Brief Review

Generating Evidence From Computerized Healthcare Utilization Databases

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Preliminary Remarks

Randomized clinical trials (RCTs) are regarded as the highest level of therapeutic evidence because they are based on random allocation of participants to ≥2 treatment groups, which provides patients with superimposable initial demographic and clinical characteristics and allows the results to reflect the effect of the treatment strategies under study safely. Also, new treatments are compared with placebo or current interventions, which offers information on their absolute or added value. Finally, end points of documented clinical relevance are selected, the results having an immediate bearing for patients' health.

However, RCTs also have limitations that can make their results of uncertain and limited application to daily life medicine.[1–4] For example, in RCTs, treatments are delivered according to preselected plans that make management more rigid than the one adopted in real-life. Two, treatments are delivered in a highly controlled environment by operators with specific competence, which results into a much lower chance of mistreatment or errors. Three, for several reasons (cost, progressive patients' dropout, changes of patient residence, job instability of investigators, etc), RCTs can have a few year duration only, extrapolation been required to apply their results to daily life patients with a much longer life expectancy. Four, to make data scientifically interpretable, in RCTs, vulnerable patients are usually avoided and patients are recruited based on restricted eligibility criteria, which do not reflect the demographic and clinical heterogeneity of the individuals to whom the trial results are eventually applied. Finally, in RCTs, high motivation and close follow-up make patients well compliant to treatment, at variance from clinical practice in which a low and variable treatment adherence is common, with unmeasured but probably substantial modifications of the original trial results.[5–12]

Recognition of the above limitations has favored the design and conduction of trials, which could may more appropriately reflect clinical practice. One example is the expansion of the end points by which to determine the efficacy of the intervention to events (eg, revascularization procedures) diagnostically more open to errors or bias, but nevertheless of a large prevalence and decision relevance in real life.[13] Furthermore, to ensure a better generalizability of the results, the so-called pragmatic trials are more and more frequently performed, with the aim of selecting patients more similar to those in whom the trial results are applied.[14] However, it is widely thought that this does not substantially reduce the gap between the artificial environment where trial data are collected and real-life medicine.[15] This has been instrumental in the growth of interest on observational studies, which could complement the results of clinical trials with information on how strong and persistent the effects of healthcare interventions are in real-life conditions. These studies can make use of 3 different data sources, ie, in-field collected data, disease registries, and electronically stored databases generated for administrative purposes by health providers or by general practitioners or specialists. In this review, we will discuss the approach based on computerized healthcare databases with the aim to highlight their strengths, weaknesses, and potential. We will offer examples of the importance of the information provided by these databases on treatment of cardiovascular disease with particular reference to hypertension and to the large healthcare database covering since several years the entire citizenship (10 millions) of the Lombardy region in Italy.

Definition of a Healthcare Database

A healthcare database can be defined as an electronic system designed to store, on an ongoing basis, disease-related data (eg, drug prescriptions, hospital diagnoses, outpatient visits, and so forth) from a well-defined dynamic population, eg, that covered by a public or private healthcare delivery system or attended by a network of general practitioners or specialists. In other terms, disease-related data of interest from a specific target population need to be available in the definition of a healthcare database.

Types, Sources, and Characteristics of Large Healthcare Data

Databases collecting healthcare data can be classified into 2 broad categories: (1) those collecting information for administrative purposes (ie, administrative or healthcare utilization [HCU] databases) and (2) those generated by medical records [MRs] to allow physicians to track information on their patients over time (ie, MR databases).[16] A description of HCU

and MR databases, in comparison with conventional sources of healthcare information, is provided in Table 1.[17–21]

HCU databases were initially created to supply payments to providers of health services within public or private healthcare delivery systems.[22] Their management requires electronically stored data on patients' demography, healthcare procedures, and services representing a cost for Health Authorities, such as drug dispensations, hospital admissions and diagnoses, surgical and other interventions in and outside hospitals, outpatients visits by general practitioners and specialists, laboratory examinations, vaccinations, etc. HCU databases are widespread in United States where they are funded by the government (Medicare, Medicaid, and Veteran Administration), large health insurance companies (eg, United Health), or health maintenance organizations (eg, Kaiser Permanente).[16] More recently, HCU databases have spread to several countries of the European Union, with the advantages, compared with United States, that data are usually collected from more stable populations and that health coverage is extended to all diseases and involves virtually all individuals. Despite these advantages, HCU databases are not as popular in Europe as in the United States, mainly because of the difficulty posed by strict privacy regulations, which has to date favored the use of MR databases.

The most important MR database is probably the UK General Practice Research Database, a large computerized database of anonymized longitudinal patient records from hundred general practitioners and about 3 million patients (ie, ≈5% of the United Kingdom population).[21–23] Similar databases, however, are available in other European countries. In the Netherlands, the Integrated Primary Care Information database involves ≈150 general practitioners and up to half a million patients.[24]

In Italy, the Health Search MR database involves ≈900 general practitioners and >1.2 million patients.[25] In Sweden, a database that includes >75 primary care centers covering an area with ≈800 000 individuals is used for investigating several fields of healthcare research, including hypertension.[26,27] In general, the clinical information provided by MR databases is much more extensive than that of HCU databases, the data including lifestyle habits, risk factors, blood pressure values, and patients' clinical history. MR databases, however, suffer from the fact that physicians usually provide information on patients' diagnoses and care they are more directly responsible for, which means that clinical data may not infrequently be partial and the patient's overall clinical status unlikely to be available in a comprehensive database format. Data quality may also be a problem and selection of participating physicians may be such as to make MR-generated data of uncertain representativeness of the more general healthcare standard.

Strengths of HCU Databases

HCU databases have important advantages. One, information can be obtained at low cost, over long time frames, and quickly because data are laid down in an electronic format. Two, available data include many different healthcare services (prescription of drug medicaments, medical visits, laboratory and instrumental examinations, hospitalizations, etc), which can be electronically linked by an unique patient code so that for each individual the assigned care, its changes over time, and its effect on ≥1 outcomes can be tracked. Three, because of the large size of the covered population (often up to million patients), data can reliably and timely identify trends in the use of healthcare interventions, drugs, and devices, which may allow to verify the consequences of medical recommendations

Table 1.   Relative Advantages (+) and Disadvantages (−) of Major Data Sources in Health Research

Desired Traits for Health Research	Prospective Data Collection		Analysis of Existing Databases	
	Controlled Randomized Trials	Longitudinal Observational Studies	Healthcare Utilization Databases	Medical Record Research Databases
Less expensive	…	…	+++	+
Promptness of data availability	…	…	+++	+++
Patient awareness/level of intrusion	…	…	+++	+++
Data applicability to multiple conditions/diseases	…	−	+++	+++
Size of collected data	…	…	+++	++
Patient heterogeneity representativeness	…	++	+++	+
Real life clinical practice representativeness	…	+++	+++	+
Quality/extent of clinical information	+++	++	−	−
Absence of confounding by indication/group comparability	+++	…	…	…
Accessibility by health services investigators	…	…	+	…
Accuracy of disease coding	+++	+	−	+
Upcoding of diseases or services*	+++	+++	—	+++
Control of collected information by investigators	+++	+++	…	…
Example	Scandinavian Simvastatin Survival Study[18]	The Framingham Heart Study[19]	Medicaid database[20]	General Practice Research Database[21]

Reprinted from Gandhi et al.[17]

*Done to maximize reimbursement.

or changes in healthcare regulations suitably. Four, because they are recorded independently of patient agreement, data are immune from the bias related to the selection of patients by their willingness to participate, an often forgotten limitation impossible to exclude in conventional research studies.[28] Finally, and most importantly, HCU databases guarantee that the information reflects the state of clinical practice in the general population, this being particularly the case where healthcare is assured by a system covering the whole citizenship. The above advantages are listed in Table 2.

Research Applications of HCU Databases

HCU databases are particularly suitable for investigating the following areas.

Profiles of Drug Use

HCU data offer accurate information on the prevalence, incidence, and duration of drugs' use, which is obviously essential for health system planning and for assessing appropriateness of prescribing. Drug use measures (including the number of current users, the new or incident users, and the duration of use) can be directly obtained and comparisons can be made between individual drugs or drug classes and between drug use at different times or in different geographical areas. This provides a comprehensive picture of the therapeutic habits of a population and of their temporal modifications.

Of special interest is the possibility offered by HCU data to study persistence and adherence with chronic therapy,[29] ie, (1) the overall duration of uninterrupted drug therapy often measured as the cumulative proportion of patients who do not experience any episode of treatment discontinuation during follow-up (persistence) and (2) the duration of drug use often measured by the ratio between the cumulative number of days in which the medication is available and the days of the overall follow-up (adherence). Because of patients' unawareness, the HCU data are free from the so-called Hawthorne effect, namely the behavioral distorsion that occurs when human beings know to be under observation.[30] Furthermore, the adherence/persistence patterns can be determined over prolonged follow-ups and their relationship to events can be assessed by linking the results to those derived from hospitalization or other sources. Using this approach, in the HCU database from Lombardy, we showed that about one third of newly treated hypertensive patients discontinued treatment after the first prescription[31] and that only slightly <50% of the remaining patients did not experience an episode of prolonged (≥3 months) treatment discontinuation during the follow-up.[10]

This also occurred for antidiabetic and lipid-lowering drugs, the rate of prescription coverage being in all instances related to the rate of hospitalization for cardiovascular morbid events.[31] HCU data have been also shown to help clarifying the factors related to, and possibly responsible for, treatment discontinuation. In the Lombardy HCU database, discontinuation of antihypertensive treatment was found to be closely dependent on the type of drug or treatment strategy (mono or combination treatment) prescribed.[10,32] It was also found to be majorly affected by patients' demography, cotreatments, type and severity of diseases of cardiovascular or noncardiovascular nature, and even adversely influenced by unexpected variables, such as residence in metropolitan areas and density of the population where the patient lived.[33] It should be emphasized that knowledge of the factors involved in low adherence to treatment is preliminary to and fundamental for any action that aims at reducing the extent of this phenomenon in real life. For hypertension, dyslipidemia, and diabetes mellitus, this would be the most crucial means to improve cardiovascular prevention strategies because for all these diseases nonadherence is majorly responsible for the strikingly low rate of their therapeutic control. This low control is the primary reason for the maintenance of cardiovascular disease as the main cause of death worldwide.[34]

Postmarketing Studies on Treatment Effectiveness

As pointed out by Cochrane ≈40 years ago,[35] RCTs that test drug efficacy for regulatory purposes aim at assessing the extent to which an intervention does more good than harm under ideal circumstances (ie, whether it can work). However, once its efficacy is established, a medical intervention has to be and is applied to people and in circumstances that can be different from the original ones, making the assessment of its effect in real-world practice (ie, whether it not only can but also does work crucially important). HCU databases can provide information on the effectiveness of treatment: (1) in patients often excluded from premarketing studies or clinical trials, eg, frail elders, patients with comorbidities, women, adolescents or younger patients, sometimes with the first demonstration of unanticipated beneficial effects; (2) over times much longer than those compatible with RCTs or with numbers far greater than those available in in-field observational studies; and (3) under the low and variable adherence to the prescribed treatment regimen that is typical of the real-life population. In this context, HCU data from Lombardy showed that in the real-world setting, patients who persisted with antihypertensive drug therapy had a 37% reduction in the risk of

Table 2.   Major Advantages of Using Healthcare Utilization Databases

Data Characteristics	Advantage
Data are available in electronic format	Low cost of investigation
Data include all healthcare services supplied to delivery system beneficiaries	A comprehensive healthcare history of each beneficiary of healthcare system may be available
Patients and doctors are not involved in data collection	Findings are free from bias generated by awareness of being under observation
Data cover large populations	Outcomes that rarely occur may be investigated
Data collected from unselected populations	Information reflects the state of clinical practice in the general population (particularly where healthcare is assured to the whole citizenship)

coronary events and a 36% reduction in the risk of cerebrovascular events.[36] Likewise, good adherence with statins prescriptions was associated with a 19% reduction of the risk of ischemic heart disease[37] and a 25% reduction of the risk of dementia.[38] This shows that the protective effect of antihypertensive and lipid-lowering drugs is not lost when these treatments are implemented in real life, but also that in real life the degree of protection is highly variable, factors such as adherence to the treatment regimen playing a major role.

Safety Concerns

The longitudinal nature, large size (up to several million individuals), and quick availability make use of HCU databases extremely attractive also for safety studies, with perhaps an unsurpassed advantage in the case of treatment-dependent rare events or long-term effects of drugs and interventions. The advantage is made even greater by the fact that benefits and harms of a given medicament or therapeutic strategy can be assessed on a comparable scale, thereby providing regulatory agencies and caregivers with material for a balanced decision on the net beneficial effect of a therapeutic approach when applied to the general population.[1] An example is offered by the examination, via the HCU database, of the long-term benefit and harm of statin administration in the Lombardy population, the benefit consisting of the reduction of coronary events and the harm of the reported greater risk of new onset type 2 diabetes mellitus. Over a 6-year follow-up patients with high adherence to the prescribed statin therapy showed an increased risk of developing diabetes mellitus than patients with low adherence.[39] They also showed, however, a clear-cut reduction of the risk of coronary events,[37] the protective effect exceeding the diabetes mellitus risk, despite its observed greater size (+32%) than that detected in randomized trials.[40] Indeed, the long-term balance may probably be even more in favor of the beneficial effect of statins than that calculated in the Lombardy HCU database because in RCTs statins have also been shown to reduce the risk of stroke.[41] Furthermore, as mentioned above, patients with a high level of adherence to lipid-lowering treatment also showed a significant reduction in the incidence of dementia,[38] a condition associated with a marked increase in the direct and indirect costs to be covered by health service systems.

Cost–Effectiveness

Cost–effectiveness analyses are a major challenge for cardiovascular disease, particularly when applied to conditions such as hypertension, dyslipidemias, and diabetes mellitus in which both the risk of events and the need of treatment are spread over the lifetime. It is also an analysis of key importance for healthcare decisions because, for a given level of benefit, resource allocation to the less costly alternative is necessary,[42] especially at times of financial crises. This is also an area on which HCU databases may offer an important contribution because (1) calculation of benefit can be based on a real-life long-term event incidence and (2) direct costs can comprehensively include all or most healthcare items (drugs, medical visits, hospitalizations, etc), also based on a real life.[43] An example of the results that can be obtained is offered by the calculation of the cost–effectiveness of healthcare strategies that would increase the adherence to antihypertensive or lipid-lowering treatments in

the Lombardy population.[44,45] From the cost and event incidence data provided by the database itself, it was possible to conclude that in either case the increase of cost associated with an increased adherence was, at any adherence level, largely outweighed by the saving inherent to the event reduction, supporting the need for health authorities to engage into an effective adherence implementation policy. Methodological improvements of the model are desirable to raise the potentiality of HCU data in this direction and thus make them the basis for more and more evidence-based healthcare providers' decisions.

Linkage With Other Databases

HCU databases can be linked with MR data or primary care center databases (as done by the Swedish Board of Health and Welfare[26,27]), as well as with other cohorts that are more rich in clinical information. This helps reducing the main limitations (small amount of clinical data, see below), while providing these other databases with the chance of longitudinal follow-up on outcomes they would otherwise be deprived of.[46]

Limitations of HCU Databases and Their Possible Correction

The Figure shows that interpretation of HCU databases need to consider several sources of bias. Three main possible biases are discussed in detail below.

Prescription Versus Consumption

The validity of studies performed with HCU data is based on the assumption that drug prescriptions correspond to drug consumption. There is, however, no guarantee that this is always the case, and indeed it is likely that in many patients the prescribed drugs are not consumed. This implies, however, that in the real world, discontinuation of and adherence to treatment may be even worse than the quantification obtained via the HCU databases. In other words, that the HCU data, disappointing as they appear, may only err for optimism, the possibility that they provide an erroneously unfavorable view of the real-life situation being highly unlikely.

It should also be mentioned that this type of bias, ie, that an unknown fraction of patients to whom the drug of interest is
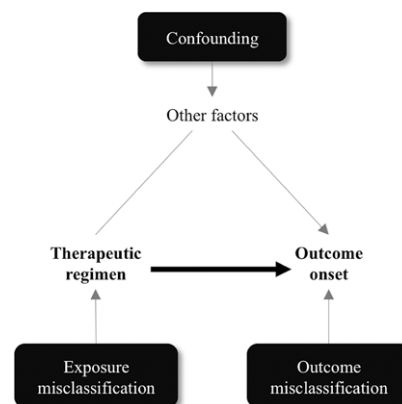
Figure. Observational studies based on Healthcare Utilization Databases, investigating the relationship between therapeutic regimen and outcome that are affected by 3 sources of uncertainty, ie, exposure misclassification, outcome misclassification, and confounding.

prescribed does not consume the drug, means the introduction in the database of false-positive drug users. If the medication does not affect the outcome of interest, this does not produce any distorsion of the results. On the contrary, if the drug has an effect, this type of bias tends to mask (namely to drag toward the null) the estimated drug–outcome association.

Other Types of Drug Exposure Misclassification

Drug prescription data may be misclassified because prescription is incomplete, its reading is erroneous or mistakes in drug coding are made. However, when filling drug prescriptions, pharmacists have little room for interpretation and reimbursement by Health Authorities are made on the basis of detailed, complete, and accurate claims that are submitted electronically.[47–49] Pharmacy dispensing information is, therefore, expected to provide highly accurate data, also because filling an incorrect report about dispensed drugs has legal consequences.[50]

In spite of these reassuring considerations, in several databases, incompleteness of information may generate exposure misclassification. Incompleteness often consists of missing data on (1) free sample drugs, (2) nonreimbursed over-the-counter medications,[51] (3) drugs dispensed during hospitalizations,[52] and (4) calculations of days covered by a given dispensation. For instance, when comparing 2 antihypertensive medications, if 1 of the 2 is (1) more often delivered by the pharmacist over-the-counter (eg, because of its lower cost), (2) dispensed also in the hospital setting, or (3) prescribed at a higher than the defined dose (eg, because this is indicated for more severe patients), a misclassification is generated, more person-time being classified as unexposed when it is in fact exposed (or vice versa) in one than the other comparison group. Thus, some forms of approximation are unavoidable for most HCU-based studies.[53,54] The effect of these approximations on the validity of the results will have to be always explored by sensitivity analyses (ie, by evaluating the robustness of the findings through modifications of the approximation criteria).[55,56]

Outcome Misclassification

To generate reliable data, a HCU database must guarantee that the selected outcome is assessed with sufficient sensitivity and specificity. For example, if the database misses a noticeable fraction of patients experiencing an acute myocardial infarction or a stroke, sensitivity is limited, whereas if the database erroneously attributes to a myocardial infarction or a stroke, a noticeable number of hospitalizations is generated by other diseases, the limitation involves specificity. It is important to mention that for proper assessment of the relationship of a given treatment with outcome, a limited specificity is more damaging than a limited sensitivity, a 100% specificity of the outcome assessment allowing an unbiased estimate of the measured association, irrespective of the sensitivity value.[57] It should also be mentioned that, based on the available literature, in HCU data diagnostic misclassifications is not as common as it might at first sight appear.[58] A recent comprehensive study has shown that in the HCU databases, sensitivity was only small or moderate, whereas specificity was usually ≥95% (Table 3).[58,59] In general, a high specificity may be expected when diagnoses are based on hospital records, whereas performance is likely to be worse when diagnoses are based on

Table 3. Sensitivity and Specificity of Diagnoses Made at Discharge From Hospital or Outpatient Care

Disease	Outpatient Care Billing Diagnoses		Hospital Discharge Diagnoses	
	Sensitivity	Specificity	Sensitivity	Specificity
Hypertension	60.6	87.7	65	99.9
COPD	53.4	87.9	91	98.8
Diabetes mellitus	62.6	97.2	88	99.4
Renal failure	18.6	99.0	88	99.4
Chronic liver disease	27.6	99.8	100	100
Any cancer	44.8	95.0	91	100
Peptic ulcer disease	27.6	94.6	92	100
Congestive heart failure	41.5	96.1	85	99
Acute myocardial infarction	25.4	96.8	94	100
Neutropenia	…	…	…	97
Stevens–Johnson syndrome	…	…	…	95

Reprinted from Schneeweiss and Avorn.[58] COPD indicates chronic obstructive pulmonary disease.

out-of-hospital identification of diseases (eg, by general practitioners or specialists).

Despite these considerations, diagnostic validation is usually recommended not only for out-of-hospital but also for hospital-derived data. This may make use of findings from published validation studies performed in other populations although some[60] thought that validation data generated from the in-study database are always required. In this context, however, a major difficulty is represented by the privacy regulations that in several countries prevent individual MRs from being thoroughly reviewed. Thus, diagnostic validation via sensitivity analyses that verify the robustness of the findings by applying credible sensitivity and specificity ranges to the source of diagnostic information is often the only practical option.

Another potential limitation of HCU database is that certain diseases cannot be reliably identified from hospital records because they rarely lead to hospitalization. However, the issue can be approached by identifying the addition of their therapeutic drugs to the medical prescription, provided that the drugs are only used for the disease under study. A pertinent example is the effect of statins on the onset of type 2 diabetes mellitus because (1) except perhaps in its late stage, only occasionally diabetes mellitus is the cause of hospital admission and (2) antidiabetic drugs are not used for any other disease. The use of antidiabetic medications as a proxy for diabetes mellitus onset has allowed to make interesting observations on the influence of cardiovascular treatments on the development of diabetes mellitus in the general population.[39,61] It should be emphasized, however, that this approach is likely to have a low sensitivity because in several cases appearance of the disease may not be associated with specific treatment initiation. Specificity, on the other hand, may be optimized by using strict criteria for the disease identification (eg, by diagnosing new onset diabetes mellitus only in patients with several consecutive prescriptions of antidiabetic drugs. This strengthens the above-mentioned need, for the

HCU database approach, to always check the validity of the results by sensitivity analysis.

Confounding

There is no question that the most important concern against HCU databases is confounding. This is particularly the case for that common and often insidious and uncorrectable form of confounding, endemic to pharmacoepidemiology and healthcare research studies, that is known as confounding by indication. Namely, the observation that a given medication is associated with an increased likelihood of outcome onset for which is thought to be responsible while the explanation lies in its greater use in patients more prone to develop the outcome.

Strategies to adjust for such a bias vary depending on the amount of information included in the database. If all or most factors representing potential confounders are available, propensity-score methods simultaneously accounting for a large number of patient characteristics can be used with an effective reduction of confounding biases.[62] However, because HCU databases generally have a limited amount of clinical information, methods accounting for unmeasured confounders should be adopted to avoid or at least limit the effect of bias. One such method, called user-only design, is to restrict the cohort analysis to patients under the in-study medicaments, thereby comparing only individuals in which the need to use them was initially established.[63]

Other methods aim at ensuring a better comparability of different therapeutic strategies by other types of restriction of the original cohort. In this respect, a pivotal study of statin treatment and 1-year mortality showed a reduced influence of confounding by using progressively stricter criteria for cohort inclusion.[64] Starting from a mortality reduction of 68% among the entire cohort of statin users, the restriction of the cohort to incident users only,[65] the selection of a comparison group similar to the intervention group and the exclusion of patients with contraindications and low adherence to treatment led to a final estimate of a 28% reduction, a figure similar to that obtained from the pooled estimate by RCTs.[64] In general, it is thought that a set of 3 restrictions can be adopted in comparative effectiveness research with no major impairment of data generalizability.[28]

Restricting the investigated cohort only to patients who experience the in-study outcome (case-only design) is another possibility, its use in pharmacoepidemiology and healthcare research via methods such as the case-crossover[66] and the self-controlled case series design[67] being regarded as attractive (particularly in patients with transient exposure to or acute outcomes from drug use) because of the ability to evaluate time-invariant confounders. For antihypertensive therapy, an example has recently been provided by a study that compared the risk of discontinuing antihypertensive therapy in patients under generic versus brand-name drugs.[68] Given the possibility that physicians would prescribe one or the other drug type according to the severity of clinical profile, only patients discontinuing treatment who experienced both generic and brand-name drug exposures during a suitable follow-up were analyzed. The results showed that treatment discontinuation did not differ in the 2 conditions, a conclusion drawn by a within-patient comparison that could be reasonably assumed to be exempted from the above-mentioned possible between patient imbalance.

Finally, new analytic techniques, such as sensitivity analysis,[69] instrumental variable methods,[70] or propensity score calibration,[71] are increasingly applied to HCU databases to account for residual confounding. Although a description of their rationale and functioning is beyond the scope of the present review, an example of the advantages of the use of these methods may help the reader to penetrate this complex area. In a study on the Lombardy HCU database, it has been observed that, compared with hypertensive patients starting treatment with a fixed-dose combination of 2 antihypertensive drugs, those on a free or liberal combination exhibited a 15% significant increase in the risk of coronary or cerebrovascular morbid events.[72] Although considering a medical explanation of this finding, the possibility of its origin from confounding (ie, a more frequent use of free combinations in patients with more severe hypertension or a worse cardiovascular risk profile in the belief that giving drugs separately makes titration to full effect easier and blood pressure reduction more balanced) prevented any reliable interpretation of the results. By omitting sources of selective prescribing (eg, because these data are not available from the HCU database used for investigating this issue) biased estimates of the drug–outcome association are systematically generated. However, biased estimates may be externally adjusted if information on physicians' prescriptive behavior and on the strength of the confounder–outcome association (ie, to what extent patients' clinical characteristics affect prescribing and cardiovascular risk, respectively) is available. Information on physician's prescriptive behavior may be obtained from MR data on a sample of the population covered from the HCU database, whereas data on the confounder–outcome association may be derived from epidemiological or intervention studies (hopefully in the same or in a similar population), the 2 sets of data combined being used to estimate the bias factor (ie, the residual bias that would result from failure to check for these confounders). In addition, a Monte Carlo sampling procedure may be used to deal with the random uncertainty of externally adjusted estimates,[73] the results being tested against an unmeasured confounder, selected among those known to be common in the population at study and to have a substantial effect on the outcome of interest. In the above-mentioned case, the use of the above-mentioned corrections abolished the increased cardiovascular risk seen in patients starting treatment with a free compared with a fixed-dose drug combination (odds ratio, 1.00; 95% confidence interval, 0.89–1.12).

Challenges and Concluding Recommendations

HCU databases are attractive because they provide huge amounts of data. Their representativeness of the population under investigation and capacity to offer longitudinal type of information for extended follow-ups at individual patient level make this approach useful for clinical observational research, especially on drug use and outcomes. Its application also includes studies of physician prescribing and patient compliance, as well as those focusing on safety, effectiveness, and cost–effectiveness of therapeutic strategies. HCU data cannot

substitute RCTs but they may fill in gaps where RCTs will probably not be done and generate real-life–based hypotheses to be tested by RCTs.

However, quantity has little merit in the absence of a sufficient level of quality, and as far as HCU databases are concerned several examples have been given that debatable eligibility criteria, incompleteness or incorrectness of linkage variables, errors in quantification of care exposure, inaccurate identification of outcome and, above all, confounding resulted into incorrect conclusions.[74,75] This may produce damage because HCU databases offer great opportunities but they also carry, as it has been emphasized in a recent editorial,[76] the responsibility that their conclusion may lead to decisions that involve the health care of a large number of beneficiaries. Proper use of HCU databases need not forget challenges that are still inherent to this approach. Although technical progress allows in most instances to collect, store, and disclose quickly to analysis even huge and rapidly growing amounts of data, some concern remains on privacy and security regulations. Furthermore, completeness and quality of data continue to remain an issue for some HCU databases, the great disparity between data included in different databases (because they are usually collected under different jurisdictions for financial rather than for clinical or research purposes),[77] representing a barrier to their pooling and comparisons between different regions or countries. Finally, if data are analyzed uncritically, ie, without consideration for possible misclassification and confounding, skepticism is generated and the credibility of the approach is undermined. Fortunately, data collection and analysis have undergone substantial progress in the past decade,[15,58,78–80] so that poor quality or incomplete databases cannot anymore be justified on technical grounds. Further important improvements are expected in the near future because preservation of privacy and security are being addressed by new authentication approaches and policies that better safeguard patient-identifiable data. Furthermore, reimbursement policies are making more and more use of automatic devices (eg, individual magnetic card) that will automatically generate data virtually free from errors or omissions. All these justify the opinion of the authors of this review that HCU data will be more and more recognized to be a powerful tool in the research area in which they belong, as long as they are (1) used with appropriate attention to their potential limits, (2) based on transparent protocols[81] and recognized quality standards,[82] and (3) analyzed by proper statistical methods that allow the pitfalls inherent to this approach to be at least, in part, corrected.

Disclosures

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