Acta Cardiol Sin 2017;33:581–587
Review Article
doi: 10.6515/ACS20170331B

The Application and Future of Big Database Studies in Cardiology: A Single-Center Experience

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As medical research techniques and quality have improved, it is apparent that cardiovascular problems could be better resolved by more strict experiment design. In fact, substantial time and resources should be expended to fulfill the requirements of high quality studies. Many worthy ideas and hypotheses were unable to be verified or proven due to ethical or economic limitations. In recent years, new and various applications and uses of databases have received increasing attention. Important information regarding certain issues such as rare cardiovascular diseases, women's heart health, post-marketing analysis of different medications, or a combination of clinical and regional cardiac features could be obtained by the use of rigorous statistical methods. However, there are limitations that exist among all databases. One of the key essentials to creating and correctly addressing this research is through reliable processes of analyzing and interpreting these cardiologic databases.

Key Words: Big database • Cardiovascular diseases • National Health Insurance Research Database (NHIRD)

INTRODUCTION

The field of medicine is an ancient science. Over the centuries, medicine has developed through careful observation, thoughtful hypotheses, and detailed verification of experiments that in many instances involve the connection of seemingly different factors. In order to apply results to the real world, studies should be rigorously controlled to minimize potential bias. Randomized controlled trials in the cardiovascular field have simplified issues of interest, and have been used to exclude or equalize factors that might interfere with a hypothesis.[1,2] Controlled trials can answer specific, selected questions, however there remains some doubt as to how these results can be applied to a real scenario. Moreover, to create the possibility of statistical significance, it is important to minimize potential sampling bias, ensure baseline equalization, and monitor unexpected effects and results. Furthermore, taking the issue of medical ethics into consideration, the sample size of experimental subjectsis also a problem. Therefore, considerable funding and time is required for such studies, making it increasingly difficult for single centers and young investigators to afford.

In recent years, many different methods have been developed to analyze different kinds of medical databases. For example, the National Health Insurance Research Database (NHIRD) in Taiwan (http:/nhird.nhri.org.tw/en/) consists of comprehensive information about the health of residents in Taiwan, including sex, age, diagnosis of diseases, records of hospitalization, major medical management, and mortality. As of 2014, the NHIRD included 99.9% of the population of Taiwan. The

Received: November 26, 2016 Accepted: March 31, 2017
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specific features of the database have been reported in numerous earlier studies. It contains both generalized and specific medical data of substantial importance to medical researchers, reflecting real world medicine in Taiwan. The NHIRD is used for 12.6% (290/2308 as of October 2016) of PubMed publications relating to cardiovascular diseases, and at least 15 manuscripts from Acta Cardiologic Sinica.[1-15]

The contents of the NHIRD are encrypted to protect personal information, and researchers need to extract interesting content from the database. The major contents include age, sex, diagnoses, admissions, prescriptions, operations, and costs. Because some quantitative data are not available, such as the level of blood hemoglobin, appropriate topics should be chosen to minimize these limitations. Investigators provide the category of encrypted data first, and then targeted information is extracted and "cleaned" to remove unwanted information. Raw data are created which can then be analyzed. Controlled groups are matched by propensity scoring. Common statistical tools including descriptive statistics, chi-square test, analysis of variance, linear regression, logistics regression, and survival analysis, such as life tables, Kaplan-Meier estimates, and log-rank tests should be chosen on the basis of the study design.

APPLICATION OF DATABASES FOR CARDIOVASCULAR STUDIES FROM TAIWAN

The application of information derived from large databases in the research of cardiovascular diseases can include major adverse cardiovascular events (MACEs) resulting from pregnancy, multidisciplinary diseases, and post-marketing analysis of cardiological treatment. The cardiological studies which have used the NHIRD or single-center databases in our hospital are listed in Table 1. Their conclusions and influences are summarized

Table 1. The published cardiological studies which analyzed NHIRD or single-center based databases in Chang Gung Memorial Hospital, Linkou Medical Center

Category	Authors	Disease or intervention	Specific population	Main outcomes
Cardiology	Li et al. (2015)[29]	Atrial fibrillation		MACEs
	Tung et al. (2016)[34]	Re-admission	Heart failure	MACEs
	Lin et al. (2014)[19]	Grown-up congenital heart disease		MACEs
Woman's health	Tang et al. (2009)[17]	Pre-eclampsia and eclampsia	Pregnant women	Peripartum stroke
	Lin et al. (2011)[16]	Pre-eclampsia and eclampsia	Pregnant women	Peripartum MACEs
	Wu et al. (2014)[18]	Systemic lupus erythromatosus	Pregnant women	Postpartum MACEs
Multidisciplinary	Tsai et al. (2012)[20]	Acute kidney injury	Post surgeries for aortic dissection	Mortality
	Tsai et al. (2014)[23]	Acute kidney injury	Acute cardiovascular disease	MACEs
	Chen et al. (2016)[21]	Pre-operative hemodialysis	Post coronary bypass surgery	MACEs
	Chen et al. (2016)[22]	Acute respiratory distress syndrome	Post valvular heart surgery	Mortality
	Chen et al. (2015)[24]	Dental procedures		Incidence of endocarditis
	Chou et al. (2015)[26]	Treated periodontitis		MACEs
	Liu et al. (2016)[27]	Erectile dysfunction		Incidence of atrial fibrillation
	Lin et al. (2016)[28]	Obstructive sleep apnea		Renal dysfunction
Post-marketing analysis of medications	Hsiao et al. (2015)[25]	Fixed combination of anti-hypertensive medication	Hypertension	MACEs
	Tung et al. (2015)[30]	Fixed combination of anti-hypertensive medication	Hypertension	Clinical costs
Biomarkers	Tsai et al. (2015)[31]	High-sensitivity C-reactive protein	Metabolic syndrome	Arterial stiffness
	Yang et al. (2016)[35]	Urinary biomarkers	Heart failure	Detection of acute kidney injury

in the following paragraphs.

Pregnancy medicine and cardiovascular diseases

Safety is the first priority among most earlier clinical studies. Thus, researchers may often have difficulty in collecting data focusing on women's health, especially during a woman's childbearing years. The ultimate experimental design, therefore, should be carefully crafted to avoid or minimize any adverse effects for mothers and their fetuses. Thus, studies enrolling this patient population tend to be retrospective and small in scale. This causes the research to have minimum "power," thus making hypotheses difficult to confirm. However, with such a comprehensive database as the NHIRD, study "power" is typically not a issue in that a large sample size and real world relevance are apparent.

For example, pre-eclampsia is a disease specific to women. In such cases, the vascular bed of the placenta is abnormal, leading to an elevated systemic concentration of vaso-active cytokines and subsequently the development of hypertension and proteinuria. The underlying environment may be thrombogenic, leading to a higher prevalence of cardiovascular events. Our studies found a strong correlation between pre-eclampsia, stroke, and MACEs.[16,17] This connection could have been difficult to establish using traditional cohort and single-center studies, particularly when the follow-up period and patient numbers were limited.

Another issue of gestational health is systemic lupus erythematosus. Such patients are typically female, and usually in child-bearing years. In general, little medical evidence is available on pregnant lupus patients, and the cardiovascular risk factors in this group have rarely been given much attention. By using the NHIRD, we found that post-delivery lupus patients had about a 10-fold elevated cardiovascular risk compared to the control group, a finding which helped us to improve clinical decision making.[18]

These two studies highlight that despite the existence of fair cooperation between hospitals, the sample size of patients with certain diseases is relatively small, and the follow-up period is usually insufficiently long. Thus, correlation or causal relationships are usually hard to establish. Fortunately, analysis of a large database can provide an initial impression about possible correlations. With a rigorous research design, database analysis can be used not only for MACEs in gestational women but also for patients with surgically corrected congenital heart disease,[19] or to obtain useful medical information about children, the very elderly, or other vulnerable groups.

Multidisciplinary research projects in cardiovascular studies

In the traditional medical research environment, investigators typically focus on research within their specific expertise. In many cases, however, such an approach may not be sufficient to clarify certain issues involving multi-departmental or multi-disciplinary challenges with complicated data. Researchers tend to ignore information that appears unrelated to the specific topic such as geography or regional climate, however these seemingly unrelated factors may be critical to reach a correct result and conclusion. As an example, acute kidney injury (AKI) may complicate the course of aortic dissection. In order to clarify this association, cooperation was necessary between nephrologists and vascular surgeons.[20] The relationships between AKI and bypass surgery,[21] valvular operation,[22] and acute cardiovascular diseases[23] have also been elucidated in this manner. Synchronizing and analyzing databases could facilitate such research; even for apparently distinct sub-special subjects.

Dental disease is considered to be a risk factor contributing to endocarditis.[24-26] However, establishing and confirming a relationship requires expertise in many subjects, which is a challenge for single-center studies. Dentistry has been incorporated into the NHIRD, and comprehensive cohort data can be obtained. According to our research, severe periodontitis is an adverse prognostic factor for cardiovascular outcomes. Even though annually dental scaling may have a protective role for infective endocarditis and other cardiac events, dental procedures including tooth extraction, periodontal, and endodontic therapies, have been shown to have a neutral effect on the prevalence of subsequent hospitalization for endocarditis.[24,27-29] Other factors such as temperature, height, climate, or the economy can also be integrated with medical issues. Therefore, analyzing information from a comprehensive database is valuable for researchers who are dedicated to public health. Additionally, erectile dysfunction,[30] sleep apnea,[31] and new-onset atrial fibrillation[32] have been evaluated to

ascertain their association with MACEs, to provide useful treatment references.

Another category in which the NHIRD is very valuable for research is stroke. Chao et al. studied the use of risk scores and the age threshold for using anticoagulation therapy for Taiwanese patients to prevent stroke.[33-37] The population was the largest to date in East Asia, and the results highlighted the importance of racial differences in the era of atrial fibrillation. Importantly, a larger study tried to determine the net effect of using anticoagulants to prevent thromboembolic events for patients with previous intracranial hemorrhage.[38] Moreover, Chang et al. documented an increased risk of stroke in patients with atrial fibrillation not recommended for systemic anticoagulants by the current guidelines.[39] Researchers can be encouraged to conduct further prospective studies focusing on this group.

Post-marketing analysis of medications

Publication of medication information based upon any study, large or small, requires serious evaluation. Safety, efficacy and adverse events should be confirmed by highly reliable evidence. This evidence can be obtained by academic research, which often requires extensive financial support and labor. However, due to the possibility of uncertain results, many pharmacological companies take great risks to execute and publish post-marketing research, especially when the outcomes do not favor their products. Independent individual clinicians are often interested in differences between similar categories of drugs, to facilitate their practice and improve patient care. Some of this information can be derived from the analysis of large databases. For example, the combined form of anti-hypertensive drugs may be superior in clinical outcomes to individual medications, in that despite similar components, the use of the drugs in combination improves patient compliance and convenience.[26,30,40] Such a method could also analyze the real-world effects of some popular categories of medications, for example, novel oral anticoagulants, statins, oral hypoglycemic agents, or even agents used to treat rare diseases.[41-44] Results relating to this kind of analysis would establish a basis for further prospective studies.

Build specific databases

The NHIRD comprises many different categories of personal information, events, and procedures, but lacks the specific examination findings such as hemoglobin, ejection fraction of the left ventricle, or quantification of urine protein. Therefore, not all issues can be researched from such a tool, and establishing databases with specific information is essential. Such databases may have been collected for a certain purpose, or may just consist of daily recordings from clinical practice. The principal problem is determining exactly how comprehensive the included information should be. When these databases were being assembled, not all components are considered essential and thus not gathered. Inadequate collection of clinical data can limit later utility. Clinicians often try to obtain as comprehensive laboratory data as possible, but too labile collections may interfere with the quality. Therefore, "bio-banks" containing samples of blood or tissue may be a novel solution to some of these problems. We collect samples of blood for new biomarkers, and compare them to available clinical information. Occasionally, interesting and useful findings have been derived from this information. Although this method cannot replace controlled prospective trials, it can help to prevent undue expenditure of effort, and provide further direction into areas that require additional research.

Databases originate from a variety of different sources, such as a healthcare center to demonstrate in metabolic syndrome whether highly sensitive C-reactive protein can independently predict arterial stiffness,[45] a heart failure center studying the obesity and mortality paradox,[46,47] a focus on readmission and prognosis,[48] applications of urinary biomarkers,[49] and a cardiovascular surgery center for the diagnosis of aortic dissection.[20] All of these database sources can improve the diagnosis and prognosis of cardiovascular diseases.

LIMITATIONS AND BREAKTHROUGHS OF DATABASES

There are many limitations to the NHIRD. For example, the lack of information about patient lifestyles, personal patient details following decoding, and ultimate mortality due to privacy issues. Correspondingly, the most important database breakthrough should be linked with a laboratory database, and further blood or urine storage samples.

The results of different NHIRD studies, which are based on the same database, are greatly influenced by various exposures, patient selection, matching, statistic methods, and may lead to controversial conclusions. Therefore, we suggest that the characteristics of the targeted patients should be specified. Importantly, the basic study hypothesis should be well studied and considered, not only according to the association, but by means of rational cause-and-effect design.

Large, population-based database inquiries are typically retrospective studies which seek to describe potential associations. The evaluation and investigation which arises from biochemical or molecular samples may offer opportunities to identify disease-causing mechanisms. In addition, appropriate mapping techniques between heterogeneous databases can complement each other.

Other types of databases, such as a climate or air pollution databases can provide various information regarding the environment or natural resources. The spatial and/or temporal models for diseases can be used to predict disease prevalence under specific conditions, and the medical resources can be prepared promptly.

CONCLUSIONS

Analyzing databases is a developing technique with great potential in modern medical research. Similar to all scientific methodology, such database analysis should only be used to test hypotheses with meaningful clinical utilization. However, replication or over explanation of statistical results should be avoided if possible. Under rigorous design study, such database reviews can provide useful information to certain questions, highlight the relationships between components, and provide worthwhile speculation regarding future research.

ACKNOWLEDGEMENT

This work was supported by the National Science Council of Taiwan (Project NMRPG3F0561 and NMRPG 3G6181) and Chang Gung Memorial Hospital (Project CMRPG3E1051). We appreciate Wayne Chu and Yuka Chu's critical reading.

REFERENCES

1. Yen CH, Lai YH, Hung CL, et al. Angiotensin receptor blockades effect on peripheral muscular and central aortic arterial stiffness: a meta-analysis of randomized controlled trials and systematic review. *Acta Cardiol Sin* 2014;30:98-107.
2. Hsu J, Wang CH, Huang SC, et al. Clinical applications of extracorporeal membranous oxygenation: a mini-review. *Acta Cardiol Sin* 2014;30:507-13.
3. Chiang CH, Huang WC, Yang JS, et al. Five-year outcomes after acute myocardial infarction in patients with and without diabetes mellitus in Taiwan, 1996-2005. *Acta Cardiol Sin* 2013;29:387-94.
4. Chiang CH, Liu CJ, Chen PJ, et al. Primary Sjogren's syndrome and the risk of acute myocardial infarction: a nationwide study. *Acta Cardiol Sin* 2013;29:124-31.
5. Chiang CY, Ho CH, Chu CC, et al. Coronary artery complications in pediatric patients with Kawasaki disease: a 12-year national survey. *Acta Cardiol Sin* 2013;29:357-65.
6. Hsu CN, Wang TD. Secular trends in prescription patterns of single-pill combinations of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic for hypertensive patients in Taiwan. *Acta Cardiol Sin* 2013;29:49-55.
7. Liao MT, Lin LY, Yang YH, et al. ACEI and ARB did not reduce the incidence of dementia in patients with atrial fibrillation: a nationwide cohort study. *Acta Cardiol Sin* 2013;29:323-7.
8. Hung CW, Lai CL, Hsieh MY, et al. Endovascular declotting of wall-adherent thrombi in hemodialysis vascular access. *Acta Cardiol Sin* 2014;30:128-35.
9. Lai CC, Yip HK, Lin TH, et al. Drug-eluting stents versus bare-metal stents in Taiwanese patients with acute coronary syndrome: an outcome report of a multicenter registry. *Acta Cardiol Sin* 2014;30:553-64.
10. Yang HY, Huang JH, Lin YK, et al. Bipolar disorder and schizophrenia present different risks of atrial fibrillation: a nationwide population-based analysis. *Acta Cardiol Sin* 2014;30:46-52.
11. Ko RC, Liao MT, Lin L, et al. Feasibility and safety of coronary procedures via an arteriovenous graft approach in patients on maintenance hemodialysis. *Acta Cardiol Sin* 2015;31:550-6.
12. Lai CC, Chang KC, Liao PC, et al. Effects of door-to-balloon times on outcomes in Taiwanese patients receiving primary percutaneous coronary intervention: a report of Taiwan acute coronary syndrome full spectrum registry. *Acta Cardiol Sin* 2015;31:215-25.
13. Hsieh MY, Lin L, Chen TY, et al. Pulmonary hypertension in hemodialysis patients following repeated endovascular thrombectomy. *Acta Cardiol Sin* 2016;32:299-306.
14. Jhuo SJ, Tsai WC, Lin TH, et al. Statin dose and the risk of intracerebral hemorrhage: a population-based longitudinal study in Taiwan. *Acta Cardiol Sin* 2016;32:23-30.
15. Lee HH, Lee WH, Chiu CA, et al. The current status of performing

left ventriculography in Taiwan. *Acta Cardiol Sin* 2016;32:49-54.
16. Lin YS, Tang CH, Yang CY, et al. Effect of pre-eclampsia-eclampsia on major cardiovascular events among peripartum women in Taiwan. *Am J Cardiol* 2011;107:325-30.
17. Tang CH, Wu CS, Lee TH, et al. Preeclampsia-eclampsia and the risk of stroke among peripartum in Taiwan. *Stroke* 2009;40: 1162-8.
18. Wu LS, Tang CH, Lin YS, et al. Major adverse cardiovascular events and mortality in systemic lupus erythematosus patients after successful delivery: a population-based study. *Am J Med Sci* 2014;347:42-9.
19. Lin YS, Liu PH, Wu LS, et al. Major adverse cardiovascular events in adult congenital heart disease: a population-based follow-up study from Taiwan. *BMC Cardiovasc Disord* 2014;14:38.
20. Tsai HS, Tsai FC, Chen YC, et al. Impact of acute kidney injury on one-year survival after surgery for aortic dissection. *Ann Thorac Surg* 2012;94:1407-12.
21. Chen SW, Chang CH, Lin YS, et al. Effect of dialysis dependence and duration on post-coronary artery bypass grafting outcomes in patients with chronic kidney disease: a nationwide cohort study in Asia. *Int J Cardiol* 2016;223:65-71.
22. Chen SW, Chang CH, Chu PH, et al. Risk factor analysis of postoperative acute respiratory distress syndrome in valvular heart surgery. *J Crit Care* 2016;31:139-43.
23. Tsai HS, Chen YC, Chu PH. The influence of acute kidney injury on acute cardiovascular disease. *Acta Cardiol Sin* 2014;30:93-7.
24. Chen PC, Tung YC, Wu PW, et al. Dental procedures and the risk of infective endocarditis. *Medicine (Baltimore)* 2015;94:e1826.
25. Chou SH, Tung YC, Lin YS, et al. Major adverse cardiovascular events in treated periodontitis: a population-based follow-up study from Taiwan. *PLoS One* 2015;10:e0130807.
26. Hsiao FC, Tung YC, Chou SH, et al. Fixed-dose combinations of renin-angiotensin system inhibitors and calcium channel blockers in the treatment of hypertension: a comparison of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors. *Medicine (Baltimore)* 2015;94:e2355.
27. Chen ZY, Chiang CH, Huang CC, et al. The association of tooth scaling and decreased cardiovascular disease: a nationwide population-based study. *The American Journal of Medicine* 2012;125:568-75.
28. Chen SJ, Liu CJ, Chao TF, et al. Dental scaling and atrial fibrillation: a nationwide cohort study. *Int J Cardiol* 2013;168:2300-3.
29. Chen SJ, Liu CJ, Chao TF, et al. Dental scaling and risk reduction in infective endocarditis: a nationwide population-based case-control study. *The Canadian Journal of Cardiology* 2013;29:429-33.
30. Liu KL, Ye LL, Chou SH, et al. Erectile dysfunction is not a predictor of atrial fibrillation: a population-based propensity-score matched cohort study. *J Sex Med* 2016;13:55-62.
31. Lin YS, Liu PH, Lin SW, et al. Simple obstructive sleep apnea patients without hypertension or diabetes accelerate kidney dysfunction: a population follow-up cohort study from Taiwan. *Sleep Breath* 2016.
32. Li CY, Lin CP, Lin YS, et al. Newly diagnosed atrial fibrillation is an independent factor for future major adverse cardiovascular events. *PLoS One* 2015;10:e0123211.
33. Chao TF, Liu CJ, Wang KL, et al. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. *Journal of the American College of Cardiology* 2014;64:1658-65.
34. Chao TF, Liu CJ, Wang KL, et al. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? *Journal of the American College of Cardiology* 2015;65:635-42.
35. Chao TF, Wang KL, Liu CJ, et al. Age threshold for increased stroke risk among patients with atrial fibrillation: a nationwide cohort study from Taiwan. *Journal of the American College of Cardiology* 2015;66:1339-47.
36. Chao TF, Lip GY, Liu CJ, et al. Validation of a modified CHA2DS2-VASc score for stroke risk stratification in Asian patients with atrial fibrillation: a nationwide cohort study. *Stroke* 2016;47: 2462-9.
37. Chao TF, Liu CJ, Tuan TC, et al. Comparisons of CHADS2 and CHA2DS2-VASc scores for stroke risk stratification in atrial fibrillation: which scoring system should be used for Asians? *Heart Rhythm* 2016;13:46-53.
38. Chao TF, Liu CJ, Liao JN, et al. Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage. *Circulation* 2016;133:1540-7.
39. Chang KC, Wang YC, Ko PY, et al. Increased risk of first-ever stroke in younger patients with atrial fibrillation not recommended for antithrombotic therapy by current guidelines: a population-based study in an East Asian cohort of 22 million people. *Mayo Clinic Proceedings* 2014;89:1487-97.
40. Tung YC, Lin YS, Wu LS, et al. Clinical outcomes and healthcare costs in hypertensive patients treated with a fixed-dose combination of amlodipine/valsartan. *J Clin Hypertens (Greenwich)* 2015;17:51-8.
41. Wang KL, Liu CJ, Chao TF, et al. Statins, risk of diabetes, and implications on outcomes in the general population. *J Am Coll Cardiol* 2012;60:1231-8.
42. Wang KL, Liu CJ, Chao TF, et al. Risk of new-onset diabetes mellitus versus reduction in cardiovascular events with statin therapy. *The American Journal of Cardiology* 2014;113:631-6.
43. Wang KL, Liu CJ, Chao TF, et al. Sitagliptin and the risk of hospitalization for heart failure: a population-based study. *International Journal of Cardiology* 2014;177:86-90.
44. Chan YH, Yen KC, See LC, et al. Cardiovascular, bleeding, and mortality risks of dabigatran in Asians with nonvalvular atrial fibrillation. *Stroke* 2016;47:441-9.
45. Tsai SS, Lin YS, Lin CP, et al. Metabolic syndrome-associated risk factors and high-sensitivity C-reactive protein independently predict arterial stiffness in 9903 subjects with and without chronic kidney disease. *Medicine (Baltimore)* 2015;94:e1419.
46. Lin GM, Li YH, Yin WH, et al. The obesity-mortality paradox in patients with heart failure in Taiwan and a collaborative meta-analysis for East Asian patients. *Am J Cardiol* 2016;118:1011-8.

47. Wang CC, Chang HY, Yin WH, et al. TSOC-HFrEF registry: a registry of hospitalized patients with decompensated systolic heart failure: description of population and management. *Acta Cardiol Sin* 2016;32:400-11.
48. Tung YC, Chou SH, Liu KL, et al. Worse prognosis in heart failure patients with 30-day readmission. *Acta Cardiol Sin* 2016;32:698-707.
49. Yang CH, Chang CH, Chen TH, et al. Combination of urinary biomarkers improves early detection of acute kidney injury in patients with heart failure. *Circ J* 2016;80:1017-23.