ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6): 495 - 499
http://www.simm.ac.cn; www.chinainfo.gov.cn/periodical

Recurrent events in meta-analysis of multiple clinical trials

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KEY WORDS meta-analysis; clinical trials; angiotensin-converting; enzyme inhibitors; hospitalization; congestive heart failure

ABSTRACT

AIM: To study the efficacy and safety of drug or therapy with recurrent events in meta-analysis of multiple clinical trials. **METHODS**: A nonparametric approach is proposed to estimate the rates of recurrent events for meta-analysis of trails. The method was used in meta-analysis of angiotensin-converting enzyme (ACE) inhibitor clinical trials to analyze the relative rates and the excess rates between ACE inhibitor and placebo treatment groups for endpoints of hospitalizations for CHF, hospitalizations for CHF or cardiac death, and hospitalizations for CHF or any death, respectively. **RESULTS**: The estimates of those three endpoints were 69 %, 74 %, and 76 % ($P < 0.01$). Compared with placebo, ACE inhibitor reduced 30 cases of hospitalizations for CHF per 1000 person-years, or 40 cardiac deaths or hospitalizations for CHF per 1000 person-years ($P < 0.01$). **CONCLUSION**: The method was a simple and efficient approach to conduct meta-analysis of clinical trials with recurrent events.

INTRODUCTION

Rates of recurrent events such as anginas, reinfarctions, and hospital admissions for worsening cardiac diseases were often concerned by cardiologists[1]. In analysis of clinical trials, comparing these recurrent clinic events across treatment groups was important to evaluate the efficacy and safety of a studying agent or therapy.

In individual trials few patients may experience important outcomes such as hospitalizations for worsening congestion heart failure (CHF). Treatment related to these rare recurrent events was difficult to assess. Meta-analysis of clinical trials may obtain sufficient statistical power to compare those recurrent events across different treatment groups in specific subsets of patients (eg, young cardiac disease patients). However, usual approaches for meta-analysis of non-recurrent event might not be applicable to a recurrent event[2,3].

Usually three approaches were used to combine data from multiple trials to effectively increase study sample size. The first one was to analysis published trial reports. The second one was to analysis data provided in tabulate forms, and the third one was to analysis data of individual patients. Published trial reports or tabulated trial reports might not contain detail information of individual patients such as the dates of hospital admissions, although it might include the number of hospitalizations. Even in analysis of data of individual patients of multiple trials, the dates of recurring of a repeatable clinic event might not be available for all studies because some trials might not collect it or the protocol of meta-analysis might not require it. Thus, survival analysis techniques could not be applicable, and the evaluation of the rates of recurrent clinic events turns to be interested in meta-analysis of multiple trials.

Several methods for estimating the rate of a recurrent event were reported[4-7]. Approaches based on Poisson and negative binomial distributions were suggested by Whitehead *et al*[4], Lawless *et al*[5], Glynn *et al*[6], and Stukel *et al*[7] to analyze rates of recurrent events in clinical trials and epidemiology studies. For meta-analysis of clinical trials, Whitehead *et al*[3] presented a general parametric approach in

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Received 1998-04-13 Revised 1999-01-25

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

which the fixed effects and random effects of model for treatments were considered.

In this article, we extended the approach of Stukel *et al*[7] to clinical trials in which the correlation between treatment groups was concerned. The relative rate and excess rate based on the crude rate were used in meta-analysis of multiple trials, and the approach of Whitehead *et al*[3] was used to obtain overall estimates in meta-analysis. The motivation of our approach was to analyze the data of multiple hospitalizations for CHF in meta-analysis of data of angiotensin-converting enzyme (ACE) inhibitor clinical trials. The data collected from three trials included the number of multiple hospitalizations due to CHF for individual patients.

Trials of the ACE inhibitors for the treatment of myocardial infarction Recently several large randomized controlled trials had been conducted to examine the effects of a different class of therapeutic agents, the ACE inhibitors, for the treatment of patients with left ventricular dysfunction on these patients at high risk (based on measures of left ventricular dysfunction) after myocardial infarction (MI). Altogether, these trials had collected information on the effects of ACE inhibitors during and after MI on a total of more than 100 000 patients randomized in different trials. Overall the results of these trials have indicated that ACE inhibitors were beneficial for patients both in the acute phase of myocardial infarction and in long term use of ACE inhibitors. However, different designs of the trials, different drug regimens, and varying results raised doubt as to how to use these treatments most effectively. Since myocardial infarction was a major cause of mortality and morbidity, it was important to ensure that available treatments were used in the most effective manner. To help resolve issues related to the long term management of patients after MI, we were conducting a systematic overview or meta-analysis of individual patient data from the five trials of long term use of ACE inhibitors. In total data of 12 783 patients on 88 variables were collected. In meta-analysis, the number of hospitalizations for CHF was one variable to be analyzed.

STATISTICAL METHODS

Rate of recurrent event The occurrences of a recurrent event could happen at different time period during the course of a clinical trial. Usually it was assumed that the repeated times of a recurrent event followed a Poisson distribution with extra-Poisson variability[9], which indicated that the recurring of the event depended on the event rate and the follow-up time in the trial.

The measurement of person-years includes the effects of both the number of patients involved in the trial and the follow-up time spent in the trial. Following Stukel *et al* we defined the rate as the number of the events divided by person-years.

Let d_{ik} denote the sum of the recurrent event under consideration for the ith patient in the kth treatment group, and n_{ik} denote the length of follow-up for this individual, where $i = 1, 2, \ldots, m_k$, $k = 1, \ldots, K$. Following Stukel *et al*[3], we assumed that d_{ik} was a random variable with mean $n_{ik}\,\mu k$ and variance $n_{ik}\sigma^2 k$, where μk and $\sigma^2 k$ were the mean and variance of the event rate for individual in the kth treatment group, and d_{ik}'s were independent. Let $R_k = D_k/N_k$ denote the crude event rate in the kth treatment group, where $D_k = \sum_i d_{ik}$ was the sum of all outcomes to patients in the kth treatment group (for example, total hospital admissions for CHF), and $N_k = \sum_j n_{ik}$ was the total person-years of follow-up in the kth group. Stukel *et al* used an unbiased empirical sample variance $R_k = \sum_{i=1}^{mk} n_{ik}(d_{ik}/n_{ik} - R_k)^2/[N_k(m_k - 1)]$ conditioning on the known follow-up time n_{ik}. In clinical trials, patients were randomized into treatment groups so that the baseline characters of these patients were similar between groups. Thus we introduced an empirical sample covariance formula $cov(R_A, R_B) = \sum_{i=1}^{miA}\sum_{j=1}^{miB} n_{iA}n_{jB}(d_{iA}/n_{iA}-R_A)(d_{iB}/n_{iB}-R_B)/((m_A-1)(m_B-1)N_A N_B)$ to estimate the correlation between crude event rates R_A and R_B. It was straightforward to show that it was an unbiased estimate conditioning on known follow-up times n_{iA} and n_{jB}.

Evaluate the rates of recurrent events between treatment groups To evaluate the difference in the event rates between treatment group A and B, we used the log relative rate $\phi_{RR} = \log(R_A/R_B)$ and the excess rate $\phi_{ER} = \log(R_A) - \log(R_B)$ measurements. The estimate of the variance of the log relative rate was $var(\phi_{ER}) = var(R_A) + var(R_B) - 2cov(R_A, R_B)$, and the estimate of the variance of the log relative rate was $var(\phi_{RR}) = var(R_A/R_A^2) + var$

$(R_B/R_B^2) - 2cov(R_A, R_B)/(R_A R_B)$. The 95 % confidence intervals of the excess rate and the relative rate were $\phi_{ER} \pm 1.96[var(\phi_{ER})]^{1/2}$ and $\exp\{\phi_{ER} \pm 1.96[var(\phi_{ER})]^{1/2}\}$, respectively.

Meta-analysis of excess and relative rates of multiple trials It was straightforward to show that when the person-years were large then both the excess and the log relative rates would follow normal distributions. Thus we could use approach of Whitehead *et al* to estimate the overall rate of recurrent event for multiple trials. Specifically for the ith trial, let θ_i and v_i be the measurement of the difference of rates of recurrent events between two treatment groups (eg relative rate), and the inverse of the variance of θ_i, respectively. The estimate of overall θ was $\sum_i v_i\theta_i/\sum_i v_i$. A χ^2 *test* $Q = \sum_i v_i(\theta_i-\theta)^2$ was used to check whether the estimates θ_i's were homogeneous across trials. If there was no heterogeneity across trials, the estimate of the variance of overall effect θ was $var(\theta) = 1/\sum_i v_i$. If there was no homogeneity among trials, the estimate of the variance was $var(\theta) = 1/\sum_i \kappa_i$ and the estimate of overall effect was changed to $\theta = \sum_i \kappa_i \theta_i/\sum_i \kappa_i$, where $\kappa_i = (1/v_i + \lambda^2)^{-1}$ and $\lambda^2 = (Q - k + 1)/(\sum_i \kappa_i - \sum_i \kappa_i^2/\sum_i \kappa_i)$. ($k$ denotes the number of trials).

Evaluate rates of multiple hospitalizations for CHF in meta-analysis of ACE inhibitor clinic trials In meta-analysis of ACE inhibitor trials, the number of hospital admissions due to CHF for each patient was collected but not the dates of the admissions. The multiple hospitalizations due to CHF was associated with the length of time period a patient spent in the trial. Therefore the person-years instead of number of patients was an appropriate measurement for the rates of multiple hospitalizations. The proposed approach was used to analyze the excess and the relative rates between ACE inhibitor treatment group and placebo group, for endpoints of hospitalizations for CHF, hospitalizations for CHF or cardiac death, and hospitalizations for CHF and any death, respectively. Data of three ACE inhibitor trials of SAVE study, SOLVD treatment and SOLVD prevention studies were analyzed. In ACE inhibitor group, number of patients and person-years were 4 511 and 12 739, respectively. In placebo group, these two numbers were 4 517 and 12 386, respectively.

The analysis results on relative rate (RR) and excess rate (ER) were tabulated in Tab 1, 2, and 3 with respect to three endpoints of multiple hospitalizations for CHF, cardiac death plus multiple hospitalizations for CHF, and any death plus multiple

Tab 1. Relative rate and excess rate of multiple hospitalizations for CHF of ACE inhibitor arm *vs* placebo arm.

	SOLVD treatment	SOLVD prevention	Save	Meta-analysis
ACE inhibitor				
Event	694	306	303	1 303
Patient	1 285	2 111	1 115	4 511
Person-years	3 543	6 056	3 140	12 739
Placebo				
Event	974	454	336	1 764
Patient	1 284	2 117	1 116	4 517
Person-years	3 365	5 967	3 054	12 386
Relative rate				
RR	0.68	0.66	0.88	0.69
95 % CI	(0.55, 0.84)	(0.52, 0.85)	(0.57, 1.36)	(0.60, 0.81)
Excess rate				
RR	9.36	2.56	1.35	2.97
95 % CI	(4.32, 14.4)	(1.02, 4.10)	(-3.2, 5.96)	(1.57, 4.37)

Tab 2. Relative rate and excess rate of cardiac death + multiple hospitalizations for CHF of ACE inhibitor arm *vs* placebo arm.

	SOLVD treatment	SOLVD prevention	Save	Meta-analysis
ACE inhibitor				
Event	1 072	551	484	2 107
Patient	1 285	2 111	1 115	4 511
Person-years	3 543	6 056	3 140	12 739
Placebo				
Event	1 414	727	566	2 707
Patient	1 284	2 117	1 116	4 517
Person-years	3 365	5 967	3 054	12 386
Relative rate				
RR	0.72	0.75	0.83	0.74
95 % CI	(0.58, 0.89)	(0.58, 0.97)	(0.47, 1.47)	(0.63, 0.87)
Excess rate				
RR	11.8	3.09	3.12	3.97
95 % CI	(4.03, 19.5)	(0.38, 5.79)	(-6.7, 12.9)	(1.50, 6.45)

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6)
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Tab 3. Relative rate and excess rate of any death + multiple hospitalizations for CHF of ACE inhibitor arm *vs* placebo arm.

	SOLVD treatment	SOLVD prevention	Save	Meta-analysis
ACE inhibitor				
Event	1 146	619	531	2 296
Patient	1 285	2 111	1 115	4 511
Person-years	3 543	6 056	3 140	12 739
Placebo				
Event	1 484	788	611	2 883
Patient	1 284	2 117	1 116	4 517
Person-years	3 365	5 967	3 054	12 386
Relative rate				
RR	0.73	0.66	0.88	0.76
95 % CI	(0.60, 0.90)	(0.52, 0.85)	(0.57, 1.36)	(0.65, 0.88)
Excess rate				
RR	11.8	2.98	3.10	3.92
95 % CI	(3.92, 19.6)	(0.19, 5.78)	(-6.9, 13.1)	(1.37, 6.46)

hospitalzations for CHF, respectively. The meta-analysis of relative rate showed that, comparing ACE inhibitor group with placebo group, the relative rate of hospitalizations for CHF, the relative rate of hospitalizations for CHF or cardiac death, and the relative rate of hospitalizations for CHF or and death were 69 %, 74 %, and 76 % respectively ($P < 0.01$). It indicated that the ACE inhibitor increased the survival time of patients with cardiac diseases, and reduced the number of recurring of worsening CHF. The meta-analysis of excess rate showed that, compared with placebo, ACE inhibitor reduced 30 cases of hospitalizations for CHF per 1000 person-years, or 40 cardiac deaths/hospitalizations for CHF per 1000 person-years ($P < 0.01$).

DISCUSSION

In this article, we presented an approach for analyzing rates of recurrent events in meta-analysis of clinical trials. The length of subjects staying in the trials, which determined the number of recurrence of events and would be very different across trials, was taken into account in meta-analysis by measuring person-years. The recurrent events were evaluated by ratio between treatment, which was easy to interpret and to calculate. The method provided a simple and reliable approach to analysis the recurrent-events data such as the number of multiple hospital admissions in meta-analysis of clinical trials. The method took account of both the heterogeneity of event rates between individual patients within a trial, and the heterogeneity in the protocol of studies across multiple trials. The method was used in meta-analyze multiple clinical trials for evaluating the effect of ACE inhibitor on multiple hospital admissions due to CHF. The analysis results showed that the efficacy of ACE inhibitor on the relative rates of hospitalizations for worsening CHF was consistent with these found in individual trials.

As Glynn *et al*[6] and Stukel *et al*[7] pointed out, model-based approaches would be more efficient if the models were correct since it provided approximately maximal likelihood estimates (Their studies indicated a 30 % gain in efficiency). However, a model-based approach does not allow as much flexibility in the relationship between the variance and mean as the proposed approach, and its gain in the efficiency would be lost if the assumption of the model was incorrect. From such a point of view the proposed approach may be considered as a robust method. On the other hand, implementation of model-based approach was considerable more complicated and computational more intensive since special software is required. By contrast, the proposed approach was computational simple and was easy to implement in any statistical package that produced weighted means and variances. Thus, the method is useful, in meta-analysis of multiple clinical trials, for analyzing recurrent events.

REFERENCES

1 Yusuf S, Pepine CJ, Garces C, Pouleur H, Salem D, Kostis J, *et al*.
Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions.
Lancet 1992; 340: 1173-8.

2 Yusuf S, Peto R, Lewis J, Collins R, Sleight P.
Beta blockade during and after myocardial infarction: an overview of the randomized trials.
Prog Cardiovasc Dis 1985; 27: 335-71.

3 Whitehead A, Whitehead J.
A general parametric approach to the meta-analysis of randomized clinical trials.

Stat Med 1991; 10: 1665-77.

4 Whitehead J. The design and analysis of sequential clinical trials. 2nd ed.
Chichester: Ellis Horwood; 1991. p 215-45.

5 Lawless JF.
Negative binomial and mix Poisson regression.
Can J Stat 1987; 15: 209-25.

6 Glynn RJ, Stukel TA, Sharp SM, Bubolz TA, Freeman JL, Fisher ES.
Estimating the variance of standardized rates of recurrent events, with application to hospitalizations among the elderly in New England.
Am J Epidemiol 1993; 137: 776-86.

7 Stukel TA, Glynn RJ, Fisher ES, Sharp SM, Yao GL, Wennberg JE.
Standardized rates of recurrent outcomes.
Stat Med 1994; 13: 1781-91.

8 Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, *et al*.
Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators.
N Engl J Med 1992; 327: 669-77.

9 Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. The SOLVD Investigators.
N Engl J Med 1992; 327: 685-91.

10 Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. The SOLVD Investigators.
N Engl J Med 1991; 325: 293-302.

荟萃分析对多样本临床试验结果重现率分析

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关键词 荟萃分析; 临床试验; 血管紧张素转换酶抑制剂类; 住院; 充血性心力衰竭

目的: 探讨应用多样本临床试验荟萃分析进行药物和治疗方案有效性和安全性研究. **方法**: 本文采用荟萃分析, 一种非参数方法, 评价临床试验结果的重现率, 用于对充血性心脏衰竭(CHF), CHF 伴心性死亡, CHF 伴其他原因死亡病例, 对给予血管紧张素转化酶抑制剂(ACE)治疗组和给安慰剂组各自的相对率和超常率的分析. **结果**: 三组试验最后的结果分别为69 %、74 %、76 %、$P < 0.01$, 与给安慰剂组比较, ACE 治疗组减少 30/(1000 人·年), CHF 伴心性死亡组减少 40/(1000 人·年), $P < 0.01$. **结论**: 荟萃分析法是分析临床试验结果重现率的一种简单而有效的方法.

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