Understanding the Use of Observational and Randomized Data in Cardiovascular Medicine

Louise Bowman[1], Aris Baras[2], René Bombien[3], Robert M Califf[4], Zhengmin Chen[5], Chris P Gale[6], J Michael Gaziano[7], Diederick E. Grobbee[8]; Aldo P Maggioni[9,10], Evan D Muse[11], Dan M Roden[12], Stefan Schroeder[13], Lars Wallentin[14], Barbara Casadei[15]

[1] Nuffield Department of Population Health, University of Oxford, Oxford, UK

[2] Regeneron Pharmaceuticals, Tarrytown, NY, USA

[3] TÜV SÜD, Munich, Germany

[4] Division of Cardiology, Duke University School of Medicine, Durham, USA

[5] Nuffield Department of Population Health, University of Oxford, Oxford, UK

[6] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK

[7] Departments of Medicine, VA Boston Healthcare System, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

[8] Department of Epidemiology, University Medical Center Utrecht, div. Julius Centrum, Utrech, The Netherlands

[9] EURObservational Research Programme, European Society of Cardiology, France

[10] ANMCO Research Center, Florence, Italy

[11] Scripps Research Translational Institute, Scripps Clinic, La Jolla, USA

[12] Departments of Medicine, Pharmacology, and Biomedical Informatics, Vanderbilt University Medical Center, Vanderbilt, USA

[13] Bayer AG, Pharmaceuticals, Berlin, Germany

[14] Uppsala Clinical Research Center and Department Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden

[15] Division of Cardiovascular Medicine, British Heart Foundation Centre of Research Excellence, University of Oxford & UKNIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

Corresponding author: Barbara Casadei, Level 6, West Wing, Division of Cardiovascular Medicine, John Radcliffe Hospital, Oxford, OX3 9DU, United Kingdom. Telephone: +44(0) 1865 234664; email: barbara.casadei@cardiov.ox.ac.uk

Abstract

The availability of large datasets from multiple sources (e.g., registries, biobanks, electronic health records (EHRs), claims or billing databases, implantable devices, wearable sensors and mobile apps), coupled with advances in computing and analytic technologies, have provided new opportunities for conducting innovative health research. Equally, improved digital access to health information has facilitated the conduct of efficient randomized controlled trials (RCTs) upon which clinical management decisions can be based, for instance, by permitting the identification of eligible patients for recruitment and/or linkage for follow-up via their EHRs. Given these advances in cardiovascular data science and the complexities they behold, it is important that health professionals have clarity on the appropriate use and interpretation of observational, so-called "real-world", and randomized data in cardiovascular medicine.

The Cardiovascular Roundtable (CRT) of the European Society of Cardiology (ESC) held a workshop to explore the future of RCTs and the current and emerging opportunities for gathering and exploiting complex observational datasets in cardiovascular research. The aim of this paper is to provide a perspective on the appropriate use of randomized and observational data, and to outline the ESC plans for supporting the collection and availability of clinical data to monitor and improve the quality of care of patients with cardiovascular disease in Europe and provide an infrastructure for undertaking pragmatic RCTs. Moreover, the ESC continues to campaign for greater engagement amongst regulators, industry, patients, and health professionals in the development and application of a more efficient regulatory framework that is able to take maximal advantage of new opportunities for improving the design and efficiency of observational studies and RCT in patients with cardiovascular disease.

Introduction

Insights from observational studies have contributed greatly to the reduction of the burden of cardiovascular disease through 1) the identification of associations between risk factors and diseases; 2) the evaluation of geographical and temporal trends in cardiovascular care and outcomes; 3) the implementation of quality improvement through audit and feedback; 4) the investigation of the value of interventions; and 5) the generation of hypotheses for future studies. For those treatments that have big effects on rare outcomes, large-scale observational studies may be sufficient to confirm causal associations. However, for the majority of therapies only modest treatment effects on common outcomes are to be expected. In these circumstances, observational studies are at risk of uncontrolled biases, and randomized comparisons remain central to the provision of high quality evidence on the effectiveness and safety of interventions. 21st century developments in information technology provide enhanced data collection opportunities for both types of studies.

Appropriate Use of Large Randomized Clinical Trials

Unbiased Assessment of Treatment Efficacy and Safety

Randomized control trials (RCT) of sufficient size are required to ensure that any moderate benefits and any moderate harms of a treatment are assessed reliably. [1-3] By virtue of randomization, RCTs allow the allocation of groups of patients who differ from each other only by the play of chance with respect to their risks of having all types of health outcome - thus observed differences in the rates of health outcomes may be attributed causally to differences in study treatment. Additionally, non-differential outcome ascertainment between the trial arms minimizes bias in the assessment of treatment effects. The latter can

be further enhanced by blinding, which is likely to be of most value for symptomatic adverse events that are subjective.

RCTs have important limitations, although many of these can be overcome by careful trial design. [4] For example, restrictive eligibility criteria may lead to concerns about the generalizability of the results to under-represented groups (e.g., women, ethnic minorities) or complex patients with multimorbidity, as seen in routine clinical practice. On the other hand, RCTs with broad eligibility criteria may have insufficient statistical power to detect treatment effects that may only be present in a specific subpopulation. In the design phase, careful consideration of the most appropriate population to be recruited in a RCT is critical. [5]

Recruitment of large numbers of patients and long durations of follow-up circumvent many of the limitations of RCTs. Over several decades, large-scale cardiovascular trials have successfully achieved these aims, providing reliable results that have transformed clinical practice worldwide. Yet, burdensome regulations and their overzealous application by academic and commercial research organisations mean that such trials are very costly and concerns have been raised about the sustainability of this model of research. [6] There is general agreement that, whilst a tight regulatory framework may be appropriate for early-phase RCTs, its ubiquitous application to all clinical trials stifles the ability to test new treatments but does not necessarily ensure patient safety and data quality, and indeed there are moves to try to address this at an international level. [7] In the meantime, the availability of electronic health records (EHRs) to assist recruitment and follow-up of RCTs does already permit more cost-effective streamlined approaches to be used, [8] and allow high-quality robust trial evidence to be achieved at significantly lower costs. [9-11]

In spite of such developments, many questions remain unanswered because of a lack of resources to fund traditional multicentre RCTs. As a result, it is increasingly advocated that observational data from so-called "real-world" sources may be useful to address some of the limitations of RCTs. However, caution must be exercised to ensure that the shortcomings of observational data (e.g., systematic bias, confounding, reverse causality, and play of chance) do not get masked by the enthusiasm for the depth and breadth of information that can be obtained as a result of technological advances.

Appropriate Use of Observational Data

Observational data from purposely-designed cohorts and case-control studies may assess the burden and natural history of disease, evaluate quality of care, identify novel risk factors or prognostic markers of cardiovascular disease, and inform the identification of new therapeutic targets. [12] Analyses of observational data that report associations between exposures (e.g., lipid sub-particles) and outcome (e.g. stroke) can generate hypotheses for prospective testing in a RCT.[13] The results of observational analyses must, however, be interpreted in the context of their limitations. With the exception of those cases where large effects of treatment on rare outcomes are observed (for example, statin therapy and rhabdomyolysis), causality cannot be inferred, and the nature and strength of associations can be impacted by confounders. For example, observational studies have reported associations between statin use and reduced cancer incidence rates, [14] yet, based on over 10,000 cases of incident cancer in the Cholesterol Treatment Trialists Collaboration meta-analyses of individual patient data from randomized trials, there were no adverse effects seen on rates of cancer either overall or at any particular site. [15] Thus, it is important to recognize

the potential for analyses of observational data to be misleading, despite controlling for comorbidity, extent of disease, treatment used, and other characteristics and attempts to simulate an inception time to mimic randomization. [16, 17] Furthermore, even when analyses are applied to the same data set, substantial variation in the estimated effect size can emerge as a result of researchers' choices and assumptions during analysis. [18]

Disease Reclassification, Intelligent Design of RCTs and Drug Target Identification

Application of artificial intelligence and machine learning to omics data, EHRs, environmental and lifestyle information (*e.g.*, from smartphone applications and wearable sensors) may allow for improved classification of disease to inform both observational studies and RCT design. The WHO's International Classification of Disease (ICD) relies on organ systems, as reflected by the current organization of medical practice by specialty. However, biological processes may not be confined to one organ system. For example, a lung cancer with a specific somatic mutation may behave more like a tumour in another organ than other lung cancers. Better classification of disease based on mechanistic underpinnings may permit better RCT design by including individuals with a more precise disease definition. [19] There is also increasing enthusiasm for using advanced analytics to determine patient profiles which may predict treatment response or susceptibility to adverse events to enable recruitment of patients most likely to benefit and least likely to experience harm. Genetics may help identify high-risk patients, [20, 21] uncover and validate (e.g., by using Mendelian randomization techniques) novel drug targets, [21-23] predict potential off-target effects of new compounds, and facilitate the identification of patients who may be more likely to respond to a specific treatment. [24]

This strategy is attractive due to the potential to: *1)* maximize benefits to patients while minimizing potential harms; *2)* achieve larger treatment effects in specific groups enabling RCTs to be conducted more efficiently; *3)* reduce late-stage therapeutic development failures; and *4)* avoid erroneously declaring a drug as ineffective when it might be a life-saving therapy for specific patient subsets.

However, caution must be exercised in the interpretation of such results, and any new hypothesis that arises from observational data, no matter how 'precise', is likely to require confirmation by a RCT. For example, after the dal-OUTCOMES trial showed no effect of dalcetrapib compared to placebo (plus standard of care) on the primary composite efficacy endpoint,[25] a genome wide association study was performed and observed that polymorphisms in the ADCY9 gene appeared to be associated with different effects of dalcetrapib on both clinical outcomes and carotid intima-media thickness. [24] These findings led to the design of an ongoing RCT to prospectively evaluate whether dalcetrapib compared to placebo will reduce cardiovascular morbidity and mortality in ~6000 patients with the target genotype and a recent acute coronary syndrome (Dal-GenE, clinicaltrials.gov NCT02525939, which is likely to report in 2020).

Feasibility Assessments for RCTs

Observational data, particularly from EHRs or prospective continuous registries, may be used to assess the feasibility of a RCT. EHRs or registries can be pre-screened to determine the number of patients that would meet proposed eligibility criteria. If the number of potentially

eligible patient outcomes is found to be low in such analyses, the inclusion and exclusion criteria may need to be re-evaluated and modified. Review of EHRs or registries to identify potentially eligible patients can also inform site selection, such that only those centres with large numbers of potentially eligible patients are invited to participate. Similarly, the study of rare diseases (be this in observational or randomized format) may be facilitated by scoping searches for rates of prevalence or incidence within and between centres.

Registry-based and Pragmatic RCTs

Registry-based and pragmatic RCTs increase opportunities to resolve issues in medical treatment through randomization and follow-up of patients within health care systems. [26-31] Beside the non-trivial advantage of substantially lowering costs, this approach may also provide more generalizable results whilst circumventing the inherent limitations of observational analyses.[32, 33] As with all trial designs it is important to ensure that the registry is large enough to allow sufficient recruitment and statistical power for the trial's question to be addressed robustly and the use of EHRs for trial recruitment and follow-up has not been uniformly effective. Further potential limitations are the quality and accuracy of the registry data and the need for clinical end-points that may not be routinely recorded within the registry, or adequately coded by the EHR system. The potential value of very large datasets may be severely restricted by poor data quality or large amounts of missing data. Some of these shortcomings can be addressed by data linkage across different datasets within a country. Amongst the advantages of using EHRs to follow-up patients recruited to RCTs are a more complete and longer-term data collection and the possibility to detect unanticipated endpoints, such as adverse drug reactions.

SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies) is an online national cardiac registry that has provided the infrastructure for several completed RCTs (e.g., [26-29]) with many others ongoing. SWEDEHEART has the advantage of including all Swedish patients admitted to hospital for coronary artery disease and of having a complete follow-up for all types of treatments and events, including specific endpoints, adverse events, co-morbidities and concomitant treatment both during and after each RCT. However, the geographic restriction to Sweden limits the size and representativeness of participants that may be included in any RCT.

Registries in other populations have been successfully used to determine trial outcomes and can be particularly informative for long-term follow-up after the end of the scheduled treatment period. For example, the WOSCOPS study used Scottish health record data, first in a validation study (by comparison with the clinic follow-up during the active trial period) and subsequently to provide long-term follow-up beyond the active trial period. [34, 35]

Assessment of Adherence to Practice Guideline Recommendations

Adherence to evidence-based guideline recommendations has been associated with improved outcomes.[36-38] Prospective disease-specific registries can serve as a platform to evaluate the use of recommended therapies and to launch performance improvement initiatives that aim to increase the implementation of guideline recommendations in clinical practice. For this purpose, relatively small “snapshot” surveys in a variety of diverse settings

can provide generalizable information. The EURObservational Research Programme (EORP; https://www.escardio.org/Research/Registries-&-surveys) was developed by the ESC to assess the adoption of guideline recommendations and, whenever possible, evaluate its impact on patient outcomes.

Several disease and treatment-specific cardiovascular registries have been initiated (**Figure 1**), which have enabled evaluation of guidelines adherence across Europe and, importantly, provided insights into why guideline recommendations were not implemented, which in turn, may assist policymakers in designing more efficient systems.[39] Observational registries that assess physician adherence to guidelines may also be used by professional organizations (e.g., ESC or National Cardiac Societies) to develop targeted educational programs aiming to improve the implementation of evidence-based treatment of cardiovascular disease.

Evaluation of Drug Safety

Safety surveillance is an accepted use of observational evidence. The United States Food and Drug Administration (FDA) launched the Sentinel System (https://www.fda.gov/safety/fdas-sentinel-initiative/fdas-sentinel-initiative-background) in 2008 to achieve active post-market safety surveillance.[40, 41] The system includes data from administrative and claims databases, EHR systems, and registries from more than 100 million individuals. Researchers can use these large observational datasets to detect rare signals in broad populations. In addition, the system includes processes for signal generation (*i.e.*, identification of medical product-adverse event associations that may be safety signals), refinement (*i.e.*, further investigation

of potential safety signals), and evaluation (*i.e.*, study of causal relationships between exposure and adverse events). Further outcomes from this initiative are eagerly awaited.

ESC Plans for Supporting Innovation and Promoting Better Quality of Care in Europe

Partnerships for improving risk prediction using big data approaches

Clinical risk prediction and decision support algorithms in cardiovascular disease are rapidly proliferating. Data derived from EHRs and registries may outperform traditional risk scores and new approaches to data management and information pipelines may enable them to be rapidly updated in the light of new imaging, biochemical, and genomic biomarkers. Predictions may also be improved by incorporating clinical trajectories, whereby cumulative data are used to develop an electronic decision tool to stratify patient risk and / or outcomes. [42] Combining large-scale genomic data with clinical outcomes in Mendelian randomization (MR) analyses may generate new causal insights but also indicate new targets for drug treatment.

BigData@Heart is an Innovative Medicines Initiative-2 (IMI-2)-funded project, which aims to apply big data analytic approaches to improve the prediction and prognosis of the most common cardiovascular diseases in Europe. [43] The ESC, in partnership with a number of European academic research groups and pharmaceutical companies, have joined forces to develop a big data driven translational research platform. BigData@Heart has access to most of the relevant large-scale European databases, ranging from EHR and disease registries to

well-phenotyped clinical trials and large epidemiological cohorts enriched with –omics data, including data on more than five million patients with acute coronary syndromes, atrial fibrillation, and heart failure (https://www.bigdata-heart.eu/) and about 20 million controls without the diseases. By accessing and harmonizing European-wide data sets, the ambition is to design algorithms that predict the evolution of disease, based on medical history, hospital records, and country-specific statistics. Using all available data across data modalities, combined with machine learning or Bayesian network models, is expected to further refine outcome prediction. [44] In addition, BigData@Heart will explore and set standards for the use of large and heterogeneously distributed data sets. Investigations include data mapping using common standards, federated data analysis obviating the need for central data bases, and the legal and ethical aspects of using consented and unconsented data, in view of the EU general data protection regulation but also across countries with varying privacy rules.

The ESC EUROHEART Project

A particular challenge in most European countries is the lack of continuous gathering of standardized data from clinical care and of long-term follow-up of outcomes. Currently, very few countries have standardized variables in EHRs or continuous prospective registries, such as the SWEDEHEART system. There are also very few incentives and a general lack of time and funding to start-up and run such systems.

To overcome these obstacles, the ESC has decided to launch the EUROHEART (European Unified Registries for Online Heart care Evaluation And Randomized Trials) program, the aim of which is to support the development of continuous on-line registries in all countries

interested in implementing quality of care improvement in patients with cardiovascular disease at the local/national level and to support both observational research and RCTs at national and international level.

The EUROHEART collaboration will develop internationally standardized and locally adapted datasets by using an IT platform that will be adjusted to national needs and regulations and implemented at the national level by each participating country. Such a platform will also provide on-line tools to support local quality improvement initiatives. Importantly, each participating centre and country will have the opportunity to join international observational research programmes and RCTs. In parallel, the ESC will also ensure that its members are equipped with the knowledge to critically appraise such data by offering a postgraduate Master's degree (https://www.escardio.org/Education/Postgraduate-Programmes/msc-in-clinical-trials; https://www.ndph.ox.ac.uk/study-with-us/msc-clinical-trials), as well as shorter training programmes, in clinical trials and observational research.

The EUROHEART project is a pivotal component of the ESC strategy for improving cardiovascular care in Europe and for creating an international infrastructure within which affordable streamlined randomized clinical trials can be undertaken. Nevertheless, the potential of this programme will not be fully realized without reducing the regulatory obstacles to the undertaking of RCTs. [7] To this end, the ESC will continue to campaign (https://moretrials.net/) for greater engagement among regulators, industry, patients, charities (https://wellcome.ac.uk/news/pivotal-moment-clinical-trial-regulations) and scientific and academic organisations in the development of clinical trials regulations that are efficient and ensuring patient safety.

Conclusion

Rapid advances in analytic technology and increasing opportunities to mine readily accessible data sets provide exciting prospects for advancing knowledge and improving clinical care. Observational data can refine understanding and classification of cardiovascular disease, generate new hypotheses, and support the implementation and delivery of equitable care in all European countries (**Figure 2**). However, despite the depth and breadth of the data that can currently be obtained, if attempts are made to infer causality from observational data the inherent risk of confounding, play of chance, and reverse causality will still remain. Nonetheless, technological advances can significantly aid the design and conduct of RCTs and facilitate the generation of reliable evidence on the efficacy and safety of treatment. When coupled with concerted efforts to address RCTs regulatory obstacles, projects such as EUROHEART have considerable potential for promoting innovation and improving cardiovascular healthcare in Europe.

Acknowledgement

This paper arose from discussions during a Cardiovascular Round Table (CRT) workshop organized in May 2018 by the European Society of Cardiology (ESC). The CRT is a strategic forum for high-level dialogue between industry and ESC leadership to identify and discuss key strategic issues for the future of cardiovascular health in Europe.

Figure 1. The ESC EURObservational Research Programme Registries. Note that the duration of registries includes patient follow-up.

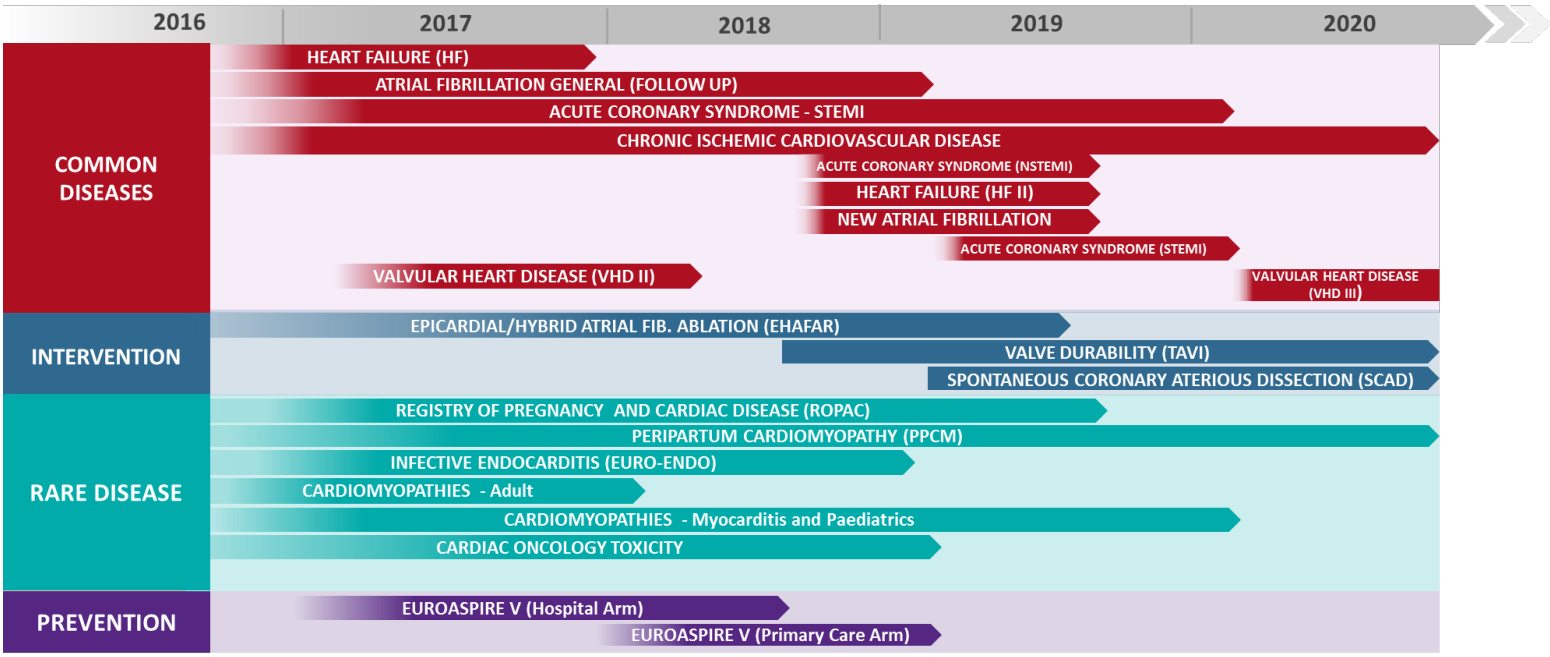

Figure 2. Pragmatic registry or electronic health record (EHR)-based randomized control trials combine the advantages of randomized and observational research and are substantially less expensive.

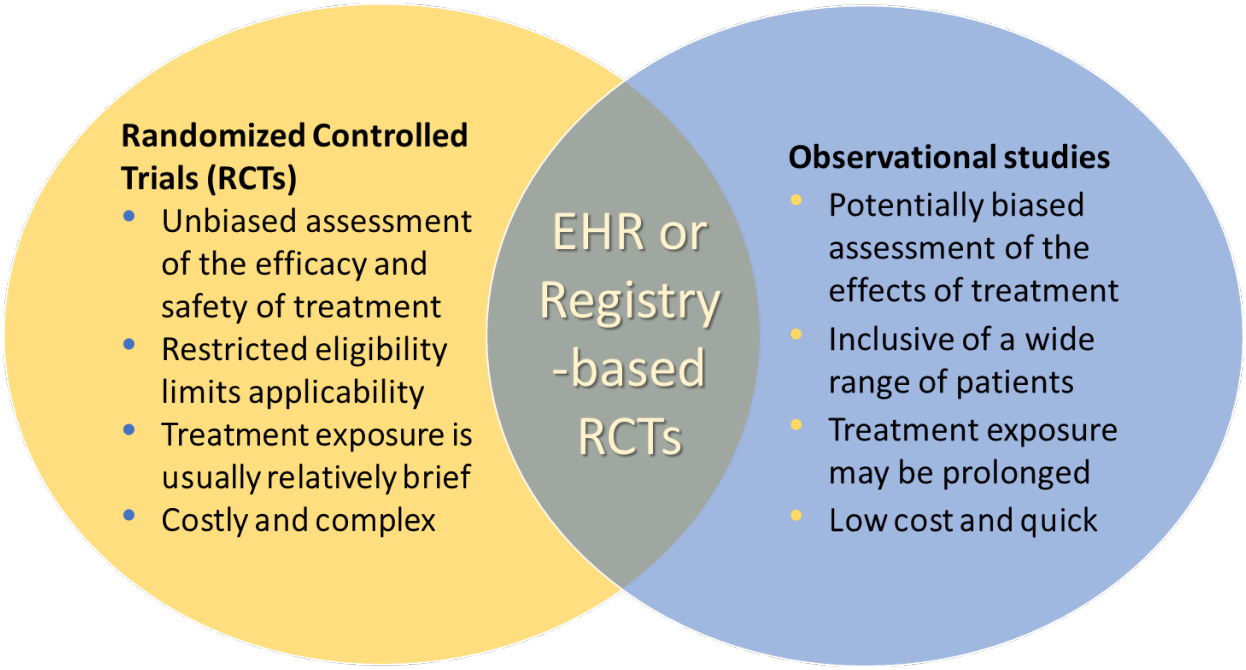

Table 1. Type of Observational Data and Potential Uses

Type	Potential Uses	Examples	Strengths	Limitations
Large prospective biobanks	To assess the link between environmental and genetic exposure and disease. To study the natural history of disease. To identify new potential drug targets. To construct or refine risk scores.	China Kadoorie Biobank http://www.ckbiobank.org/site/ UK Biobank http://www.ukbiobank.ac.uk/ All of Us https://allofus.nih.gov/	Generally less prone to problems of reverse causality. Facilitate the study of different disease outcomes. Can be integrated with other data sources (e.g., EHR).	Statistical adjustment may be unable to completely control for potential bias introduced by known or unknown confounders (*e.g.*, in nested case-control studies). Large samples needed with detailed phenotyping since effect sizes are usually modest. Biochemical and omics results may vary across different platforms.
Registries/ Surveys	To evaluate disease burden and plan resources To assess implementation of evidence-based therapies and its impact on outcomes. To provide quality improvement feedback. To inform the development of and assess the	AHA Get With the Guidelines https://www.heart.org/en/professional/quality-improvement/ SWEDEHEART http://www.ucr.uu.se/swedeheart/ EORP https://www.escardio.org/Research/Registries-&-surveys NICOR https://www.ucl.ac.uk/nicor	Generalisable. Reflect routine clinical practice. Randomization can be implemented within a registry platform	Patient population may not be comprehensive (*e.g.*, limited to patients willing to provide information). Evaluate associations not causality. In randomized registry trials, small treatment effects or treatment effects in a subset of patients may be difficult to detect since registry populations are

Type	Potential Uses	Examples	Strengths	Limitations
	response to targeted educational initiatives. To provide an infrastructure for pragmatic clinical trials.			typically heterogeneous. Missing data
Data obtained from electronic health records (EHRs)	To evaluate resource utilization and survey safety of treatments/ devices in the real world. To assess feasibility and facilitate recruitment in RCTs. To allow point-of-care randomization and comprehensive passive follow-up. To facilitate health technology assessments.	PCORnet Primary care records (eg CPRD , https://www.cprd.com/ also THIN, SystemOne, Q research in the UK) Administrative data (Hospital Episodes Statistics, HES https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics in the UK) Claims data (eg Sentinel, https://www.sentinelinitiative.org)	Representative Reflect routine clinical practice Comprehensive; i.e., Include data from every patient in a given health system Valuable resource for undertaking of high-quality low-cost RCTs.	EHR data collection has not been designed for research purposes. Heterogeneity among EHR systems Data quality may be suboptimal (e.g., subject to coding errors). Missing data

AHA, American Heart Association; EHR, electronic health records; EORP, EURObservational Research Programme; PCORnet, Patient-Centered Outcomes Research network; RCT, randomized controlled trials; SWEDEHEART, Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies; NICOR, National Institute for Cardiovascular Outcomes Research

References

1. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. Lancet 2001;**357**(9253):373-80.
2. Stone GW, Pocock SJ. Randomized Trials, Statistics, and Clinical Inference. Journal of the American College of Cardiology 2010;**55**(5):428-431.
3. McMurray JJV. Only Trials Tell the Truth About Treatment Effects∗. Journal of the American College of Cardiology 2018;**71**(23):2640-2642.
4. Kaul S, Diamond GA. Trial and Error: How to Avoid Commonly Encountered Limitations of Published Clinical Trials. Journal of the American College of Cardiology 2010;**55**(5):415-427.
5. Meeker-O'Connell A, Glessner C, Behm M, Mulinde J, Roach N, Sweeney F, Tenaerts P, Landray MJ. Enhancing clinical evidence by proactively building quality into clinical trials. Clinical Trials 2016;**13**(4):439-444.
6. Reith C, Landray M, Devereaux PJ, Bosch J, Granger CB, Baigent C, Califf RM, Collins R, Yusuf S. Randomized clinical trials--removing unnecessary obstacles. N Engl J Med 2013;**369**(11):1061-5.
7. Landray MJ, Bax JJ, Alliot L, Buyse M, Cohen A, Collins R, Hindricks G, James SK, Lane S, Maggioni AP, Meeker-O'Connell A, Olsson G, Pocock SJ, Rawlins M, Sellors J, Shinagawa K, Sipido KR, Smeeth L, Stephens R, Stewart MW, Stough WG, Sweeney F, Van de Werf F, Woods K, Casadei B. Improving public health by improving clinical trial guidelines and their application. Eur Heart J 2017;**38**(21):1632-1637.
8. Jackson N, Atar D, Borentain M, Breithardt G, van Eickels M, Endres M, Fraass U, Friede T, Hannachi H, Janmohamed S, Kreuzer J, Landray M, Lautsch D, Le Floch C, Mol P, Naci H, Samani NJ, Svensson A, Thorstensen C, Tijssen J, Vandzhura V, Zalewski A, Kirchhof P. Improving clinical trials for cardiovascular diseases: a position paper from the Cardiovascular Round Table of the European Society of Cardiology. Eur Heart J 2016;**37**(9):747-54.
9. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart 2010;**96**(20):1617-21.
10. Raman SR, Curtis LH, Temple R, Andersson T, Ezekowitz J, Ford I, James S, Marsolo K, Mirhaji P, Rocca M, Rothman RL, Sethuraman B, Stockbridge N, Terry S, Wasserman SM, Peterson ED, Hernandez AF. Leveraging electronic health records for clinical research. Am Heart J 2018;**202**:13-19.
11. Bowman L, Mafham M, Stevens W, Haynes R, Aung T, Chen F, Buck G, Collins R, Armitage J. ASCEND: A Study of Cardiovascular Events iN Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes. Am Heart J 2018;**198**:135-144.
12. Littlejohns TJ, Sudlow C, Allen NE, Collins R. UK Biobank: opportunities for cardiovascular research. Eur Heart J 2019;**40**(14):1158-1166.
13. Sun L, Clarke R, Bennett D, Guo Y, Walters RG, Hill M, Parish S, Millwood IY, Bian Z, Chen Y, Yu C, Lv J, Collins R, Chen J, Peto R, Li L, Chen Z. Causal associations of blood lipids with risk of ischemic stroke and intracerebral hemorrhage in Chinese adults. Nat Med 2019;**25**(4):569-574.

14. Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, Neaton J, Nelson J, Potter J, Rifkind B, et al. Report of the Conference on Low Blood Cholesterol: Mortality Associations. Circulation 1992;**86**(3):1046-60.
15. Cholesterol Treatment Trialists C, Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, Holland L, Peto R, Keech A, Collins R, Simes J, Baigent C. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One 2012;**7**(1):e29849.
16. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, Nichols M, Stone GW, Pocock SJ. Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. J Am Coll Cardiol 2017;**69**(3):345-357.
17. Gerstein HC, McMurray J, Holman RR. Real-world studies no substitute for RCTs in establishing efficacy. Lancet 2019;**393**(10168):210-211.
18. Silberzahn R, Uhlmann EL, Martin DP, Anselmi P, Aust F, Awtrey E, Bahník Š, Bai F, Bannard C, Bonnier E, Carlsson R, Cheung F, Christensen G, Clay R, Craig MA, Dalla Rosa A, Dam L, Evans MH, Flores Cervantes I, Fong N, Gamez-Djokic M, Glenz A, Gordon-McKeon S, Heaton TJ, Hederos K, Heene M, Hofelich Mohr AJ, Högden F, Hui K, Johannesson M, Kalodimos J, Kaszubowski E, Kennedy DM, Lei R, Lindsay TA, Liverani S, Madan CR, Molden D, Molleman E, Morey RD, Mulder LB, Nijstad BR, Pope NG, Pope B, Prenoveau JM, Rink F, Robusto E, Roderique H, Sandberg A, Schlüter E, Schönbrodt FD, Sherman MF, Sommer SA, Sotak K, Spain S, Spörlein C, Stafford T, Stefanutti L, Tauber S, Ullrich J, Vianello M, Wagenmakers EJ, Witkowiak M, Yoon S, Nosek BA. Many Analysts, One Data Set: Making Transparent How Variations in Analytic Choices Affect Results. Adv Methods Pract Psychol Sci 2018;**1**(3):337-356.
19. Lacombe D, O'Morain C, Casadei B, Hill K, Mateus E, Lories R, Brusselle G. Moving forward from drug-centred to patient-centred research: A white paper initiated by EORTC and developed together with the BioMed Alliance members. Eur Respir J 2019;**53**(2).
20. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, Kathiresan S. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nature Genetics 2018;**50**(9):1219-1224.
21. Nielsen JB, Thorolfsdottir RB, Fritsche LG, Zhou W, Skov MW, Graham SE, Herron TJ, McCarthy S, Schmidt EM, Sveinbjornsson G, Surakka I, Mathis MR, Yamazaki M, Crawford RD, Gabrielsen ME, Skogholt AH, Holmen OL, Lin M, Wolford BN, Dey R, Dalen H, Sulem P, Chung JH, Backman JD, Arnar DO, Thorsteinsdottir U, Baras A, O'Dushlaine C, Holst AG, Wen X, Hornsby W, Dewey FE, Boehnke M, Kheterpal S, Mukherjee B, Lee S, Kang HM, Holm H, Kitzman J, Shavit JA, Jalife J, Brummett CM, Teslovich TM, Carey DJ, Gudbjartsson DF, Stefansson K, Abecasis GR, Hveem K, Willer CJ. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. Nat Genet 2018;**50**(9):1234-1239.
22. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. JAMA 2017;**318**(19):1925-1926.
23. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Boren J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgozoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;**38**(32):2459-2472.

24. Tardif JC, Rheaume E, Lemieux Perreault LP, Gregoire JC, Feroz Zada Y, Asselin G, Provost S, Barhdadi A, Rhainds D, L'Allier PL, Ibrahim R, Upmanyu R, Niesor EJ, Benghozi R, Suchankova G, Laghrissi-Thode F, Guertin MC, Olsson AG, Mongrain I, Schwartz GG, Dube MP. Pharmacogenomic determinants of the cardiovascular effects of dalcetrapib. Circ Cardiovasc Genet 2015;**8**(2):372-82.
25. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012;**367**(22):2089-99.
26. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, Arefalk G, Frick M, Alfredsson J, Nilsson L, Ravn-Fischer A, Omerovic E, Kellerth T, Sparv D, Ekelund U, Linder R, Ekstrom M, Lauermann J, Haaga U, Pernow J, Ostlund O, Herlitz J, Svensson L. Oxygen Therapy in Suspected Acute Myocardial Infarction. N Engl J Med 2017;**377**(13):1240-1249.
27. Erlinge D, Omerovic E, Frobert O, Linder R, Danielewicz M, Hamid M, Swahn E, Henareh L, Wagner H, Hardhammar P, Sjogren I, Stewart J, Grimfjard P, Jensen J, Aasa M, Robertsson L, Lindroos P, Haupt J, Wikstrom H, Ulvenstam A, Bhiladvala P, Lindvall B, Lundin A, Todt T, Ioanes D, Ramunddal T, Kellerth T, Zagozdzon L, Gotberg M, Andersson J, Angeras O, Ostlund O, Lagerqvist B, Held C, Wallentin L, Schersten F, Eriksson P, Koul S, James S. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. N Engl J Med 2017;**377**(12):1132-1142.
28. Lagerqvist B, Frobert O, Olivecrona GK, Gudnason T, Maeng M, Alstrom P, Andersson J, Calais F, Carlsson J, Collste O, Gotberg M, Hardhammar P, Ioanes D, Kallryd A, Linder R, Lundin A, Odenstedt J, Omerovic E, Puskar V, Todt T, Zelleroth E, Ostlund O, James SK. Outcomes 1 year after thrombus aspiration for myocardial infarction. N Engl J Med 2014;**371**(12):1111-20.
29. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angeras O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Karegren A, Nilsson J, Robertson L, Sandhall L, Sjogren I, Ostlund O, Harnek J, James SK. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;**369**(17):1587-97.
30. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, Shaw AD, Bernard GR, Rice TW. Balanced Crystalloids versus Saline in Noncritically Ill Adults. N Engl J Med 2018;**378**(9):819-828.
31. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillamondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR, Rice TW. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med 2018;**378**(9):829-839.
32. Zuidgeest MGP, Goetz I, Groenwold RHH, Irving E, van Thiel GJMW, Grobbee DE. Series: Pragmatic trials and real world evidence: Paper 1. Introduction. Journal of Clinical Epidemiology 2017;**88**:7-13.
33. Yndigegn T, Hofmann R, Jernberg T, Gale CP. Registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era. Heart 2018;**104**(19):1562-1567.
34. McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, Cobbe SM, Ford I. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. Eur Heart J 2014;**35**(5):290-8.

35. Ford I, Murray H, McCowan C, Packard CJ. Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study. Circulation 2016;**133**(11):1073-80.
36. Komajda M, Lapuerta P, Hermans N, Gonzalez-Juanatey JR, van Veldhuisen DJ, Erdmann E, Tavazzi L, Poole-Wilson P, Le Pen C. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. Eur Heart J 2005;**26**(16):1653-9.
37. Qin D, Leef G, Alam MB, Rattan R, Munir MB, Patel D, Khattak F, Vaghasia N, Adelstein E, Jain SK, Saba S. Patient outcomes according to adherence to treatment guidelines for rhythm control of atrial fibrillation. J Am Heart Assoc 2015;**4**(4).
38. Komajda M, Schope J, Wagenpfeil S, Tavazzi L, Bohm M, Ponikowski P, Anker SD, Filippatos GS, Cowie MR. Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail 2019.
39. Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;**15**(10):1173-1184.
40. Platt R, Brown JS, Robb M, McClellan M, Ball R, Nguyen MD, Sherman RE. The FDA Sentinel Initiative — An Evolving National Resource. New England Journal of Medicine 2018;**379**(22):2091-2093.
41. Corrigan-Curay J, Sacks L, Woodcock J. Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness. Jama 2018;**320**(9):867-868.
42. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, Mohammed MA, Parry J, Marshall T. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing 2016;**45**(3):353-60.
43. Anker S, Asselbergs FW, Brobert G, Vardas P, Grobbee DE, Cronin M. Big Data in Cardiovascular Disease. Eur Heart J 2017;**38**(24):1863-1865.
44. Hemingway H, Asselbergs FW, Danesh J, Dobson R, Maniadakis N, Maggioni A, van Thiel GJM, Cronin M, Brobert G, Vardas P, Anker SD, Grobbee DE, Denaxas S. Big data from electronic health records for early and late translational cardiovascular research: challenges and potential. Eur Heart J 2018;**39**(16):1481-1495.