX03 thenalidine -
R06AX04 phenindamine -
R06AX05 antazoline -
R06AX07 triprolidine -
R06AX08 pyrrobutamine -
R06AX19 azelastine -
R06AX21 tritoqualine -
R06AX23 pimethixene -
R06AX24 epinastine -

Antipsychotics

N° ATC_V Drug literature DS
1 N05AA04 acepromazine -
2 N05AA05 triflupromazine -
3 N05AA06 cyamemazine -
4 N05AA07 chlorproethazine -
5 N05AB01 dixyrazine -
6 N05AB05 thiopropazate -
7 N05AB06 trifluoperazine - *
8 N05AB07 acetophenazine -
9 N05AB08 thioproperazine -
10 N05AB09 butaperazine -
11 N05AC04 pipotiazine -
12 N05AD02 trifluperidol -
13 N05AD04 moperone -
14 N05AD07 benperidol -
15 N05AD09 fluanisone -
16 N05AE01 oxypertine -
17 N05AE02 molindone -
18 N05AF02 clopenthixol -
19 N05AF04 tiotixene -
20 N05AH01 loxapine -
21 N05AL02 sulthopride -
22 N05AL04 remoxipride -
23 N05AL06 veralipride -
24 N05AX11 zotepine -

Anti-infectives

N° ATC_V Drug literature DS
1 J01AA01 demeclocycline -
2 J01AA03 chlortetracycline -
3 J01AA04 lymecycline - *
4 J01AA05 metacycline -
5 J01AA06 oxytetracycline -
6 J01AA09 rolitetracycline -
7 J01AA10 penimepicycline -
8 J01AA11 clomocycline -
9 J01BA02 thiamphenicol -
10 J01CA03 carbenicillin -
11 J01CA05 carindacillin -
12 J01CA06 bacampicillin -
13 J01CA07 epicillin -
14 J01CA09 azlocillin -
15 J01CA10 mezlocillin -
16 J01CA11 mecillinam -
17 J01CA13 ticarcillin and enzyme inhibitor -
18 J01CA14 metampicillin -
19 J01CA15 talampicillin -
20 J01CA16 sulbenicillin -
21 J01CA17 temocillin -
22 J01CA18 hetacillin -
23 J01CE03 propicillin -
24 J01CE04 azidocillin -
25 J01CE06 penamincillin -
26 J01CE07 clometocillin -
27 J01CF02 cloxacillin -
28 J01CF03 meticillin -
29 J01CF04 oxacillin -
30 J01CR04 sultamicillin - *
31 J01DB02 cefaloridine -
32 J01DB03 cefalotin -
33 J01DB05 cefadroxil -
34 J01DB06 cefazedone -
35 J01DB07 cefatrizine -
36 J01DB08 cefapirin -
37 J01DB09 cefradine - *
38 J01DB10 cefacetrile
39 J01DB11 cefroxadine -
40 J01DB12 ceftезole -
41 J01DC01 cefoxitin -
42 J01DC05 cefotetan -
43 J01DC06 cefonicide -
44 J01DC07 cefotiam -
45 J01DC08 loracarbef -
46 J01DC09 cefmetazole -
47 J01DC10 cefprozil -
48 J01DC11 ceforanide -
49 J01DD03 cefsulodin -
50 J01DD05 cefmenoxime -
51 J01DD06 latamoxef -
52 J01DD07 ceftizoxime -
53 J01DD09 cefodizime -
54 J01DD10 cefetamet -
55 J01DD11 cefpiramide -
56 J01DD12 cefoperazone -
57 J01DD15 Cefdinir -
58 J01DD16 Cefditoren -
59 J01DE02 Cefpirome -
60 J01DH03 Ertapenem -
61 J01DI01 ceftobiprole medocaril -
62 J01EB01 sulfaisodimidine -
63 J01EB03 Sulfadimidine -
64 J01EB03 Sulfadimidine -
65 J01EB04 Sulfapyridine -
66 J01EB05 Sulfafurazole -
67 J01EB06 Sulfanilamide -
68 J01EB07 Sulfathiazole -
69 J01EB08 Sulfathiourea -
70 J01EC03 Sulfamoxole -
71 J01ED01 sulfadimethoxine -
72 J01ED02 Sulfolene -
73 J01ED03 sulfametomidine -
74 J01ED04 sulfametoxydiazine -
75 J01ED05 sulfamethoxypyridazine -
76 J01ED06 Sulfaperin -
77 J01ED07 sulfamerazine -
78 J01ED08 sulfaphenazole -
79 J01ED09 Sulfamazone -
80 J01FA03 Midecamycin -
81 J01FA05 oleandomycin -
82 J01FA07 Josamycin -
83 J01FA08 troleandomycin -
84 J01FA11 Miocamycin -
85 J01FA12 Rokitamycin -
86 J01FA13 Dirithromycin -
87 J01FA14 flurithromycin -
88 J01FF02 Lincomycin -
89 J01FG01 Pristinamycin -
90 J01GA01 Streptomycin -
91 J01GB04 Kanamycin -
92 J01GB05 Neomycin -
93 J01GB08 Sisomicin -
94 J01GB09 Dibekacin -
95 J01GB10 Ribostamycin -
96 J01GB11 Isepamicin -
J01GB12 arbekacin -
J01MA03 pefloxacin -
J01MA04 enoxacin -
J01MA05 temafloxacin -
J01MA07 lomefloxacin -
J01MA08 fleroxacin -
J01MA10 rufloxacin -
J01MA13 trovafloxacin -
J01MA18 pazufloxacin -
J01MB01 rosoxacin -
J01MB02 nalidixic acid -
J01MB03 piromidic acid -
J01MB05 oxolinic acid -
J01MB06 cinoxacin -
J01MB07 flumequine -
J01XB02 polymyxin b -
J01XC01 fusidic acid -
J01XD03 ornidazole -
J01XE02 nifurtoinol -
J01XX02 xibornol -
J01XX03 clofoctol -
J01XX04 spectinomycin -
methenamine -
mandelic acid -
nitroxoline -
daptomycin -
bacitracin -
sulfaguanidine -
succinylsulfathiazole -
anidulafungin -
flutrimazole -
terconazole -
aminosalicylic acid -
cycloserine -
rifapentine -
capreomycin -
tiocarlide -
terizidone -
morinamide -
clofazimine -
metisazone -
idoxuridine -
vidarabine -
cidofovir -
<table>
<thead>
<tr>
<th>Code</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>J05AB12</td>
<td>penciclovir</td>
</tr>
<tr>
<td>J05AC02</td>
<td>rimantadine</td>
</tr>
<tr>
<td>J05AC03</td>
<td>tromantadine</td>
</tr>
<tr>
<td>J05AD02</td>
<td>fosfonet</td>
</tr>
<tr>
<td>J05AE05</td>
<td>amprenavir</td>
</tr>
<tr>
<td>J05AE10</td>
<td>darunavir</td>
</tr>
<tr>
<td>J05AF03</td>
<td>zalcitabine</td>
</tr>
<tr>
<td>J05AF08</td>
<td>adefovir dipivoxil</td>
</tr>
<tr>
<td>J05AF10</td>
<td>entecavir</td>
</tr>
<tr>
<td>J05AF11</td>
<td>telbivudine</td>
</tr>
<tr>
<td>J05AF12</td>
<td>clevudine</td>
</tr>
<tr>
<td>J05AG02</td>
<td>delavirdine</td>
</tr>
<tr>
<td>J05AX01</td>
<td>moroxydine</td>
</tr>
<tr>
<td>J05AX06</td>
<td>pleconaril</td>
</tr>
<tr>
<td>J05AX09</td>
<td>maraviroc</td>
</tr>
<tr>
<td>P01AA04</td>
<td>chlorquinaidol</td>
</tr>
<tr>
<td>P01AA05</td>
<td>tilbroquinol</td>
</tr>
<tr>
<td>P01AB05</td>
<td>propenidazole</td>
</tr>
<tr>
<td>P01AB06</td>
<td>nimorazole</td>
</tr>
<tr>
<td>P01AB07</td>
<td>secnidazole</td>
</tr>
<tr>
<td>P01AC01</td>
<td>diloxanide</td>
</tr>
<tr>
<td>P01AC03</td>
<td>etofamide</td>
</tr>
</tbody>
</table>
163 P01AC04 teclozan -
164 P01AR01 arsthinol -
165 P01AR02 difetarsone -
166 P01AR03 glycobiarsol -
167 P01AX01 chiniofon -
168 P01AX02 emetine -
169 P01AX04 phanquinone -
170 P01AX05 mepacrine -
171 P01AX07 trimetrexate -
172 P01AX08 tenonitrozole -
173 P01AX09 dihydroemetine -
174 P01AX10 fumagillin -
175 P01AX11 nitazoxanide -
176 P01BA06 amodiaquine -
177 P01BB02 cycloguanil embonate -
178 P01BE01 artemisinin -
179 P01BE03 artesunate -
180 P01BE05 artenimol -
181 P01CA02 benznidazole -
182 P01CC01 nifurtimox -
183 P01CC02 nitrofural -
184 P01CD01 melarsoprol -
Evidence integration represents the final step of the ARITMO project. We have adopted a multidisciplinary consensus process to aggregate heterogeneous data from various WPs, assigning a certain degree of confidence to each type of evidence to yield a final risk score, an innovative component of the ARITMO project.

The ARITMO results can be used in a flexible fashion, depending on the issue under scrutiny. For example, future applications include:

- WP8 results, especially when the final traffic light carries an asterisk (denoting evidence from three independent sources), can be used as an aid for decision making by regulators;
- WP3 results (pharmacovigilance) can be used to identify drugs to be prioritized in safety evaluation also in the light of drug utilization data; high sensitivity of this approach (possible false positives) should be taken into account;
- WP5 results can be used to quantify risk in a population perspective; high specificity of this approach (possible false negatives) should be taken into account
- WP3 and WP5 results, taken together, can help to validate preclinical predictive models by providing positive and negative control drugs.

1.3.6 ECG parameters

Recently, a number of other ECG parameters that reflect heterogeneity of repolarization have been proposed, based on T-wave loop morphology and beat-to-beat variability of repolarization. In activity 7.4 of WP7, we explored these ECG parameters in their potential to predict TdP. Deliverable 7.5 reports on the methods and results of the ECG analyses as part of that activity. Since most of the ECGs from the contributing studies were only available on paper, and the analyses required the ECGs to be in digital format, we had to develop a paper-to-digital ECG conversion pipeline.

The data in our analyses were taken from four participating studies in the ARITMO project: DARE (Drug-Induced Arrhythmia Risk Evaluation Study), FAKOS (Fall-Kontroll Surveillance), EUDRAGENE, and the Rotterdam Study. A comprehensive description of these studies has been given in Deliverable 4.1 – Protocol for Multinational Analytic Field Studies. Briefly, the DARE study is a case-control study that recruited patients with TdP or QTc prolongation with syncope or severe asymptomatic QTc prolongation...
following exposure to drugs from 2003 onwards in England. FAKOS is a hospital-based prospective case-control surveillance study that collects adult patients with symptomatic long QT syndrome in Berlin. EUDRAGENE is a European case-control study of genetic susceptibility to adverse drug reactions (ADRs), including LQT/TdP ascertained from pharmacovigilance reports, hospitals, and primary care. The Rotterdam Study is a prospective population-based cohort study, which started in 1990 and includes 15,000 elderly inhabitants from Rotterdam.

For the purpose of our analyses, we focused on cases of TdP, ventricular fibrillation (VF), and ventricular tachycardia (VT). For each case, at least one ECG that documented the event of interest had to be present. Databases that contributed cases were DARE, FAKOS, and EUDRAGENE, for a total of 113 cases. Table 1 shows the number of cases per database. Note that a case can have multiple documented events, e.g. TdP and VF. Controls were taken from the Rotterdam Study.

<table>
<thead>
<tr>
<th>Database</th>
<th>Cases</th>
<th>TdP</th>
<th>VT</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>DARE</td>
<td>69</td>
<td>48</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>FAKOS</td>
<td>36</td>
<td>30</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>EUDRAGENE</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Digital ECGs were also collected and processed from drug-related cohort studies in Bologna and Newcastle, but since none of the patients in these studies experienced an event (TdP, VF, or VT), these ECGs were not used in the present analyses.

All ECGs that were available in FAKOS and EUDRAGENE, were paper-based, i.e. the ECGs were only available as hard copies of the original paper ECG plots. In DARE, most ECGs were also paper-based, but some ECGs were stored in a digital format. The ECGs in the Rotterdam Study were all digitally stored.

The ECG analysis program that computes the ECG parameters of interest requires the ECGs to be available in a digital format. Therefore, the paper-based ECGs had to be digitized. For this purpose, we developed a paper-to-digital ECG conversion pipeline.

We measured a number of ECG parameters that reflect heterogeneity of repolarization, and were considered to be promising potential markers of TdP:

- QTc interval
- Maximum spatial T amplitude
- Frontal T axis
- QRS-T angle
- Short-term QT variability

Other measures of repolarization disturbance that have been suggested as new markers of risk for arrhythmias, are QT dispersion and the peak-to-end T interval. In previous studies, we and others have
shown that both these parameters are epiphenomena of the T-loop morphology and have no intrinsic value. We therefore did not further consider them in our present analyses.

The ECG parameters described above were automatically measured with our Modular ECG Analysis System (MEANS). For the measurement of STV, we developed a special measurement technique (fiducial segment averaging) to accurately measure cardiac time intervals.

With the use of this pipeline we processed 679 ECGs, of which 317 (47%) were converted successfully. Another important effort has been the development and validation of an algorithm for the automatic measurement of STV, one of the novel ECG risk markers. Manual measurement of STV is cumbersome and error-prone. The technique that we developed is fully automatic and was shown to provide more reliable STV estimates than a beat-by-beat measurement approach that resembles manual measurement.

Our dataset contains 102 cases with documented events, with a total of 382 ECGs that were recorded before or after the event. To our knowledge, this is the largest TdP dataset with documented events to date. To investigate the predictive value of ECG parameters, ECGs that are recorded prior to the event are especially useful. Unfortunately, the number of ECGs in our dataset before the event was relatively low. Moreover, since most of these ECGs did not have a rhythm strip, STV could only be computed in a few ECGs prior to the event.

The trend analyses show mixed results for the various ECG parameters. In the uncontrolled analysis, the QTc interval showed an increase towards the event and a decrease after the event. There are differences between QT corrected according to Bazett’s or Fridericia’s formula, but the trends for both parameters are very similar. The frontal T axis and QRS-T angle show large variability and basically no trend. The spatial T amplitude also shows large variability and little change in the median values, except for an increasing trend in the last time periods after the event. The STV finally shows a clear decrease after the event; the values before the event should be interpreted with caution because they are based on very few cases. Similar patterns were observed when the analyses were restricted to the cases with sotalol and amiodarone as the culpable drugs.

For the case-control analysis, the QTc intervals again show an increase around the event. Interestingly, the median QTc values 3 months before or after the event remain increased as compared to the control values. For the spatial T amplitude the cases show consistently lower median values than controls, without any observable trend. T axis and QRS-T angle again show large variability and no clear differences between cases and controls. STV values of cases are larger than controls, without showing a trend. In the case-control analysis for sotalol and amiodarone cases, drug-matched controls were not always available, reducing the number of cases and complicating the interpretation.

The self-controlled analysis (Figures 16) was only done on the 65 DARE cases that had a digital ECG. Due to the lower number of cases as compared to the previous analyses, variability in the estimates increases, obscuring trends (if any). Again, QTc intervals show an increased trend around the event. Remarkably, spatial T amplitude is reduced for all time periods.

Summarizing, our analyses show clear trends in increasing QTc intervals before an event. This pattern
was not observed for the other ECG parameters that we studied. An interesting finding was that the spatial T amplitude was reduced in cases as compared to controls, possibly suggesting that this parameter may be used as a general marker of risk. Although our uncontrolled analyses show that STV is increased around the event, too few ECGs prior to the event were available to establish a possible predictive value of this parameter. Overall, our analyses suffered from a lack of data. However, if larger datasets become available in the future, the tools and techniques that were developed as part of this workpackage provide a framework for large-scale ECG processing and exploration.

Figure 15. Number of ECGs per database in time periods relative to the event.

Delta QTc interval Bazett
Delta QTc interval Fridericia

Delta spatial T amplitude
Delta frontal T axis

Delta QRS-T angle
Delta STV

Figure 16. Boxplots using all cases in the self-controlled analysis on the DARE cases.

1.3.7 Patient related factors: Genetics

The aim of the genetic study was to identify mutations in known and novel candidate genes associated with drug exposure (DiLQTS). 159 patients were enrolled for the genetic study at multiple centres in Europe and UK. Cases were included if they met criteria for case definition 1 (QT prolongation with documented Torsades de Pointes, ventricular fibrillation, cardiac syncope or QT prolongation alone) or case definition 2 (cardiac arrest and/or sudden death without further documentation). In addition exposure to one or more medications deemed culpable for the event was required. Blood samples were sent from Berlin, Germany and DNA was extracted in SGUL. DNA samples were received from Italy, Denmark and Netherlands. While the majority of the cases were thought to be Caucasian this was not reported for the Berlin and Denmark cases. 103/159 (65%) were female with a mean age of 59.0 years (range 14-88).

The final list of targets for genetic studies was generated by taking the top 15 targets from an in silico list that was created in workpackage 7 and supplementing these with genes known to be involved in the congenital LQTS and additional targets generated from amiodarone and sotalol, two of the principal agents from the collection of cases. We identified putative mutations in cardiac ion channel associated genes, and a number of novel targets that require replication in other series. The details are described D 7.4.

The ARITMO genetic study has identified putative mutations in cardiac ion channel associated genes, two neurological targets and a number of CYP enzymes. The details are described D 7.4.

As part of ARITMO's work samples from Pavia and SGUL were pre-screened with Sanger sequencing.
technology for mutations in the genes involved in the congenital long QT syndrome: KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2. These data were then incorporated into the overall results of the sequencing study for samples accumulated as part of ARITMO.

Potential Impact:

Impact

Regarding the project’s impact, the ARITMO project addressed the topic published by the EC Health DG Health-2009.4.2.2 – Study of the arrhythmogenic potential of different classes of medicines. ARITMO has specifically been devoted to analyse the cardiac safety profile of one of the commonly-used classes of medications: antipsychotics, anti-infectives and H1-anti-histamines. 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 ARITMO project is the intense communication and collaboration with the EMA, which is using ARITMO generated information into its decision-making process and consults ARITMO experts regularly. See also some examples of exploitation of ARITMO results in section 1.3.5.

Dissemination Activities

It is noteworthy that the most important scientific event in the field is the Annual Conference of the International Society of Pharmacoepidemiology, and the project has been increasingly present at this conference, to the point that in the 2013 edition to held in Montreal in August had a full workshop session devoted to ARITMO. The workshop was entitled The ARITMO results: prediction of the arrhythmogenic risk of antihistamines, antipsychotics and anti-infectives by integration of translational evidence and covered the main results derived from the project.

As a general policy, only those activities that effectively reflect on the project dissemination and include the required EC funding acknowledgement have been taken into account. A Protocol for tracking dissemination activities in the Consortium was set up from the onset, consisting of a centralized repository of all Consortium dissemination activities, maintained by the Dissemination WP Leader and based on information reported by the partners.

Outreach to additional audiences and other initiatives

ARITMO has established links with related projects in the field of drug safety and beyond. In fact, ARITMO has used knowledge and tools generated by the EC-funded project EU-ADR and from previous projects (give examples) are being applied to ARITMO and will be further applied to the EC-funded project SAFEGUARD, conducting research in the field of drug safety on safety evaluation of adverse reactions in diabetes.

The project was firstly presented at EMA in October 2010 and in June 2013 and at the Dutch pharmacovigilance network in June 2010. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was interested in the project and for this reason it was presented in
some of its plenary sessions in London and in Washington (both of them took place in June 2010). The project was also presented at the Brookings Institute located in Washington in June 2010. Add more recent presentations?

The EMA and the PRAC (Pharmacovigilance Risk Assessment Committee) have been one of the main target audiences of the project. Information about the relationship established and the communication guidelines developed can be found in deliverable D9.5 Final Report on Dissemination Activities.

Communication tools

From the initial stages of the project it was considered a priority to create a “corporate” identity of the project in order to maximise the impacts of homogeneous and consistent communication across partners. For this purpose a set of dissemination tools was designed and produced; namely the project logo, website, project launch press release, a flyer and poster and presentation templates. These have been widely used in all project communication activities and have contributed to visualize ARITMO as a relevant international research initiative. Some examples of tools are shown below:

Figure 17: ARITMO logo

Figure 18: ARITMO homepage screenshot

Exploitation of Results

The primary results of the ARITMO 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 ARITMO 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 ARITMO 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 ARITMO are already being used in other drug safety related projects (i.e. SAFEGUARD), such as 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.

Many of the lessons learned in ARITMO are in the form of experience at the various sites and managing arising difficulties that may arise when workflows have dependencies. This experience will be invaluable for future projects that have similar goals such as ARITMO, SAFEGUARD, and GRIP (Global Research in Pediatrics)

List of Websites:
Project coordinator: Prof. Miriam CJM Sturkenboom, Erasmus Universitair Medisch Centrum Rotterdam

Project manager: Eva Molero, Synapse Research Management Partners

Contact details:

www.aritmo-project.org

List of Partners

• Erasmus Universitair Medisch Centrum Rotterdam (Netherlands) - Coordinator
• Fundació Institut Mar d'Investigacions Mèdiques (Spain)
• London School of Hygiene and Tropical Medicine (UK)
• Alma Mater Studiorum, University of Bologna (Italy)
• Universitaet Bremen (Germany)
• University of Newcastle (UK)
• Université Victor-Segalen Bordeaux II (France)
• Fondazione Salvatore Maugeri Clinica del Lavoro e Della Riabilitazione (Italy)
• Charite - Universitätsmedizin Berlin (Germany)
• Università Degli Studi di Verona (Italy)
• St. George's Hospital Medical School (UK)
• Astra Zeneca AB (Sweden)
• PHARMO Coöperatie UA (Netherlands)
• Fondazione Scientifica SIMG-ONLUS (Italy)
• Aarhus Univesitetshospital, Aarhus Sygehus (Denmark)
• Academisch Medisch Centrum bij de Universiteit van Amsterdam (Netherlands)
• Drug Safety Research Trust (UK)
• Institut für Epidemiologie und Präventionsforschung GmbH (Germany)
• Synapse Research Management Partners SL (Spain)

Related documents

final1-aritmo-final-report-v2-0final.pdf

Last update: 8 July 2014
Record number: 141814