Acute myocardial infarction and stroke registries. The Italian experience

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ABSTRACT

Cardiovascular diseases (CVD) are the leading causes of death and hospitalisation in nearly all European countries and accounted for almost 40% of all deaths in 2013. With the exception of few rigorous but limited studies carried out in some geographical areas, available data on CVD incidence and prevalence are generally limited and of poor quality, despite the magnitude of the CVD phenomenon. The EUROCISS Project, supported by the Health Monitoring Programme of the DG SANCO from 2000 to 2007, provided general guidance and updated methods for the surveillance of Acute Myocardial Infarction (AMI) and Stroke. The Italian population-based registry of major coronary and cerebrovascular events was set up following EUROCISS Project recommendations; it also took into account the experience acquired by Italy in the WHO-MONICA project since the mid-1980s and continued with the coordination of the EUROCISS Project. The project: "A population-based AMI register: assessing the feasibility for a pilot study to implement a surveillance system of AMI in Mediterranean countries according to EUROCISS recommendations", in the framework of the EuroMed Programme, followed major practical and operative issues for the implementation of a population-based registry for coronary and cerebrovascular events, which are here described. This paper includes the definition of target population, data sources, events, indicators, quality methods, and the description of a software used to implement the registry.

Key words: epidemiology, public health, population-based registry, disease registry, myocardial infarction, stroke

INTRODUCTION

Cardiovascular diseases (CVD) are the leading causes of death and hospitalisation in nearly all European countries and accounted for almost 40% of all deaths in 2013 [1]. Clinically speaking, CVD are characteristic of middle and old age, and manifest themselves after many years of exposure to unhealthy lifestyles and risk factors. Even though the clinical onset is mainly acute, CVD often evolve gradually. Unlike the general belief of CVD leading to a sudden death and hence a death free of suffering, non-fatal coronary and

cerebrovascular events cause substantial loss of quality of life, disability, and life-long dependence on health services and medications. CVD mortality has been decreasing in most Western European countries over the years, and, in recent years, also in Eastern Europe [2]. However, this did not cause a decrease in the absolute number of patients in need of health services for CVD conditions, as increased survival rates and population ageing led to an increase in CVD prevalence [3]. CVD have major economic consequences as well as human costs. CVD alone account for 20% of global total DALYs (Disability Adjusted Life Years) in persons over 30 years of age [4]. In terms of health, acute events may lead to an increased number of treatment-dependent, chronically ill, and disabled people: this may cause increased healthcare costs and put healthcare services under severe pressure.

Ischaemic Heart Disease was responsible for 644,000 deaths across all EU countries in 2013, i.e. about 13% of all deaths; stroke was responsible for 433,000 deaths across all EU countries in 2013, accounting for about 9% of all deaths [1].

In the last decade, innovations in diagnostic technologies facilitated an early diagnosis at an earlier stage of the natural history of disease or in presence of less severe tissue damage. The use of new biomarkers, such as the routine introduction of new myocyte damage markers (troponins), involved a rethinking of the concept of myocardial necrosis and led to a new and more exhaustive definition of acute coronary syndrome [5-7].

The use of diagnostic technologies such as computed tomography (CT) scan and magnetic resonance imaging (MRI) has greatly improved the diagnostic accuracy of hospitalized cerebrovascular events, and the delineation of the location and type of lesion [8]. Coding changes in international disease classifications have also posed new challenges for the reliability and comparability of disease frequency in the general population. All these factors may produce spurious trends in disease frequency, severity, prognosis and subsequent variations in medical practice, if not properly controlled with the adoption of updated and valid epidemiological methods.

With the exception of few rigorous but limited studies carried out in some geographical areas, available data on CVD incidence and prevalence are generally limited and of poor quality, despite the magnitude of the CVD phenomenon. At the European level, the World Health Organization (WHO), the Organisation for Economic Co-operation and Development (OECD), and the Statistical Office of the European Communities (EUROSTAT) collect CVD indicators (mortality, hospital discharge rates) and process them into tables available on their web-sites [9-11]. Comparisons among the different datasets are rarely possible, due to the different methodologies and the peculiar health system of each country.

The Italian experience

The experience acquired by Italy on population-based registries of coronary and cerebrovascular events started with the WHO-MONICA Project (MONItoring trends and determinants in CArdiovascular disease) [12], designed to answer key questions arising from the 1978 Bethesda Conference on the Decline in Coronary Heart Disease Mortality [13]. It was a very wide project conducted across all the world between the mid-1980s and mid-1990s, which allowed, for the first time, (a) to collect and register 166,000 events in men and women aged 35-64 years, during a 10-year surveillance of 37 populations in 21 countries; (b) to classify all suspected fatal and non-fatal events as 'definite', 'possible ischemic cardiac arrest with successful resuscitation' and 'insufficient data', following the same standardised diagnostic criteria (site and duration of chest pain, evolution of ECG findings, variation of cardiac enzyme values, history of Ischemic Heart Disease, and, if performed, necropsy). The introduction of a quantitative ECG coding system, the Minnesota Code, led to an important improvement in the use of standardized diagnostic criteria [14].

The EUROCISS Project, supported by the Health Monitoring Programme of the DG SANCO from 2000 to 2007, and coordinated by the Istituto Superiore di Sanità (ISS), provided general guidance and updated methods for the surveillance of Acute Myocardial Infarction (AMI) and stroke to those EU countries lacking appropriate surveillance systems and wishing to implement a population-based registry in order to produce comparable and reliable indicators [15]. Taking into account the developments occurred in recent years in new diagnostic criteria, treatment and information technologies, a standardised and simple model was developed and manuals of operations were produced to implement a population-based registry of coronary and cerebrovascular events [8, 16]. In some countries, the implementation of the pilot phase was carried out under the coordination of a central body and the support of experts involved in CVD population-based registers and was recommended by the EUROCISS Project.

The Italian Pilot Registry of Coronary and Cerebrovascular events, covering fatal and non-fatal coronary and cerebrovascular events in the general population aged 35-74 years, was implemented at national level. It was launched in 2000 following the MONICA and EUROCISS experiences; it was coordinated by the ISS and aimed at achieving a periodical estimation of attack rates and case fatality rates of coronary and cerebrovascular events in several geographical areas representative of the country, in order to monitor the time trends of those CVD having a major impact in the adult population. A simplified methodology was applied, in which suspected current events were assessed through record-linkage between death certificates and hospital

discharge records (HDR) and identified through the International Classification of Diseases (ICD) codes and duration. Samples of 1,000 suspected current coronary and cerebrovascular events, consecutively selected in each geographical area since the beginning of each calendar year, were validated applying the MONICA diagnostic criteria [17] to estimate the Positive Predictive Value (PPV) for each ICD code of the main cause of death of fatal events and for each ICD code of the first hospital discharge diagnosis of non-fatal events. To calculate the number of estimated events, the number of suspected current events was multiplied by the PPV of each specific mortality or discharge ICD code; attack rates, including first plus recurrent events, were then calculated by dividing the number of estimated events by the resident population; the case fatality rate at the 28th day was determined by the ratio between estimated fatal events and total events [17-19]. When the populations included in the registry are very wide, or the period of registration is short (2/3 years), it is difficult to make a distinction between the first event and the recurring events, and consequently, it is difficult to estimate the incidence rate (which includes only the first event); in this case, the attack rate is a more appropriate indicator than incidence rate. Basically, the incidence rate considers all persons experiencing a major coronary or cerebrovascular event, whereas the attack rate considers all events occurring in a population.

In the framework of the EuroMed Programme, launched by the EC in 2008 with the purpose of promoting economic integration and democratic reform across neighbours countries to the EU's South in North Africa and the Middle East, the ISS led the project: "A population-based AMI register: assessing the feasibility for a pilot study to implement a surveillance system of AMI in Mediterranean countries according to EUROCISS recommendations". During the Programme, a population-based CVD registry was set up and a validated simplified methodology was developed, to facilitate the setting up and the implementation of CVD surveillance systems by utilizing a step-wise procedure, as described in the EUROCISS Project [16]. The registry procedure was based on standardized data collection, appropriate record-linkage and validation methods, according to scientific criteria defined by MONICA, the European Society of Cardiology and the American College of Cardiology (ESC/ACC).

Within the EuroMed Project, an English version of the software allowing the record-linkage of the sources of information (mortality and HDRs) needed for the implementation of the AMI population-based register was developed and implemented. Moreover, coronary events, fatal and non-fatal attack rates and case fatality rates were calculated for the population under surveillance. The software, described below, is downloadable on request from the website www.cuore.iss.it and supported by training guidelines.

A pilot AMI registry was implemented in Croatia. Training sessions for the AMI registry setting up and implementation were conducted in Zagreb (Croatia) in 2000. In Zagreb, PPVs were not calculated ad hoc on the selected population, but PPVs, estimated from the Italian registry, were applied to calculate attack rates and case fatality.

POPULATION-BASED REGISTRIES

A population-based registry is an organized system that uses observational study methods to collect all new cases of a disease in a defined population (most frequently a geographical area); data serve for one or more predetermined scientific, clinical and health policy purposes [adapted by 20].

The objectives of population-based registries are: (a) to evaluate the frequency, distribution and prognosis of the disease providing indicators, such as incidence rate (or attack rate when recurrent events are also included) and case-fatality rate; (b) to evaluate trends; and (c) to monitor preventive actions.

A team of trained epidemiologists fully dedicated to record-linkage and validation procedures is required. The surveillance system is based upon the definition of the following key categories:

Target population

The target population should preferably cover a defined geographical and administrative area or region for which population data, vital statistics, and HDRs are routinely collected and easily available each year.

To assure the completeness of the registry, it is important that all cases reported among the resident population in the area are recorded, even if the case occurs outside the area; conversely, all cases treated in the hospitals within the area, but involving patients resident outside the area, must be excluded. If this is not possible, it is important to give an estimate of the magnitude of the loss of cases and establish whether it could be changing and interfering with the validity of the observed trends in the rates over a period of years.

Populations should be large enough to provide robust and reliable statistical estimates of disease rates in order to design time trends and ensure comparability.

Age: The EUROCISS Project suggests the use of the 35-74 age-range, or even up to 84 years, when possible, considering that more than half of the events occur in patients aged above 65 years. On the other hand, the diagnostic information tends to be less reliable for patients above the age of 75. It is recommended to present morbidity and mortality by 10-years age groups (35-44, 45-54, 55-64, and 65-74).

Sex: the differences in AMI and stroke incidence and mortality between men and women are well documented in literature [12, 21]. Therefore, it is important that the

same high quality data collection methods are applied to both women and men.

Population size: To estimate the size of the population under surveillance for the registry, the age range 45-74 years is taken into consideration, since in a younger age range the number of events is low. To be eligible to participate in AMI and stroke population-based registries, a minimum of 300 coronary or stroke events (fatal and non-fatal, men and women together) per year are necessary. The minimum of 300 events has been established in order to detect a 2% decrease in attack rate per year [8, 16].

Patient eligibility: a patient is considered eligible for inclusion in a population-based registry only if he/she is resident in the area under surveillance, meets the selected age range, and has a coronary or cerebrovascular event within the defined time period.

Data sources

To monitor AMI and stroke events in the general population, the following sources of information should at least be available: mortality records, including death certificates, and HDRs with clinical information. These two sources of information are fundamental to assess the number of events: some fatal events occur suddenly and the person never reaches the hospital; these events can be identified through mortality records; however, fatal events occurring in hospital have a corresponding death certificate, and therefore they risk to be counted twice; these are the main reasons to check the number of suspected events by operating a linkage between HDR and mortality records. Mortality is not used to assess the survival rate only, but also to evaluate the proportion of events that do not receive any treatment and do not reach the hospital. Rarely, some non-fatal events may occur without symptoms; in this case, the patient is not aware of having suffered such event, and the event may be discovered later during a survey or a clinical examination for a different purpose.

In recent years, thanks to information technology, substantial volumes of data are recorded on hospital admissions and discharges, in-patient care utilization, drug prescriptions, outpatient visits, exemption, general practitioner (GP) databases or, more generally, records from primary care physicians, surgical operations and invasive procedures. These data are not primarily planned for research purposes, but they are increasingly used in epidemiological research. Their strength lies in the fact that they cover the whole country, and completeness is close to 100%. On the contrary, their weakness lies in the fact that data are not standardised in the specific disease data collection and that available clinical and lifestyle data are limited. These data, if checked for quality and validated, might represent a relevant "added value" for completeness and validity of coronary and stroke population-based registries. Information on those events that do not reach the hospital and for those patients who are hospitalised outside the area of their usual residence can be drawn from GP records, or HDRs presenting old myocardial infarction (e.g. ICD-9 code 412), or longitudinal studies; GPs can provide clinical data and thus integrate information from other sources (HDR, death certificate, etc.).

Definition of events

The diseases under surveillance are:

acute myocardial infarction (AMI: ICD-9 410; ICD-10 I21, I22) and the broader diagnostic group of *acute coronary syndrome* (ACS: ICD-9 410-411; ICD-10 I20.0, I21, I22);

ischaemic stroke (ICD-9 434; ICD-10 I63), *intracerebral haemorrhage*, bleeding from one of the brain's arteries into the brain tissue, with neuroimaging recordings (ICD-9 431, 432; ICD-10 I61, I62), *subarachnoid haemorrhage* (ICD-9 430; ICD-10 I60), *unspecified stroke* (ICD-9 436; ICD-10 I64).

European Core Health Indicators-ECHI Indicators [22]

Incidence rate

This indicator can be estimated only if information on first events is available. Usually, a 5-year period of retrospective observation of HDRs and death certificates is needed in order to be confident of selecting 'first' events only. This indicator measures the rate of occurrence of new cases (persons experiencing an event for the first time) in a population within a specified period of time.

Attack rate

The attack rate is calculated by identifying the events (first and recurrent event) using primary or secondary hospital discharge diagnoses from HDRs or the underlying cause of death from out of hospital death certificates. Almost 32% of the patients die before they reach the hospital, and therefore a hospital discharge register alone is not sufficient to assess current events [23]. This indictor measures the rate of occurrence of all cases (first and recurrent cases) in a population within a specified period of time.

Case-fatality

The case fatality is the proportion of fatal events calculated as the ratio between the number of events that are fatal at a given time threshold (typically, 1st day or 28th day after the onset of the event) and the overall number of events (first and recurrent).

The EUROCISS Project recommends 1-day and 28-day case fatality. All in- and out-of-hospital fatal and non-fatal events are to be considered as denominator.

Survival rate

The survival rate is the proportion of patients included

in the registry and still alive at different time periods after experiencing an event (e.g., 28 days, 6 months, 1 year, and 5 years).

QUALITY CONTROL METHODS

Data quality indicators are very important to assess AMI and stroke frequency indicators; among the quality indicators, the most important ones are completeness of coverage (sequence of events), completeness of information, internal validity and external validity (representativeness). In a registry, the inclusion of all (milder and more severe) events influences incidence as well as case fatality, that's why completeness is fundamental.

Completeness of coverage and completeness of information

Completeness of coverage means that all the events in the target population are included; that is, all events are covered, irrespective of whether they occur in the region or outside it. The register must also cover events whenever they occur, irrespective of the time of day/night or winter/summer, as well as events occurring outside the hospital (e.g. sudden death among patients who never reach the hospital). Completeness of information means that all relevant information should be registered (e.g. place of treatment, date of admission, date of discharge, PIN, sex, hospital discharge diagnostic codes, intervention/procedure codes, department/ward, and date of birth). The most important source of systematic bias in estimating incidence is related to the coverage of event registration. The registration system must attempt to identify all possible cases of the disease that have come to the attention of the existing medical and medico-legal sources. The completeness of event identification (acute care hospital, primary healthcare, and nursing home) and the completeness and availability of information, obtainable for each event recording and diagnosis, depend on the existing standards of medical care: if the medical care system misses or misdiagnoses cases, a register cannot remedy the omission. When the event is defined (codes and duration), it might be possible to identify duplicate coding and extract information for quality control purposes. Duplicate codes might include events transferred from one ward to another, for example, for rehabilitation. In some cases, the duration of the admission is very short (<2 days) either because of transferral difficulties or because of misclassification of the diagnosis. These events can also be picked up for validation. Patients not admitted to general hospitals are a problem, from the point of view of their registration, if the system is based only on hospital records. Another source of potential loss of identification is private practice: private physicians and hospitals might be less cooperative than those in the public system. In private hospitals, the staff might be more sensitive to criticism and more anxious to show how they register medical documents. GP patient records are usually inadequate for full registration because the patients are frequently looked after at home. The identification of fatal events is in some ways less difficult than that of non-fatal events. Although survivors might be lost in the totality of inhabitants of the area under surveillance, death is unequivocal. The registration of the causes of death might, however, not be correct and it will need to be validated. It is to be expected that some deaths occur outside the hospital. If the proportion of fatal events coded as hospitalized is very high, it might indicate incomplete registration of out-of-hospital event deaths. High case fatality can also indicate loss of non-fatal cases. The identification of potential events can be based on many different data sources. This might involve a considerable amount of record-linkage, which is facilitated if the PIN system is adopted. Another problem relates to medical records, the quality of which might vary: younger patients might have had no other episodes, and the records might be restricted to the relevant event. In older patients, the identification of the event is more complicated, due to the existence of co-morbidities.

Internal validity

The most important question regarding validity concerns the diagnostic information. The diagnostic criteria for the event definition are valid if they measure the disease they claim to measure. Validation evaluates the sensitivity, specificity, and predictive value of the registered diagnosis by comparing them to a golden standard [24].

Validation studies of routine statistics have been carried out over the years with heterogeneous results that were due to differences in methodology, or which reflected true differences among countries in the validity of the routinely collected data. Some studies comparing community registers with national statistics and data from the MONICA project have been carried out. Findings stress the importance of validating routine mortality and hospital statistics against the national register, to determine whether and how they can be used to reflect true incidence and mortality [25]. Particular attention, in this type of validation, should be given to secondary discharge diagnoses or causes of death, especially to diagnostic codes, to detect potentially hidden cardiovascular diagnoses. Consistency of the coding with the diagnosis, and consistency of coding/comparability of the information over different areas of the country and over time represent other problems for validation. If it is not possible to validate all the diagnoses included in the disease register or in the mortality routine statistics, the validation should aim at evaluating a sample of events. The sample should be distributed across a full year, to ensure that potential seasonal or other time-related variations of

diagnostic patterns are traced. The sample could include a feasible fraction of the 365 days (working and weekend days). For example, given 'n' days/month, all consecutive hospital admissions and deaths with eligible ICD codes can be validated.

External validity

It is not essential that the whole country should be covered by a surveillance system, but it is essential that the registration system of events should be complete with regard to events occurring in the target population. It is important to know how representative the registry is for the whole country according to the CVD mortality rate, age and sex distribution, health determinants (socioeconomic status and health behaviour), and healthcare services distribution (specialized hospitals and GPs).

For the chosen population, there must be good demographic data subject to at least an annual revision; inaccuracies might be discovered years after the period being studied, and shall be found in the results of a decennial national census. A careful description of the population characteristics can help to describe how representative the target population is for the whole country.

Methods to evaluate the diagnostic quality

Using the diagnostic criteria, it is possible to evaluate whether the tools used to establish the application of valid methods are different for hot pursuit and cold pursuit. Validation of the diagnostic information recorded in the register can include the examination of either all the events or some random samples. The relevant register data must be checked periodically by sampling, as it is usually not feasible to check all data [25]. Validation has to be carried out by an epidemiological team not involved in the patient's treatment. In the case of local registers with a limited number of cases, it might be possible to validate each single event, whereas (for practical reasons) national registers can only validate data on the basis of random samples of suspected cases recorded during a selected period or during some days each month. An example of selection method consists in choosing some days each month and evaluating all the events that have occurred in those days, extracted either from HDR or mortality records, applying diagnostic criteria. In this way, seasonal variation can be traced. The most important phase is the evaluation of the diagnostic information, although other information in the register also needs to be included in the validation. In the Italian Pilot Registry of Coronary and Cerebrovascular events, samples of about 7,000 suspected coronary events and 8,000 suspected cerebrovascular events were validated applying the MONICA diagnostic criteria.

To produce valid indicators, the conditio sine qua non is to get access to the relevant medical records and to the routine raw data of health statistics. In some cases, it is possible to validate a register by linking the register to an independent data source, for example, a high quality register for a small area within the region.

POPULATION-BASED REGISTRIES IMPLEMENTATION TOOLS

Record-linkage to identify suspected current events and clean databases

In the Northern countries, where every citizen has a PIN included in national registry of HDRs and deaths, record-linkage for event identification is efficient and reliable. For countries that have not adopted the PIN system, it may be much more difficult to perform this fundamental activity. Files have to be organised with the same format and have to include the same personal variables needed to univocally identify subjects (family name, first name, sex, date of birth, place of birth, residency). Death certificates and HDRs databases provide main information for record-linkage implementation.

It is recommended to:

- explore the feasibility of record-linkage within HDRs - *deterministic or probabilistic* approach based on personal variables or PIN use (within the same hospital, among hospitals of the area under surveillance, among hospitals at regional level). When hospital records are collected at national level, it is possible to include also those non-fatal events occurring out of the surveillance area. This activity is crucial to detect and fix all HDRs related to the same subject;
- explore the feasibility of record-linkage within mortality records - *deterministic or probabilistic* approach based on personal variables or using a PIN system within the area under surveillance or at regional level. When mortality records are collected at national level, it is possible to include also those fatal events that occur out of the surveillance area. This activity is crucial to detect and fix possible duplication of death records related to the same subject;
    - The record-linkage *deterministic* approach implies the exact matching, in each used source of information and for the same subject, of all the variables that univocally identify a subject: e.g., in the comparison between mortality and HDRs databases to identify hospitalised fatal cases, or to identify all the hospital discharges related to the same subject in the same HDRs database;
    - The record-linkage *probabilistic* approach [26] implies that the identifying variables in different

sources of information shall match, with the exception of one digit, or two digits, and so on. This means that the higher the number of digits we accept as exception, the greater will be the number of matching records, but the detection of suspected current events will become more difficult and less reliable;

- Before implementing the record-linkage to identify suspected current events, it is highly recommended to conduct a propaedeutic but unavoidable activity, which consists in accurately checking and cleaning both mortality and HDRs administrative databases for possible errors in the identifying variables used for record-linkage (family name, first name, sex, date of birth, place of birth, residency). This is necessary to avoid possible double counting of the same record or, on the contrary, to avoid a missing record-linkage between corresponding records. These kinds of errors can considerably bias results, since they influence the identification of the first event, the dates of the first and recurrent events, and, consequently, the number of events for the same subject and for the overall population included in the registry.

Software description

A specific software was built as a tool to implement the Registry of Coronary and Cerebrovascular events according to the methodology adopted and previously described. The software is downloadable from the web site of the Progetto CUORE (www.cuore.iss.it). The user can install the software following a stand-alone scheme, where both the software and database are located on the same computer, or a client-server scheme, where the database is installed on one server and the software is installed on one or more computers connected to this server. Some operative information to perform both software administrator and user activities and to implement the register is summarized here below.

The main administrator features include user management, events loading, events generation and management; the main user activities include the validation procedure, the estimation of PPVs from a sample of validated events or the inclusion and use of an already estimated set of PPVs, the estimation of the number of events, and the elaboration of attack rates and case fatality.

Administrator activities

User management functions consent to manage user authentication by username and password, add a new user, change, and delete the user.

Events loading functions permit to load mortality and HDRs that are necessary to run the event generation. Before performing this operation, it is very important to check the format of all data according to the defined format provided by the software.

After loading mortality and HDRs, it is possible to add a new event or change or delete a selected event.

An internal check, based on comparison of birth and death or discharge dates, consents to fix ages of loaded subjects both for mortality and HDRs.

Events generation and management: after selecting residence codes, calendar years, age ranges, ICD code version, duration of hospitalization in days (excluding 'day-hospital'), the number and modality (consecutive or random) of sample selection for the events to be validated, the software will implement the record-linkage and will generate the separate record lists of first Coronary (CE) and Cerebrovascular (CVA) Events (suspected current events) and the record lists of the two extracted samples of CE and CVA to be validated.

User activities

Event validation procedure: for each event to be validated, included in the extracted CE and CVA samples, it is possible to fill in and save specific forms, including all the medical information drawn from the clinical chart, which are necessary for the validation of the event.

CE validation can be implemented following MONICA diagnostic criteria (electrocardiogram codified by Minnesota code, in particular evolution of Q waves, ST elevation or negativity, symptoms defined by duration and localization, cardiac enzymes, positivity for past history of ischaemic heart diseases, lesion of myocardial infarction at the necropsy) [27] and 'new' ESC/ACC diagnostic criteria (based on troponin elevation in two subsequent tests) [5-7].

CVA validation can be implemented following MONICA diagnostic criteria (based on clinical signs and symptoms of focal (or global) disturbance of cerebral function lasting more than 24 hours) [28].

The list of all events included in the extracted samples for validation, both CE and CVA, are displayed and divided in two different families: 'already validated events' and 'events still to be validated'.

The User can filter the content of these lists by calling the search procedure, before introducing one of the search key (medical records, surname, name or hospital code), or selecting the options 'Show CVA only' or 'Show CE only'.

Once all the selected events are validated, it is possible to estimate the PPV for each ICD code as underlying cause of death (fatal event) or first discharge diagnosis (non-fatal event) and to display and export them as an excel file. The software consents to apply PPVs to the overall Coronary and Cerebrovascular suspected current events using the corresponding ICD code in order to estimate the number of fatal and non-fatal CE and CVA, and display and export them as an excel file. Upon an estimated number of events

and an uploaded excel file describing the population by age group and sex (according to the stratification chosen during the 'Event generation' procedure), the software allows to estimate case fatality indicators, as the ratio between fatal and total events, and attack rates, as the ratio between fatal or non-fatal events and population, and display and export them as an excel file.

In alternative, if available, it is possible to upload a file including PPVs by ICD code for fatal and non-fatal events and, by-passing the procedure to estimate PPVs from the validation of the extracted sample of events, estimate case fatality and attack rate indicators directly.

CONCLUSIONS

Although in many countries data extracted from routine datasets (mortality and HDRs) are now available thanks to their insertion in IT infrastructures, they are rarely reliable and comparable. These data can produce reliable indicators only if properly processed, validated by independent epidemiological sources and checked for quality control. The EUROCISS represents a valid manual to build the core indicators (attack rate, incidence, case fatality) recommended by the European Community Health Indicators Monitoring (ECHIM) Project [15, 29].

Cardiovascular population-based registers can be implemented if the following conditions are met:

- availability of mortality and HDRs for the age range 35-74 years. The age range 25-34, where few events occur, and the age range 75+, for which diagnostic information tends to be less reliable due to the existence of co-morbidities, were excluded;
- possibility to perform record-linkage (by personal identification number [PIN] or by family name, first name, sex, date of birth, place of birth, residency);
- population large enough to produce 300 total events per year in the age range 45-74 years in order to assess trends;
- epidemiologic team interested in the development and improvement of surveillance systems of CVD.

Given the still very high CVD out-of-hospital case fatality, population-based registers are very important as they allow evaluating fatal and non-fatal (first and recurrent) events occurring in a well-defined population.

The strength of the registry is based on the collection and validation of routine data-bases: HDRs and death certificates are available in all countries, in a population large enough to produce stable indicators over time. Moreover, the population-based register is based on the experience of the MONICA and EUROCISS projects.

The main weakness is represented by the potential difficulty in linking records from two sources of information (HDRs and causes of death), when a non-unique identifier is available in the country. In this case, the record-linkage will be based on sensitive information, such as name, date of birth and place of birth.

The record-linkage is meant only to univocally identify the events, in order to prevent any double counting. Once the event has been identified, all the sensitive records are eliminated.

The main risk is represented by the impossibility of implementing record-linkage due to the country's specific regulations: the possibility of record-linking depends on the legal, ethical and data confidentiality issues established in each country.

The new European Regulation (EU) 2016/67 and the European Directives (EU) 2016/680 and 2016/681 of the European Parliament and Council dated 27 April 2016, related to the protection of individuals and specifically to the processing of personal data by competent authorities for the prevention, investigation, detection and prosecution of criminal offenses or the execution of criminal penalties, and the free circulation of such data, will help country authorities in facing and solving ethical and privacy issues for the use, integration, and record-linkage of health data with the finality of disease prevention.

The same problems may occur for the access to clinical records to validate the sample of suspected events.

The availability of reliable and standardised data on AMI and stroke, comparable across and among EU countries, is a great opportunity for the community, stakeholders and other health operators. This shall allow studying CVD trends in the population and assessing the efficacy of preventive actions at individual and population level.

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Statement

The findings and conclusions provided in this paper are those of the authors, who are responsible for their

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