Cardiology Research and Practice

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Lead Guest Editor: Rajesh Tota-Maharaj
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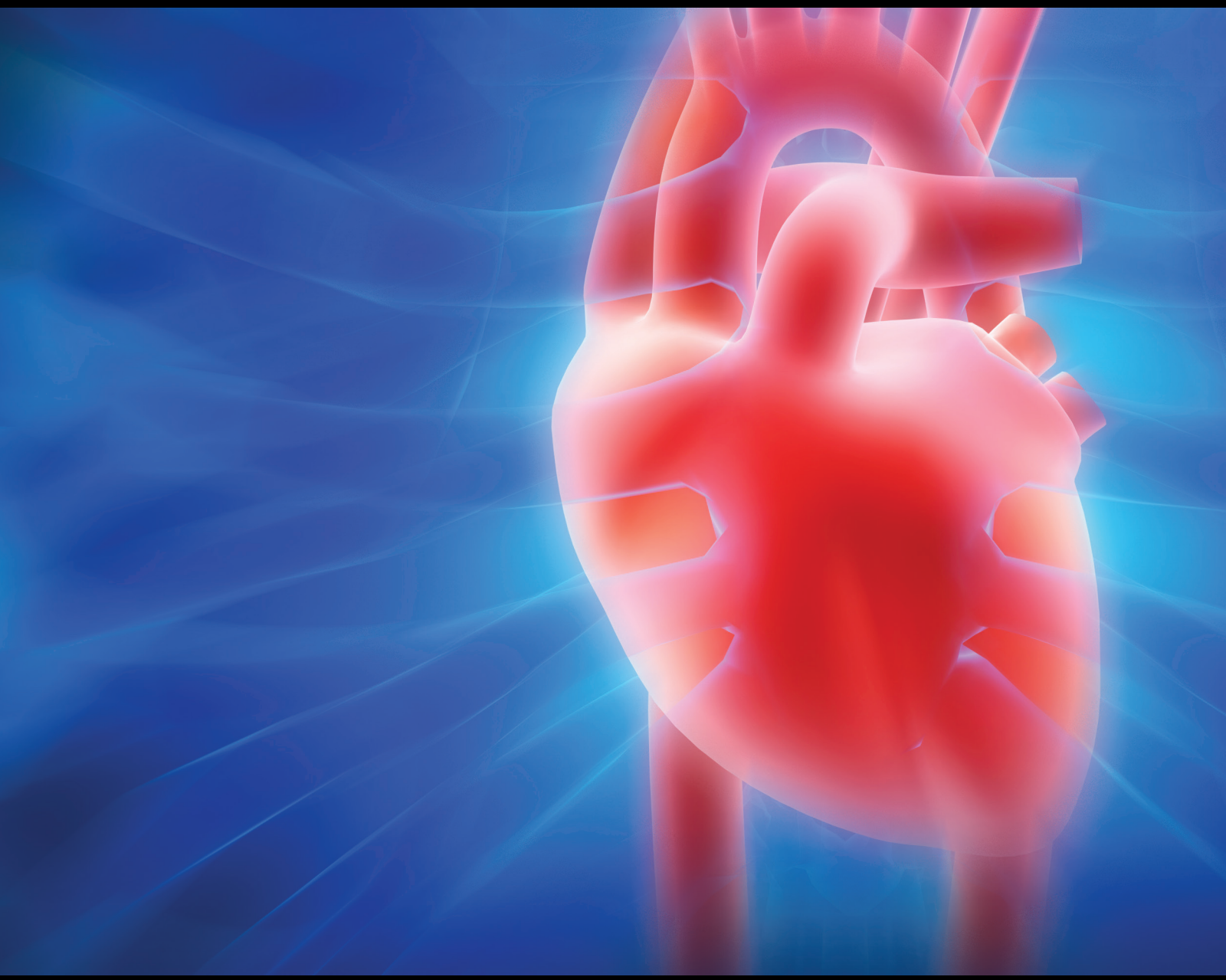

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Editorial Board

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Hindawi
Cardiology Research and Practice
Volume 2019, Article ID 1840894, 11 pages
https://doi.org/10.1155/2019/1840894

Review Article

Cost-Effectiveness of Cardiac Rehabilitation in Patients with Coronary Artery Disease: A Meta-Analysis

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Received 1 February 2019; Accepted 7 May 2019; Published 4 June 2019

Guest Editor: Rajesh Tota-Maharaj

Background. Medical costs associated with cardiovascular disease are increasing considerably worldwide; therefore, an efficacious, cost-effective therapy which allows the effective use of medical resources is vital. There have been few economic evaluations of cardiac rehabilitation (CR), especially meta-analyses of medical cost versus patient outcome. *Methods*. The target population in this meta-analysis included convalescent and comprehensive CR patients with coronary artery disease (CAD), the status most commonly observed postmyocardial infarction (MI). Here, we evaluated medical costs, quality-adjusted life year (QALY), cost-effectiveness, mortality, and life year (LY). Regarding cost-effectiveness analysis, we analyzed medical costs per QALY, medical costs per LY, and the incremental cost-utility ratio (ICUR). We then examined the differences in effects for the 2 treatment arms (CR vs. usual care (UC)) using the risk ratio (RR) and standardized mean difference (SMD). *Results*. We reviewed 59 studies and identified 5 studies that matched our selection criteria. In total, 122,485 patients were included in the analysis. Meta-analysis results revealed that the CR arm significantly improved QALY (SMD: −1.78; 95% confidence interval (CI): −2.69, −0.87) compared with UC. Although medical costs tended to be higher in the CR arm compared to the UC arm (SMD: 0.02; 95% CI: −0.08, 0.13), cost/QALY was significantly improved in the CR arm compared with the UC arm (SMD: −0.31; 95% CI: −0.53, −0.09). The ICURs for the studies (4 RCTs and 1 model analysis) were as follows: −48,327.6 USD/QALY; −5,193.8 USD/QALY (dominant, CR is cheaper and more effective than UC); and 4,048.0 USD/QALY, 17,209.4 USD/QALY, and 26,888.7 USD/QALY (<50,000 USD/QALY, CR is costlier but more effective than UC), respectively. Therefore, there were 2 dominant and 3 effective results. *Conclusions*. While there are some limitations, primarily regarding data sources, our results suggest that CR is potentially cost-effective.

1. Introduction

Healthcare resources are growing increasingly sparse in advanced nations due to declining birth rates, aging populations, and weakening of the underlying economic foundations. Annual national health expenditures showed a 1.3-fold increase in the ratio of financial burden to gross domestic product (GDP) from 2015 to 2017 compared with that from 1985 to 1989 in both the Organisation for Economic Co-operation and Development (OECD) and G20 countries [1]. The continuation of public health insurance systems in advanced nations will require vigilant use of cost-effective medical technology. Coronary artery disease (CAD) has attracted considerable social attention because of its relatively high-associated medical costs.

The American Heart Association (AHA), American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), and European Association of Cardiovascular Prevention and Rehabilitation (EACPR) [2, 3] currently recommend convalescent cardiac rehabilitation (CR) as the standard of care for patients with cardiovascular disease. CR has been proven to improve exercise capacity and quality of life (QOL) and reduce cardiovascular death and total mortality in patients with CAD [4].

Several meta-analyses have reported the beneficial clinical effects of CR by mainly investigating QOL improvements by exercise therapy, or comparisons with other interventions in patients with CAD and chronic heart failure [5, 6]. Regarding economic evaluation, cost-effectiveness of CR in different settings has been previously reported [7, 8].

To our knowledge, no previous meta-analysis has focused on patient utility values as patient-reported outcomes (PROs), in addition to cost-effectiveness analysis. While CR can be beneficial in preventing cardiovascular death and improving patients' QOL, it consumes medical resources. Therefore, the objective of this meta-analysis was to evaluate the cost-effectiveness of CR from the healthcare-payer perspective.

2. Methods

2.1. Target Technology and Population. The target population in this study was patients with CAD (mainly acute coronary syndrome (ACS) including acute MI (AMI)), who were undergoing convalescent and comprehensive CR.

CR was defined as prescribed exercises which were performed under safe conditions, with or without supervision as an inpatient, outpatient, or at home, with the goal of establishing a healthier physical condition by improving exercise capacity and reducing arteriosclerosis risk factors. Since the physical condition and degree of interest (enthusiasm for health) varies widely among patients, the exercise prescription differed depending on the purpose and patient characteristics. The exercise had 5 components: (1) type of exercise, (2) exercise intensity, (3) duration of exercise, (4) frequency of exercise, and (5) represcription due to an increase in physical activity. A CR which includes exercise therapy, patient education, and psychological or lifestyle guidance is called "comprehensive CR" [9]. The comprehensive CR in this meta-analysis was in accordance with the AHA Scientific Statement [2].

The control group of this meta-analysis included patients who were undergoing usual care (UC) with medication and lifestyle guidance only and not including those with an exercise prescription.

2.2. Systematic Review. We conducted an electric literature search in May 2015 (updated August 2016) and performed a comprehensive review of the literature using MEDLINE and EMBASE.

We used the keywords "cardiac rehabilitation" and "exercise training" for the parameters of rehabilitation and the keywords "cost-effectiveness," "cost-benefit," "cost-utility," and "economic evaluation" for economic parameters. In general, CR is indicated when a patient's status is post-AMI or open-heart surgery and in patients with angina pectoris, great vessel disease, chronic heart failure, or peripheral arterial disease. In this meta-analysis, we targeted MI, as there are many publications with substantial evidence in this regard.

We selected randomized controlled trials (RCTs) and systematic reviews as we considered these to represent high levels of evidence. Since the number of publications was not large in this area, we incorporated a model analysis if sensitivity analysis was conducted to evaluate the robustness of the result.

We limited our search to English-language publications and searched for the period from 1990 to 2016. After titles and abstracts were reviewed, we extracted papers that compared CR with UC. Medical costs, quality-adjusted life years (QALYs), cost-effectiveness, mortality, and life year (LY) were used as the evaluation parameters in this meta-analysis. Since most study periods were <2 years, in accordance with the analysis method of the previous study, we did not perform a discount for either cost or utility. We did not exclude a study based on the number of samples.

2.3. Medical Costs and Treatment Efficacy. Costs associated with CR, testing, diagnosis, and treatment during the observation period, were extracted from each study (Supplementary Material Table 1). Expense items related to CR included room rent, equipment, and staff costs. Coronary angiography, echocardiography, Holter monitoring, exercise tests, electrocardiogram, blood tests, and chest X-rays were included as methods of testing and diagnosis during the observation period. We did not include patient out-of-pocket costs in this analysis (i.e., travel costs, cost for equipment purchased to participate in the CR program, and childcare cost). Healthcare system differs between countries, and we could not obtain information regarding how the CR cost was covered in each country.

We converted the unit of cost to United States Dollar (USD) using the annual average exchange rate in the published year of each study. When the study did not report the standard deviation (SD) of cost, in accordance with Furukawa's method recommended in the Cochrane Handbook, we imputed values presented in the report by Fitzgerald et al. [10]. As the SD of cost was twice the mean value in the report, we set the SD as twice the mean value.

QALY is used as an indicator of patient outcome when performing an economic evaluation. Here, we used QALY as a measure of efficacy. Rather than simply representing the extension of the survival period, QALY is obtained by weighting with the utility value that contains QOL. If QALY is used as the evaluation index, both survival (quantitative profit) and QOL (qualitative benefit) can be evaluated at the same time. Utility values are measured on a scale of 0 to 1, where 0 represents death and 1 represents perfect health (Supplementary Material Figure 1). Direct and indirect

methods can be used to evaluate utility. The direct method involves asking patients to estimate their QOL value relative to their health condition, whereas the indirect method involves calculating utility values using a scoring algorithm from the answers obtained from the QOL questionnaire. The most commonly used direct methods are the standard gamble (SG) and the time-trade-off (TTO); the most common indirect methods are the EuroQol-5 dimension (EQ-5D) and Health Utilities Index (HUI) [11].

When a study did not report the SD of a utility value, in accordance with the Cochrane Handbook, we used sample size, 95% confidence interval (CI), or standard error to calculate the SD [12].

The TTO was used to measure patient utility in the study of Oldridge et al. [13]. As the SD was not reported in their study, we calculated the SD using the following formula:

$$\text{standard error (SE)} \times \sqrt{N}. \quad (1)$$

The TTO was also used in the report by Yu et al. [14]. As this study included several phases, we added the values of all phases together and calculated the SD in a similar manner. The study by Briffa et al. [15] used the Utility-Based Quality of Life-Heart (UBQ-H) questionnaire [16], which includes TTO. As the SD was not included in that report, we calculated SD as follows:

$$\frac{\sqrt{N} \times (\text{upper limit} - \text{lower limit of 95\% CI})}{3.92}. \quad (2)$$

Using the EuroQol-5 dimension questionnaire level 3 (EQ-5D-3L), Leggett et al. [17] calculated scores in the CR and UC arms of 9.77 and 9.70, respectively. As these were the results of model analysis, we imputed the mean and SD in the UC arm for meta-analysis using the report by Fitzgerald et al. [10]. As the difference between CR participants and controls reported by Leggett et al. was 0.07, we set the mean in the CR arm by adding the difference to the mean in the UC arm. As the SD of QALY was one-third the mean value in the report by Fitzgerald et al. [10], we set the SD of QALY in the CR arm as one-third the mean values. Hautala et al. [18] calculated CR and UC arm scores of 0.013 and −0.012, respectively, using the 15D questionnaire, a generic, comprehensive, 15-dimensional, and self-administered measure of health-related quality of life among adults that can be used both as a profile and single index score measurement [19]. As the SD of QALY was not described in the studies by Leggett et al. and Hautala et al., we set the SD of QALY of both arms as one-third the mean values, as reported by Fitzgerald et al. [10].

We used the difference from baseline as the standardized index in the meta-analysis of patient utility.

To ensure consistency with previous studies, we conducted meta-analyses of mortality and LY by using the literature which was collected as described in the systematic review section.

The definition of LY differs according to published reports [20, 21]. We defined LY as an evaluation index indicating the extension in years of life that is expected during the observation period. We calculated LY by subtracting the number of people who died from the number in each arm and dividing it by the same number in each arm. The SD of LY was calculated as 1-LY.

2.4. Cost-Effectiveness. As cost-utility analysis does not reveal the degree of cost reduction of CR over that of UC, we analyzed the medical costs per QALY, per LY, and the incremental cost-utility ratio (ICUR) to evaluate cost-effectiveness.

We calculated the medical cost per QALY by dividing the costs by the QALY. We assumed the SD of cost-effectiveness by applying the error propagation [22, 23] to both cost and utility. To avoid using negative values, we adjusted it to the absolute value where needed. We calculated the medical cost per LY by dividing the costs by LY. The SD for this was calculated as above.

We measured ICUR as the ratio of medical costs to the utility value, which estimates the cost per unit of the utility that was incurred by switching to a different treatment, and is represented as the difference of cost divided by the difference of utility. The formula used to calculate the ICUR is as follows:

$$\text{ICUR} = \frac{\text{cost of intervention arm (CR)} - \text{cost of control arm (UC)}}{\text{utility of intervention arm (CR)} - \text{utility of control arm (UC)}}. \quad (3)$$

In general, the level of cost-effectiveness is expressed by the ICUR. The ICUR is compared with a predetermined threshold (a measure of decision). If this value is less than the threshold, it is categorized as cost-effective; otherwise, it is categorized as not cost-effective. When the intervention is less costly and more effective, it is categorized as dominant. When it is costlier and more effective, it is categorized as effective. If it is less costly and less effective, it is categorized as doubtful, and if it is costlier and less effective, it is categorized as dominated (Figure 1). Although there is no absolute value for the threshold of ICUR, as it varies depending on economic conditions and the perceptions of individuals, we used 50,000 USD/QALY in the United States [24–26] as a reference.

2.5. Meta-Analysis. We compared the differences in effects for the CR and UC categories. For dichotomous outcomes, studies were combined using risk ratios (RRs) with the corresponding 95% CIs. For continuous outcomes, standardized mean difference (SMD) with 95% CI was calculated to allow direct comparison of the results.

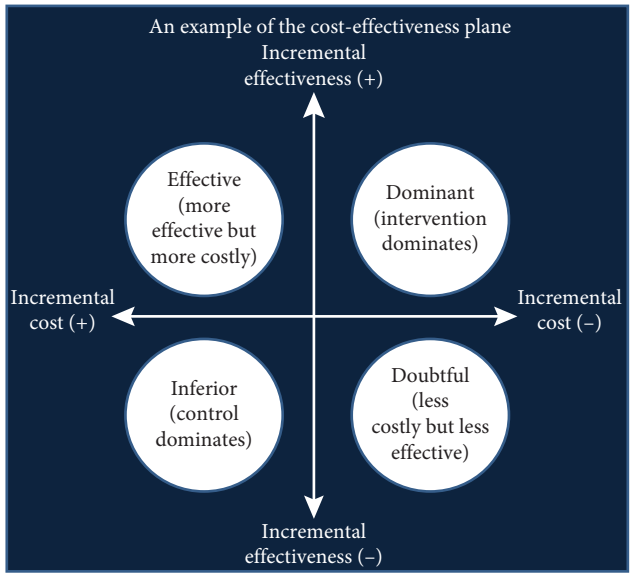


Figure 1: Example of the cost-effectiveness plane. Source: T. Takura, "Creating new value in medical care—methodology of social evaluation of medical technologies," *Iyaku Keizai*, vol. 1339, pp. 16–17, 2009.

We used the random effects model on the grounds that there was a difference in patient population, including regional differences, for each study, and there was a possibility that the bias in each of those studies influenced the outcome of the analysis. We measured statistical heterogeneity using the I^2 statistic, and I^2 values were classified as low (<25%), moderate (<50%), or high (<75%) inconsistency [27]. A P value < 0.05 was considered to be statistically significant.

We conducted 1-way sensitivity analysis for QALY and 2-way sensitivity analysis for cost/QALY. We included a model analysis and assumed the mean and SD, taking into account the difference between CR and UC arms, as reported by Leggett et al. [17]. In general, if the difference does not change from the value written in the report, the meta-analysis results would not be affected by assumed values. However, as the assumed SD is not steady, we conducted one-way sensitivity analysis for QALY.

For 2-way sensitivity analysis of cost/QALY, we varied the medical cost and utility and examined the result by meta-analysis. As the number of studies used in this analysis was small, we did not consider the risk of bias.

To examine the results of cost-effective analysis, we then conducted meta-analyses of mortality and LY.

All analyses were conducted using Review Manager (RevMan for Windows, Version 5.3 Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

3. Results

3.1. Systematic Review. The search identified 71 potentially relevant studies. Of these, we removed 12 duplicates and excluded 48 based on the information in the titles and abstracts. Eleven articles matched the selection criteria (6 systematic reviews; 4 RCTs; and 1 model analysis). After reviewing the studies in the 6 systematic reviews, we identified 4 RCTs [13–15, 18, 28] and 1 model analysis to be included in the meta-analysis (Figure 2).

The model analysis [17] was included as it fit the criteria which were described previously, that is, those which performed cost-utility analysis to compare CR with no CR in patients who had undergone cardiac catheterization. The data source of this model analysis was the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database, which captured detailed clinical information on all patients who have undergone cardiac catheterization in Alberta since 1995 [29]. A cohort of MI or stable/unstable angina patients ($n = 121,763$) captured in this database was used. Although we could not calculate LY, cost/LY, or mortality from this model analysis, we included this cohort in our meta-analysis of medical costs, QALY, and cost/QALY. Due to the publication not mentioning the numbers of patients with CR and those without CR (no CR), we referred to a previous publication [30] on the APPROACH database and defined the number of CR and no CR participants as 5,641 and 116,122, respectively, by subtracting the number of CR participants from the cohort total.

In total, there were 518 patients in the analysis of mortality, LY, and cost/LY. The analysis of medical costs, QALY, and cost/QALY included 122,485 patients. Summaries of selected studies are shown in Supplementary Material Table 2. Papers differed in reporting mortality to mean all-cause death or vascular death. Briffa et al. [15] regarded mortality to mean all-cause death. In the study by Leggett et al. [17], the duration of observation was set at 1 year because the time horizon, cost, and QALY were also calculated at 1 year.

Patient characteristics in the selected studies are shown in Supplementary Material Table 3. In the 1993 paper by Oldridge et al. [13], detailed descriptions of percutaneous coronary intervention (PCI) in the acute phase of MI, coronary artery bypass grafting (CABG), and drug therapies were not provided. Furthermore, with the exception of the report by Oldridge et al. [13], most studies did not discount medical costs and QALY, and sensitivity analyses were not addressed. Due to the nature of the analyses used, the reports by Leggett et al. [17] provided no description of patient backgrounds.

3.2. Meta-Analysis. Although meta-analysis of medical expenses did not show a significant difference between the CR and UC arms, the CR arm had a tendency of higher expenses (SMD: 0.02; 95% CI: −0.08, 0.13). There was moderate heterogeneity among the studies ($P = 0.23$, $I^2 = 29\%$) (Figure 3(a)). We conducted a meta-analysis of cost without studies by Leggett et al., and it showed same tendency (SMD: 0.01; 95% CI: −0.19, 0.22) (Figure 3(b)).

Meta-analysis of QALY demonstrated that the CR arm offered a significantly better QALY than the UC arm (SMD: −1.78; 95% CI: −2.69, −0.87). There was substantial statistical

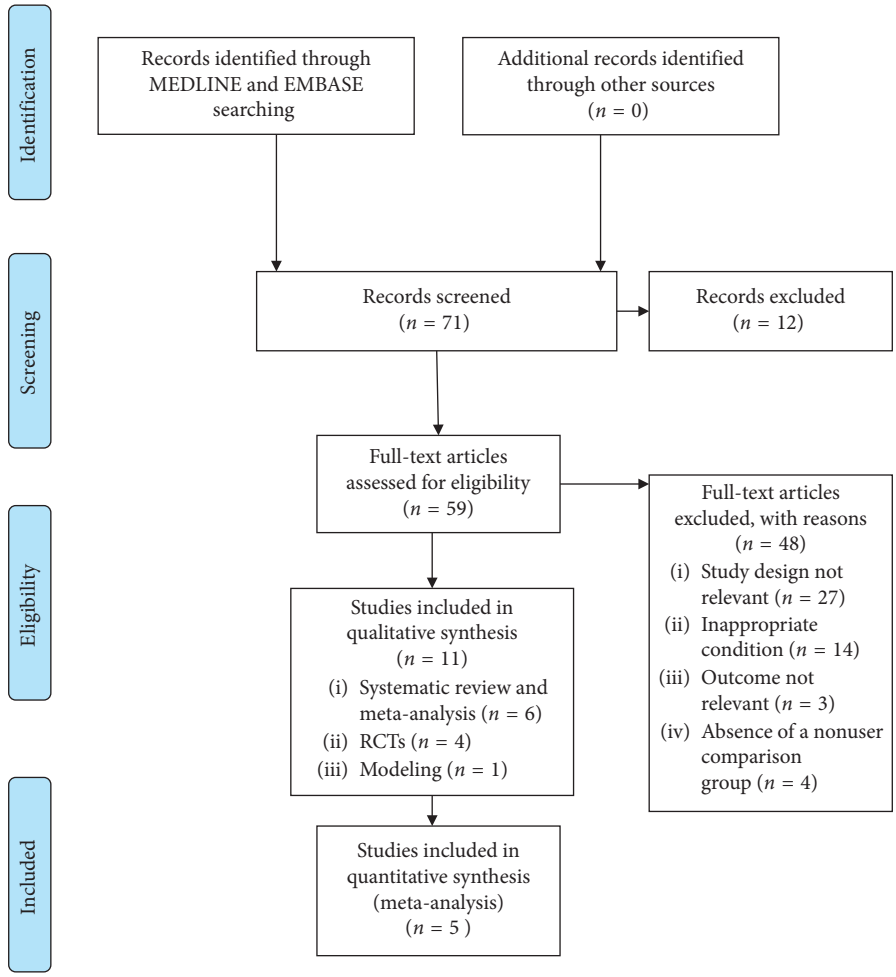


Figure 2: PRISMA 2009 flow diagram.

heterogeneity among the studies ($P < 0.00001$; $I^2 = 98\%$) (Figure 3(a)). One-way sensitivity analysis of QALY showed that changing Leggett et al.'s value of QALY while keeping the 0.07 difference between CR and UC did not affect the outcome. These results confirmed the robustness of the QALY findings. We also conducted meta-analysis of QALY without studies by Leggett et al., and it showed same tendency (SMD: −1.98; 95% CI: −3.67, −0.29) as well (Figure 3(b)).

Though we were mainly investigating cost-effectiveness, subjects in the CR arm did not show a significant difference in mortality compared to those in the UC arm. However, the CR arm had a favorable tendency of decreasing mortality (RR: 0.57; 95% CI: 0.22, 1.47). There was no evidence of significant statistical heterogeneity between the studies ($P = 0.72$; $I^2 = 0\%$) (Figure 3(c)).

Meta-analysis of the LY revealed that CR significantly improved LY compared with UC (SMD: −0.77; 95% CI: −1.34, −0.19). There was substantial statistical heterogeneity between the studies ($P < 0.0001$; $I^2 = 89\%$) (Figure 3(a)).

Regarding cost-effectiveness, cost/QALY in the CR arm was better than that of the UC arm to a statistically significant degree (SMD: −0.31; 95% CI: −0.53, −0.09). There was substantial statistical heterogeneity between the studies ($P = 0.0008$; $I^2 = 79\%$) (Figure 4(a)). Two-way sensitivity analysis showed that worsening cost/QALY in the CR arm with simultaneous improvement in the UC arm of up to 11% did not affect the outcome (SMD: −0.25; 95% CI: −0.49, 0.00). In addition, we also conducted meta-analysis of cost/QALY without studies by Leggett et al. same as that above, and it showed the same tendency (SMD: −0.36; 95% CI: −0.70, −0.02) (Figure 4(b)). From these results, we conclude that the finding is robust.

The cost/LY showed no difference between the CR and UC arms (SMD: 0.11; 95% CI: −0.10, 0.31). Furthermore, there was no evidence of significant statistical heterogeneity between the studies ($P = 0.26$; $I^2 = 26\%$) (Figure 4(a)).

3.3. Evaluation of Robustness. The ICUR for each study was 4,048.0 USD/QALY (Oldridge et al. [13]), −5,193.8 USD/QALY (dominant) (Yu et al. [14]), 17,209.4 USD/QALY (Briffa et al. [15]), 26,888.7 USD/QALY (Leggett et al. [17]), and −48,327.6 USD/QALY (dominant) (Hautala et al. [18]). In summary, these results indicate 3 effective (Oldridge et al. [13], Briffa et al. [15], and Leggett et al. [17]) and 2 dominant (Yu et al. [14] and Hautala et al. [18]) results (Table 1).

Endpoint	Study	CR Mean	CR SD	CR Total	UC Mean	UC SD	UC Total	Weight (%)	Std. mean difference IV, random, 95% CI
Cost	Oldridge [13]	438.09	876.18	99	255.93	511.86	102	11.6	0.25 (−0.02, 0.53)
	Yu [14]	15291.9	30583.80	132	15707.40	31414.80	72	11.0	−0.01 (−0.30, 0.27)
	Briffa [15]	3521.01	7042.02	57	3245.66	6491.32	56	7.2	0.04 (−0.33, 0.41)
	Legget [17]	32981.44	65962.88	5641	31099.23	62198.46	116122	58.6	0.03 (0.00, 0.06)
	Hautala [18]	2168.73	4337.46	109	3376.92	6753.84	95	11.7	−0.22 (−0.49, 0.06)
	Total (95% CI)			6038			116477	100.0	0.02 (−0.08, 0.13)
	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.62$, df = 4 ($P = 0.23$); $I^2 = 29\%$								
	Test for overall effect: $Z = 0.43$ ($P = 0.66$)								
QALY	Oldridge [13]	0.154	0.05	99	0.109	0.04	102	20.3	−0.99 (−1.29, −0.70)
	Yu [14]	0.12	0.12	132	0.04	0.24	72	20.3	−0.46 (−0.75, −0.17)
	Briffa [15]	0.026	0.05	57	0.01	0.04	56	20.0	−0.35 (−0.72, 0.02)
	Legget [17]	0.228	0.076	5641	0.158	0.056	116122	20.7	−1.23 (−1.25, −1.20)
	Hautala [18]	0.013	0.004	109	−0.012	0.004	95	18.6	−6.23 (−6.90, −5.56)
	Total (95% CI)			6038			116447	100.0	−1.78 (−2.69, −0.87)
	Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 265.54$, df = 4 ($P < 0.00001$); $I^2 = 98\%$								
	Test for overall effect: $Z = 3.82$ ($P = 0.0001$)								
LY	Oldridge [13]	0.97	0.030	99	0.96	0.040	102	34.5	−0.28 (−0.56, −0.00)
	Yu [14]	0.98	0.020	132	0.96	0.040	72	34.1	−0.70 (−0.99, −0.40)
	Briffa [15]	0.999	0.001	57	0.96	0.040	56	31.4	−1.38 (−1.79, −0.96)
	Total (95% CI)			288			230	100.0	−0.77 (−1.34, −0.19)
	Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 18.79$, df = 2 ($P < 0.0001$); $I^2 = 89\%$								
	Test for overall effect: $Z = 2.63$ ($P = 0.009$)								

Forest plot: Favors (CR) / Favors (UC)

CR: cardiac rehabilitation; Std. mean difference = the mean difference is standardized by dividing by the standard deviation of the control arm in the study; Tau^2 = variance between studies analyzed; Chi^2 = result of square test of heterogeneity; I^2 = index that shows the degree of heterogeneity among studies; test for overall effect: statistical significance of the overall result is expressed with the probability value (P value); 95% CI = 95% confidence interval.

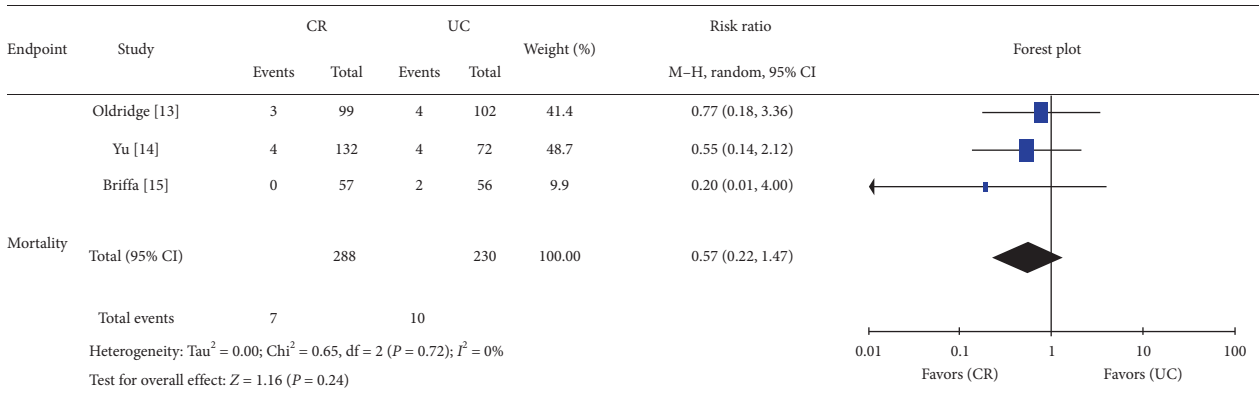
(a)

Endpoint	Study	CR Mean	CR SD	CR Total	UC Mean	UC SD	UC Total	Weight (%)	Std. mean difference IV, random, 95% CI
Cost	Oldridge [13]	438.09	876.18	99	255.93	511.86	102	27.1%	0.25 (−0.02, 0.53)
	Yu [14]	15291.9	30583.80	132	15707.40	31414.80	72	26.1%	−0.01 (−0.30, 0.27)
	Briffa [15]	3521.01	7042.02	57	3245.66	6491.32	56	19.6%	0.04 (−0.33, 0.41)
	Hautala [18]	2168.73	4337.46	109	3376.92	6753.84	95	27.2%	−0.22 (−0.49, 0.06)
	Total (95% CI)			397			325	100.0%	0.01 (−0.19, 0.22)
	Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.57$, df = 3 ($P = 0.13$); $I^2 = 46\%$								
	Test for overall effect: $Z = 0.14$ ($P = 0.89$)								
QALY	Oldridge [13]	0.154	0.05	99	0.109	0.04	102	25.2%	−0.99 (−1.29, −0.70)
	Yu [14]	0.12	0.12	132	0.04	0.24	72	25.2%	−0.46 (−0.75, −0.17)
	Briffa [15]	0.026	0.05	57	0.01	0.04	56	25.1%	−0.35 (−0.72, 0.02)
	Hautala [18]	0.013	0.004	109	−0.012	0.004	95	24.4%	−6.23 (−6.90, −5.56)
	Total (95% CI)			397			325	100.0%	−1.98 (−3.67, −0.29)
	Heterogeneity: $Tau^2 = 2.92$; $Chi^2 = 259.07$, df = 3 ($P < 0.00001$); $I^2 = 99\%$)								
	Test for overall effect: $Z = 2.29$ ($P = 0.02$)								

Forest plot: Favors (CR) / Favors (UC)

(b)

Figure 3: Continued.



CR: cardiac rehabilitation; Tau^2 = variance between studies analyzed; Chi^2 = result of square test of heterogeneity; I^2 = index that shows degree of heterogeneity among studies; test for overall effect: statistical significance of the overall result is expressed with the probability value (P value); 95% CI = 95% confidence interval.

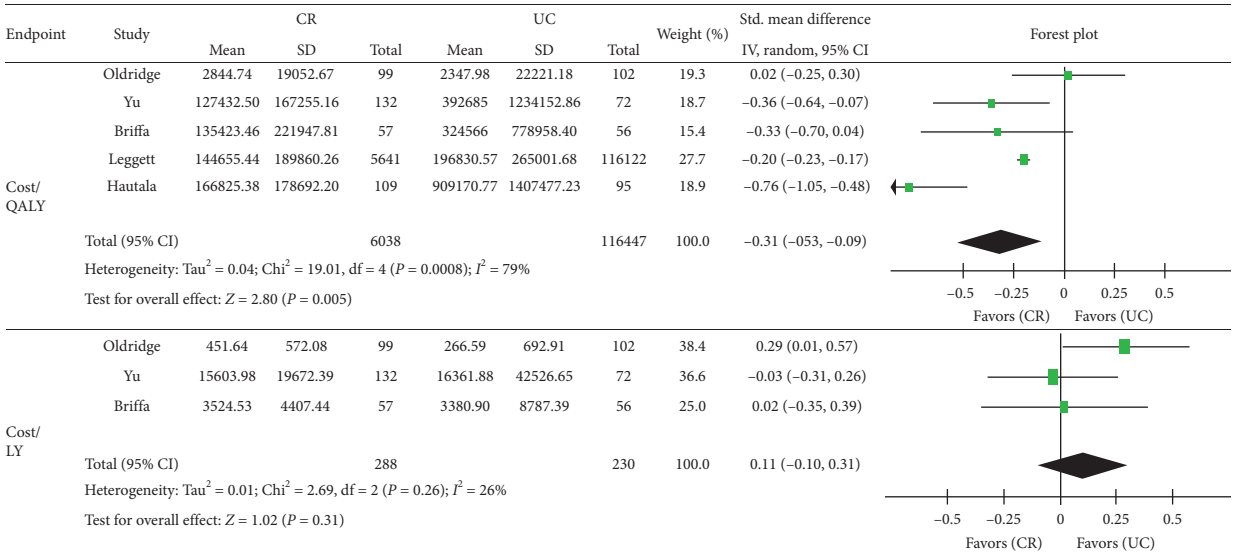
(c)

Figure 3: Comparison of cost, efficacy, and mortality between the cardiac rehabilitation (CR) arm and the usual care (UC) arm in patients with myocardial infarction (MI): meta-analysis. (a) Cost and efficacy, (b) cost and efficacy without the study by Leggett et al., and (c) mortality.

4. Discussion

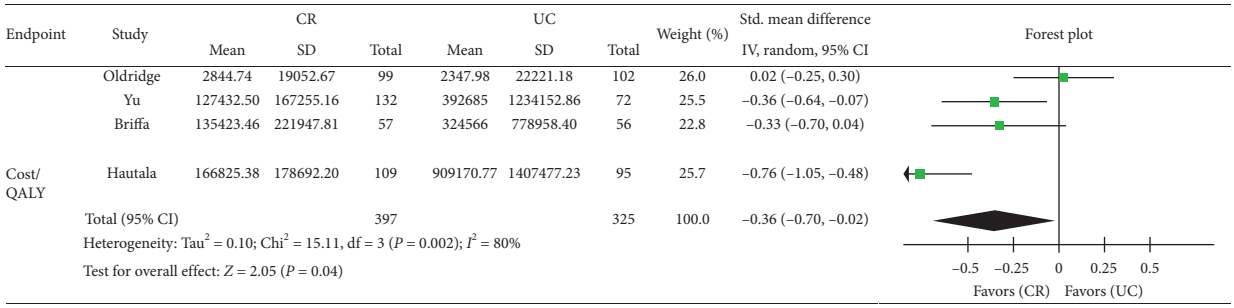
The meta-analysis indicates that CR significantly improved QALY, LY, and cost/QALY compared to UC, whereas medical cost, cost/LY, and mortality did not differ significantly between the CR and UC arms. As cost/QALY was significantly improved in patients with CR, and the ICUR for each study showed two dominant and three effective results, we suggest that CR is cost-effective when patient utility is considered. We present the results of both cost-utility analysis (CUA) and ICUR. We conducted both analyses as CUA that did not reveal the degree of cost reduction of CR over that of UC. In the studies by Briffa et al. [15] and Leggett et al. [17], the ICER was reported as 42,535 AUD/QALY (31,149.38 USD/QALY) and 37,662 CAD/QALY (27,125.31 USD/QALY), respectively. However, the range of cost differed from that of our present analysis. We calculated ICUR using cost and QALY as described earlier. In this analysis, determining cost-effectiveness using cost/LY failed to show an advantage of CR. Conversely, we observed statistically significant differences in the meta-analysis of cost-effectiveness that used QALY as the evaluation index. In addition, the ICUR results for each study were 2 dominant and 3 effective. Of the relative balance of costs and benefits, increased utility rather than increased cost was the strong tendency in CR as compared to UC. In particular, the analysis by Yu et al. [14] found that the CR arm costs more for rehabilitation, while the UC arm had more costs associated with many treatments and more frequent visits. As a characteristic of the efficacy index, large fluctuations over the short term are of greater patient utility than over the long-term survival period; thus, it is presumed that the sensitivity at the endpoint is also greatly affected.

The threshold of ICUR is a measure used to determine cost-effectiveness. In the UK, economic analysis for the evaluation of medical technology, including pharmaceuticals, has been introduced and has been used for the provision of standard treatment and prescriptions. The National Institute for Health and Care Excellence (NICE) discusses the decision-making in accordance with the position of the target drug in the public market against criteria that are judged to be capable of providing the same level as the NHS (National Health Service), as well as comparing the costs and benefits of the drug to be evaluated. In the medical technology assessment by NICE, 20,000–30,000 GBP (24,393.96–36,590.94 USD) are set as the upper limit of the cost required to gain one additional QALY. Although there are some countries that use cost-effectiveness in deciding which drugs should have costs reimbursed, the number of countries publicizing the threshold is small. In this analysis, we converted costs to USD and set the threshold at 50,000 USD. ICUR varies widely depending on the economic conditions and the perceived economic health of the country, and we should discuss the criteria for thresholds on a regional basis, depending on the circumstances of the regions where studies were conducted. However, no relevant data are available. The threshold in the United States is also not an official standard and is used as a guide. Although no ICUR thresholds have been formally established in Japan, two studies have estimated the values as 5,000,000 JPY (43,843.79 USD) and 6,700,000 JPY (58,750.68 USD), respectively, for the willingness to pay to gain 1 QALY in Japan [31, 32]. Although costs were standardized to USD, this does not fully account for differences in different regions. Exchange rates do not always ensure that a dollar has the same value in all countries. Purchasing power parity (PPP) is a common tool used by macroeconomic analysts to compare economic productivity and standards of living internationally, and we could use PPP to convert the costs. However, since PPP is based on traded goods, it might be more useful to evaluate with price indices for tradable goods, rather than nontradable price indices, as with many services [33]. Moreover, PPP is limited, in which each country's unique circumstances are not taken into consideration. Therefore, we used exchange rates to standardize the cost in this analysis.



95% CI = 95% confidence interval.

(a)



(b)

Figure 4: Comparison of cost-utility between the cardiac rehabilitation (CR) arm and the usual care (UC) arm in patients with myocardial infarction (MI): meta-analysis. (a) Cost-utility and (b) cost-utility without the study by Leggett et al.

Table 1: Results of ICUR for comprehensive CR in patients with MI.

Study	Item	CR	UC	Difference	ICUR (USD/QALY)*
Oldridge et al. [13]	Cost	438.09	255.93	182.16	4,048.0
	QALY	0.154	0.109	0.045	
Yu et al. [14]	Cost	15,291.9	15,707.4	−415.5	−5,193.8 (dominant)
	QALY	0.12	0.04	0.08	
Briffa et al. [15]	Cost	3,521.01	3,245.66	275.35	17,209.4
	QALY	0.026	0.01	0.016	
Leggett et al. [17]	Cost	32,981.44	31,099.23	1,882.21	26,888.7
	QALY	0.228	0.158	0.070	
Hautala et al. [18]	Cost	2,168.73	3,376.92	−1,208.19	−48,327.6 (dominant)
	QALY	0.013	−0.012	0.025	

*ICUR rounded off to one decimal place; ICUR, incremental cost-utility ratio.

We conducted supplementary meta-analyses of mortality and LY to examine the result of cost-effectiveness analysis. Although CR significantly improved LY compared with UC, the actual effect of CR compared with UC is still uncertain. Anderson et al. reported a meta-analysis of mortality in patients with CHD [34]. There were differences between their report and our study in the definition of CR. We defined CR as "comprehensive" CR as mentioned earlier, while Anderson et al. [34] included both comprehensive and exercise-only CR. The 2 studies did not clarify whether mortality was all-cause mortality or vascular death. Because all-cause mortality and vascular death differ, we cannot exclude their impact on the costs and LY. Moreover, as medical technology has evolved since 2005, we presume that

divergence between some clinical realities and economic circumstances has occurred. With these limitations, the results of our study should be interpreted carefully.

The observation period of the included studies of mortality, LY, medical cost, and QALY ranged from 1 year [13, 15, 17, 18] to 2 years [14]. Therefore, it is necessary to consider the consistency of the observation period, and it is desirable to equalize the observation periods. For example, we should have considered using 1-year unified values. However, as it was not realistic to think that an event (death) would have occurred consistently in each of the 2 years, we did not correct values. To provide a reference point, we corrected the values in the report by Yu et al. [14] to 1 year and repeated the analysis. Consequently, the range of 95% CI became wider and the robustness decreased, but there was no change with respect to mortality. Furthermore, there was no change in the results with respect to medical costs using the 1-year analysis. These results suggest that the differences in the observation period between the studies did not have a significant impact on the present analysis. The cohort used by Leggett et al. [17] was larger than that of the other studies and had almost 99% of the overall number of patients included in this meta-analysis. While this difference might have an impact on the results, exclusion of the Leggett data showed the same tendency with respect to medical costs, QALY, and cost/QALY. Therefore, we suggest that inconsistencies in the sample size did not affect the present analysis.

Problems with meta-analysis, including integrating research with different backgrounds of participants or intervention, the risk of including low-quality studies, and the tendency not to publish negative results, have been discussed [35]. In this analysis, we have set the target disease at MI with a number of evidence. Since the number of studies used in this analysis was small, we used the paper by Yu et al. [14], in which patients with MI and PCI performed for angina pectoris were included. However, the proportion of MI patients was approximately 70% in this paper.

Regarding QALY, we should have used the effectiveness of CR itself to evaluate it accurately, but we could not separate the effectiveness of CR from medications and other variables among studies. However, as 4 of the studies used in this analysis were RCTs, we think that the bias is likely minimal. Moreover, utility values are measured on a limited scale, from 0 to 1, and small differences would not have a huge effect on the results.

Assessing the efficacy of CR in patients with CAD is not appropriate using these results because included studies were heterogeneous regarding the definition and cost of the CR and UC arms and the methods used for calculating the QALY. Currently, there are insufficient data to determine the cost-effectiveness of CR. Specifically, to evaluate the effect of CR properly, the impact on mortality and QALY must be considered over the long term (>5 years). Therefore, we support the promotion of a large-scale clinical trial to evaluate the long-term cost-effectiveness of CR.

In meta-analysis, it is important to consider not only the quality of the paper but also the selection bias. However, a funnel plot was not possible due to the small number of included studies [36]. Therefore, publication bias could not be determined.

5. Conclusions

This meta-analysis indicates that comprehensive CR is potentially cost-effective as determined using QALY as an evaluation index. In addition, the ICUR of each data source was dominant or effective.

Conflicts of Interest

NE is an employee of Pfizer Japan Inc.

Authors' Contributions

TT contributed to study design and interpretation. NE performed literature search, analyzed the data, and drafted the manuscript; MK, YG, MN, KO, TK, and HI contributed to interpretation and revised the manuscript critically. All the authors approved the final manuscript and agreed to be accountable for all aspects of the work, thereby ensuring integrity and accuracy.

Supplementary Materials

Supplementary Material Figure 1: concept of QALY. Recent research reports increasing use of the selection of outcome-oriented indices that apply utility (desire or satisfaction of recipients) to explain the results of medical interventions. The quality-adjusted life year (QALY) is one of the global standards used to evaluate both survival (quantitative profit) and quality of life (qualitative benefit). As a broader measure, the cost-utility analysis (CUA) is an index used to evaluate how much a health system should pay to maintain perfect health for 1 year. QALY does not necessarily cover all of the patient's health conditions; some clinical conditions have low sensitivity as a health measurement tool. Supplementary Material Table 1: medical costs and interventional behavior of selected studies by systematic review. Costs associated with CR, testing, diagnosis, and treatment during the observation period were extracted from each study. We converted the unit of cost to United States Dollar (USD) using the annual average exchange rate in the published year of each study. Supplementary Material Table 2: summaries of selected studies by systematic review. We identified 4 RCTs and 1 model analysis and summarized the details of each study, including demographics, interventions, and method of cost-effectiveness analysis. The observation period of the included studies of mortality, LY, medical cost, and QALY ranged from 1 year to 2 years. Supplementary Material Table 3: patient characteristics in selected studies by systematic review. In the 1993 paper by Oldridge et al., detailed descriptions of percutaneous coronary intervention (PCI) in the acute phase of MI, coronary artery bypass grafting (CABG), and drug therapy were not provided. The reports by Leggett et al. provided no description of patient backgrounds because it is a model analysis. (*Supplementary Materials*)

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Hindawi
Cardiology Research and Practice
Volume 2019, Article ID 7059806, 4 pages
https://doi.org/10.1155/2019/7059806

Review Article

The Evolving View of Coronary Artery Calcium: A Personalized Shared Decision-Making Tool in Primary Prevention

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Received 22 February 2019; Accepted 16 May 2019; Published 2 June 2019

Guest Editor: Jonathan Feig

The 2018 American Heart Association and American College of Cardiology (AHA/ACC) cholesterol management guideline considers current evidence on coronary artery calcium (CAC) testing while incorporating learnings from previous guidelines. More than any previous guideline update, this set encourages CAC testing to facilitate shared decision making and to individualize treatment plans. An important novelty is further separation of risk groups. Specifically, the current prevention guideline recommends CAC testing for primary atherosclerotic cardiovascular disease (ASCVD) prevention among asymptomatic patients in borderline and intermediate risk groups (5–7.5% and 7.5–20% 10-year ASCVD risk). This additional sub-classification reflects the uncertainty of treatment strategies for patients broadly considered to be "intermediate risk," as treatment recommendations for high and low risk groups are well established. The 2018 guidelines, for the first time, clearly recognize the significance of a CAC score of zero, where intensive statin therapy is likely not beneficial and not routinely recommended in selected patients. Lifestyle modification should be the focus in patients with CAC = 0. In this article, we review the recent AHA/ACC cholesterol management guideline and contextualize the transition of CAC testing to a guideline-endorsed decision aid for borderline-to-intermediate risk patients who seek more definitive risk assessment as part of a clinician-patient discussion. CAC testing can reduce low-value treatment and focus primary prevention therapy on those most likely to benefit.

1. Introduction

The aim of this article is to review the 2018 American Heart Association and American College of Cardiology (AHA/ACC) cholesterol management guideline, and to place new recommendations on coronary artery calcium (CAC) in greater context. The role of CAC for cardiovascular risk prediction differs from the 2013 to the 2018 AHA/ACC guidelines and reflects the considerable amount of research development on CAC scoring over the last years [1]. Estimation of atherosclerotic cardiovascular disease (ASCVD) risk using the Pooled Cohort Equations (PCE) remains an important step in clinical decision making for primary prevention of ASCVD in asymptomatic individuals [2]. Additionally, it provides an avenue to identify patients who might benefit from preventive pharmacotherapies. Although the 2018 AHA/ACC cholesterol management guideline recommends the use of these equations, it acknowledges its limitations with risk discrimination and overestimation. Studies have shown that these equations exhibits just moderate risk discrimination, and commonly overestimates ASCVD risk [3]. This may be especially true among non-Caucasian and non-African American populations, and also among older populations since PCE is heavily weighted towards patient age [4]. However, AHA/ACC guidelines assigned a class IIA recommendation for the use of supplementary tools, such as CAC scoring, for more accurate risk assessment beyond the PCE "when risk or the decision

to treat is uncertain" [5–8]. Head-to-head comparison of CAC with other traditional risk factors in the Multi-Ethnic Study of Atherosclerosis (MESA) has shown that CAC is the best prognosticator of coronary heart disease (CHD) risk [1, 9, 10]. The Dallas Heart Study (DHS) has observed similar results [11]. In the Heinz Nixdorf RECALL (HNR) study it has been shown that persons with severe CAC had higher hazard ratios than those with a CAC score of 0 [1, 12]. CAC scoring has been demonstrated to be useful for re-classifying risk and moving patients to lower or higher risk groups.

More endeavors have been required to understand how to convey CVD risk estimation and to use these approaches for shared decision making as current approaches for the prevention of ASCVD are explicitly risk-based [1, 7]. So far, traditional risk factors were incorporated in cardiovascular risk assessment (e.g. gender, family history, smoking status, age, diabetes, total cholesterol and HDL). However, risk calculators that exclusively include traditional risk factors have moderate risk calibration, and commonly overestimates ASCVD risk. In the United States, risk estimation begins with the PCE, which were first introduced in the 2013 AHA/ACC guideline [6]. The new 2018 AHA/ACC guideline still recommends use of these equations as a prudent first step in clinical decision making, despite acknowledging that they provide only moderate risk discrimination [4, 8].

CAC has nowadays extended from traditional risk prediction studies to patient-centered research with direct implications for personalized clinical practice. CAC scoring measures ASCVD risk by capturing lifetime accumulated exposure to measurable and unmeasurable risk factors. Therefore, it is a strong surrogate of total burden of atherosclerosis. The ability to effectively detect CAC resulted in a paradigm shift in cardiovascular risk calculation, as it allowed direct measurement of subclinical disease, instead of only paying attention to one time measurement of traditional risk factors that only partially reflect an individual's true risk [13]. Since publication of the 2013 guideline, concern has been raised that risk overestimation could lead to statins being recommended to many patients who are less likely to receive net benefit from therapy. For patients at either high or very low risk for ASCVD, imprecise risk estimation may not be clinically relevant. However, for all other patients, using the PCE as a standalone risk assessment tool may be insufficient for definitive decision making [2].

This central limitation is echoed in the current AHA/ACC prevention guidelines of 2018, as these specifically state that "identification of subclinical atherosclerosis rather than use of serum biomarkers is preferred, because of the extensive body of evidence demonstrating the superior utility of atherosclerosis disease assessment" [8]. Consideration of additional clinical factors and other tests to more accurately assess cardiovascular risk for many adults with 10 year risk for ASCVD between 5% and 20% are recommended. The presence of these risk enhancers, such as rheumatologic disease, HIV infection, South Asian ancestry, inflammatory biomarkers and a family history of premature ASCVD, can increase risk. However, risk enhancers are only valuable for identifying persons who may be at higher risk than otherwise expected. Their absence does not reclassify risk downward, and borderline to intermediate risk patients especially those with no traditional risk factors may still face risk overestimation and consequently potential overtreatment. [2, 8, 14].

2. Current 2018 AHA/ACC Cholesterol Management Guideline

The current 2018 AHA/ACC cholesterol management guideline implements learnings from previous guidelines and current evidence on CAC testing. More than any previous guidelines, this set encourages CAC testing to implement shared decision making and to individualize treatment plans [15]. Specifically, the current prevention guideline recommends CAC testing for primary ASCVD prevention in asymptomatic patients and in borderline and intermediate risk patients (10-year ASCVD risk 5–20%). Lifestyle modification should be the focus in patients with CAC = 0. Statin therapy is recommended for patients with a CAC score between 1 and 99 and strongly indicated at a CAC score >100 or if patients are in the >75th percentile. The guidelines suggest that CAC testing can be repeated after 5 years if the CAC score is 0 or 1–99 [8]. An important novelty is further separation of risk groups. The 2018 AHA/ACC cholesterol management guideline consider individuals with a 5% 10-year ASCVD risk as low risk, 5–7.5% as borderline and 7.5–20% as intermediate and >20% as high risk. This additional sub-classification reflects the uncertainty of treatment strategies for patients with intermediate risk groups, as treatment recommendations for high and low risk groups are well established [15]. As suggested by earlier guidelines, the 2018 AHA/ACC cholesterol management guideline emphasize that "clinical judgment and patient preferences should guide decision making." Importantly, the new guidelines recognize that the CAC can be used to increase as well as decrease risk scores of patients, while the CAC in previous guidelines was used to select high risk patients for more aggressive treatment. Multiple studies have suggested the effectiveness of CAC testing for both upwards and downwards reclassification of ASCVD risk. The net reclassification index (NRI) was 0.66 for CAC in intermediate risk patients, while it was 0.02–0.1 for other biomarkers [16]. More studies have shown that in a group of individuals with 10-year risk of 5–20%, 50% can be reclassified with CAC testing [17, 18].

The 2018 guidelines, for the first time, more clearly recognize the significance of a CAC score of 0, where intensive statin therapy is not beneficial and not recommended. This update is a response to multiple studies demonstrating the high negative predictor value of CAC = 0, also known as "the power of zero." For instance, in a study evaluating 13 risk factors using data of the MESA study, CAC = 0 was the strongest negative risk factor [19]. Moreover, a CAC score of 0 was found to be the greatest factor of downward risk reclassification among all negative risk parameters like low levels of high sensitivity c-reactive protein or low ankle brachial index [20]. The current guidelines also state that CAC testing for further risk stratification is not suitable for diabetics, smokers, patients with premature cardiovascular disease. The 2018 guidelines emphasize that

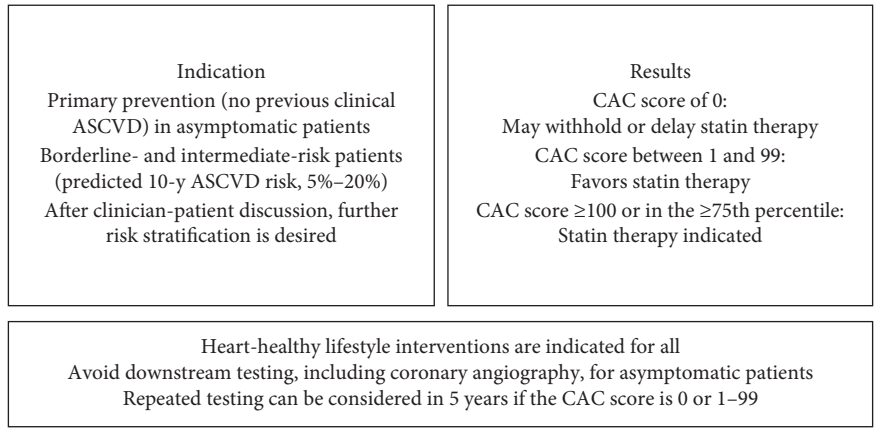

Figure 1: Coronary artery calcium testing.

CAC is not a screening tool but an extra tool which helps to "minimizes" patients in risk, and discriminates individuals, who do not profit from intensive statin therapy regime [2].

3. Conclusion

In summary, CAC scoring has evolved from a research tool to a firm part of the decision algorithm to create individualized therapies. It is the most valuable test to reduce low value treatment and offer primary preventive care to patients who will truly benefit. The development of the role CAC over time can be observed through guidelines changing recommendation on CAC testing. Originally, guidelines recommended CAC as a tool to identify high risk patients for additional risk stratification [15]. Current guidelines however recommend CAC testing for ASCVD (5–20%) intermediate risk patients. CAC is recommended by present guidelines to implement shared decision making on order to design optimal treatment plans for each individual patient. Health care professionals should ensure that patients are informed about all available options in the context of a risk-based approach. The shared decision-making process means not only to include sharing the best scientific evidence with patients but also considers patients values and preferences. Therefore, CAC scoring is an option that should be made available for intermediate risk patients who desire additional risk information. Safety concerns regarding CAC scoring, such as implications of potential incidental pulmonary findings or radiation exposure, vs. benefits of more accurate risk stratification to start lifelong statin therapy, should be part of the shared decision-making approach. Shared decision-making provides patients with the opportunity to weigh pros and cons of treatment without or with further testing and improves potentially their engagement in disease management [1].

3.1. Take-Home Message. It is critical that physicians understand the newly proposed role for CAC testing and do not equate it with screening. Rather than bringing in many additional statin candidates, this testing should serve as a decision aid to "de-risk" certain patients and distinguish those who may benefit from preventive pharmacologic therapies. The updated 2018 AHA/ACC cholesterol management guideline strongly endorses selective CAC testing, but the decision to use this testing is not always straightforward. CAC testing is now a guideline-endorsed decision aid for borderline-to intermediate risk patients who seek more definitive risk assessment as part of a clinician—patient discussion. This testing can reduce low-value treatment and focus primary prevention therapy on those most likely to benefit (Figure 1).

Abbreviations

ASCVD: Atherosclerotic cardiovascular disease
CAC: Coronary artery calcium
CVD: Cardiovascular diseases
DHS: Dallas heart study
HNR: Heinz nixdorf recall study
MESA: Multi ethnic-study of atherosclerosis
NRI: Net reclassification index
PCE: Pooled cohort equations.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Hindawi
Cardiology Research and Practice
Volume 2019, Article ID 7135604, 6 pages
https://doi.org/10.1155/2019/7135604

Review Article

A Review of the Epidemiological Evidence for Adducin Family Gene Polymorphisms and Hypertension

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Received 27 December 2018; Revised 11 March 2019; Accepted 17 April 2019; Published 2 June 2019

Guest Editor: Rajesh Tota-Maharaj

Hypertension is one of the most common cardiovascular diseases that seriously endangers human health and has become a significant public health problem worldwide. In the vast majority of patients, the cause of hypertension is unknown, called essential hypertension (EH), accounting for more than 95% of total hypertension. Epidemiological and genetic studies of humans and animals provide strong evidence of a causal relationship between high salt intake and hypertension. Adducin is one of the important candidate genes for essential hypertension. Adducin is a heterodimeric or heterotetrameric protein that consists of α, β, and γ subunits; the three subunits are encoded by genes (*ADD1*, *ADD2*, and *ADD3*) that map to three different chromosomes. Animal model experiments and clinical studies suggest that changes in single-nucleotide polymorphisms (SNPs) at part of the adducin family gene increase the Na^+-K^+-ATPase activity of the renal tubular basement membrane and increase the reabsorption of Na^+ by renal tubular epithelial cells, which may cause hypertension. This review makes a summary on the structure, function, and mechanism of adducin and the role of adducin on the onset of EH, providing a basis for the early screening, prevention, and treatment of EH.

1. Introduction

Hypertension, typically defined as a resting systolic BP (SBP) 140 mm·Hg or higher, or diastolic BP (DBP), 90 mm·Hg or higher, or receiving therapy for the indication of BP-lowering, afflicts a substantial proportion of the adult population worldwide [1, 2] and leads to cardiovascular events (some of which, such as stroke, myocardial infarction, sudden death, heart failure, and peripheral artery disease), as well as end-stage renal disease [3]. Numerous studies have examined potential genetic susceptibilities for hypertension [4, 5]. Current genetic epidemiological studies suggest that adducin may be the susceptible gene of essential hypertension (especially salt-sensitive EH) [6–11]. Hence, the association between adducin gene polymorphisms and EH has been widely concerned. Herein, we describe the structure and function of adducin, summarize the current knowledge on the relationship between adducin family gene polymorphisms and EH, and propose a more comprehensive approach to the prevention and treatment of EH.

2. Structure of Adducin

Adducin is a ubiquitously expressed cytoskeleton protein, which was initially been purified from human erythrocytes by Gardner and Bennett in 1986 [12] and was soon separated from bovine brain cells. In 1991, Joshi et al. found two subunits of adducin termed α-adducin (*ADD1*) and β-adducin (*ADD2*), respectively [13]. Dong et al. in 1995 reported that adducin still had γ subunits (*ADD3*) [14]. The three subunits are produced from distinct genes but share a similar structure [14–17]. All the three adducin proteins contain an N-terminal globular head domain, a neck domain and a C-terminal protease-sensitive hydrophilic C-tail domain [18]. At the end of the tail domain, there is a 22-residue MARCKS-related domain that has high homology to myristoylated alanine-rich C kinase substrate (MARCKS) protein. The MARCKS-related domain has clusters of lysine residues and is highly conserved among the three adducin subunits. α- and γ-adducins are ubiquitously expressed. In contrast, β-adducin is expressed at high levels in the brain and hematopoietic tissues.

Human *ADD1* is localized at chromosome 4p16.3 [19], the spans of which was about 85 kb and contained 16 exons ranging in size from 34 to 1892 bp [17]. Mutations in *ADD1* have been shown to be associated with both human and rat hypertension [11, 20, 21]. Human *ADD2* is localized on chromosome 2p13-p14 and has 13 exons [22, 23], whereas human *ADD3* is on chromosome 10q23.2-24.3 and composed of at least 13 introns and 14 exons spanning over 20 kb [24]. *ADD1*, *ADD2*, and *ADD3* are highly homologous with rats, with 94.3%, 91.7% and 91.9% amino acid sequences similar to those of rats, respectively [17, 22, 24].

3. Function of Adducin

3.1. Adducin Is Essential for the Formation and Stabilization of Membrane Cytoskeleton. Previous studies have shown that adducin promotes the binding of spectrin to actin filaments and is concentrated at the cell-cell contact sites in epithelial cells [25]. It selectively binds to the spectrin-actin complex at the end of its α and β subunits with a significantly higher affinity than that of either spectrin or actin monomer [26]. Electron microscope confirmed that adducin also contributes to the formation of a complicated meshwork of spectrin and spectrin-actin complexes and the polymerization of actin filaments [25]. This function is regulated by Ca^{2+}/calmodulin, protein kinase A and C, and Rho kinase and needs MARCKS-related domain [25, 27–32]. Previous reports indicated that there were two linkages between membrane skeleton and lipid bilayer: band 3-ankyrin-β-spectrin and glycophorin C-protein 4.1-β-spectrin [33–35]. Anong et al. in 2009 demonstrated that adducin formed a bridge of band-3-adducin-spectrin to consolidate the stabilization of the membrane [35]. Additionally, adducin can also inhibit capping of the fast-growing ends of actin filaments as an actin-capping protein. In this way, adducin could prevent addition or loss of actin subunits and make it easier to bundle actin filaments, as found by Kuhlman and Fowler in 1996 [36, 37].

3.2. Adducin Is Involved in the Process of Cell Signal Transduction and Ionic Transportation. Adducin, an in vivo substrate for PKC, PKA, and Rho-associated kinase [27–30], gets involved in cell signal transduction. Moreover, adducin also interacts with other components of membrane skeleton and various membrane proteins to exert effects on ionic transport, particularly with Na^+ transportation, for instance, the epithelial Na^+ channels, Na^+-H^+ exchange, Na^+-Li^+ countertransport, Na^+-K^+-Cl^- cotransport, and be associated with human EH [6, 38–40]. The adducin gene regulates blood pressure mainly by affecting the activity of the Na^+-K^+-ATPase and changing the reabsorption of sodium by the renal tubules [6, 41, 42]. Point mutations in α- or β-adducin can lead to hypertension as the phosphorylation pattern changes from tyrosine kinase to PKA site [43]. It has been confirmed that mutated α-adducin variants have been shown to interact with the Src-SH_2 domain (Src homology 2), increasing Src activity and Src-dependent Na^+-K^+-ATPase phosphorylation and activity. Rostafuroxin, a new antihypertensive drug, blunted this interaction and disrupted Src activation and Na^+-K^+-ATPase phosphorylation, resulting in blood pressure normalization in the hypertensive rats [44–46].

4. Current Status of the Association between Adducin Family Gene Polymorphisms and EH

Recently, many studies focused on the polymorphisms of adducin family genes and their correlation with EH. Currently, three major loci were highlighted, i.e., Gly460Trp of ADD1, C1797T of ADD2, and A386G of ADD3. However, no clear consensus has been reached on the three major loci and EH, and the relationships remain inconsistent [47–51]. An overview of recent advances on the association between EH and the three main loci is given in the following.

4.1. α-Adducin Gly460Trp Polymorphism with Hypertension. α-Adducin has long been controversial as a risk factor for hypertension. In 1997, Cusi et al. reported for the first time that α-adducin Gly460Trp polymorphism is related to EH, especially salt-sensitive hypertension by affecting sodium balance, and suggested that adducin gene could be thought to be one of the candidate genes of EH [21]. Later, Tamaki et al. reached a similar result in the Japanese population; they found that the genotype frequency of Gly460Trp polymorphism and plasma renin activity were significantly different in the normotensive, borderline, and hypertensive groups and that the 460Trp allele might be associated with hypertension, especially the low renin-type hypertension [52], which to some extent supported the result of Cusi's study. In 2007, Nakamura et al. conducted a large-scale community-based research, involving 4,640 participants, including 2,414 subjects with hypertension and 2,226 normal controls, and the results showed that α-adducin Gly460Trp polymorphism is associated with high blood pressure and homozygous mutant risk was 1.6 times that of homozygous wild type (OR: 1.6, 95% CI: 1.3–1.9), and they found α-adducin Gly460Trp polymorphism can act as an independent risk factor of hypertension in Japanese population [53]. Watanabe et al. carried out a cohort study on Japanese people with normal blood pressure for 12 years recently and found that four SNP sites of different genes, including ADD1 Gly460Trp, were related to EH, and could independently predict the risk of hypertension progression after multiple logistic regression correction [54].

However, cumulative case-control studies came to paradoxical results that the association between α-adducin Gly460Trp polymorphism and hypertension varies among ethnic groups [47, 55–57]. All these studies have demonstrated racial differences in genetic polymorphisms associated with EH. Additionally, a Swedish cohort study, including 3,827 subjects with hypertension and 2,178 with normal blood pressure, concluded that α-adducin Gly460Trp polymorphism might have few functions in the maintenance of blood pressure and contribution to high blood pressure unless in combination with gender and body mass index (BMI) [58]. Furthermore, the pathological effect

of α-adducin Gly460Trp polymorphism as a hypertensive disease susceptibility gene in the Russian population was only influenced by environmental factors [59]. These studies suggested that the association of genetic polymorphisms with hypertension is not only related to differences in race and environment but also related to the clinical or biological characteristics of individual subjects. In 2010, two studies about the association between α-adducin Gly460Trp polymorphism and EH had reported that there is no association between α-adducin Gly460Trp polymorphism and EH in general or in any of the subgroup [51, 60]. It is speculated that the reason may be that the meta-analysis failed to include all the current studies about the association between the polymorphism of α-adducin Gly460Trp polymorphism and hypertension. The results of two recent meta-analyses support the hypothesis that T-allele carriers had a higher risk of developing EH in Asian populations, but there was no exact correlation between blacks and whites, highlighting significant ethnic differences in *ADD1* genes [61, 62]. Taken together, the evidence linking α-adducin Gly460Trp polymorphism with hypertension is still scanty.

4.2. C1797T β-Adducin Polymorphism with Hypertension. By now, the association between α-adducin Gly460Trp polymorphism and EH has many reports, but the study on the C1797T β-adducin polymorphism with hypertension is still in the incipient stage and has many controversies. Wang et al. randomly selected 2,272 Caucasian subjects in northern Belgium to study whether the C1797T polymorphism of the β-adducin gene was associated with the risk of hypertension. They found the 1797T allele of the β-adducin gene is associated with increased risk of hypertension in postmenopausal women and users of oral contraceptives, especially in woman carrier of the mutated α-adducin Trp allele [63], suggesting that the two genes may have potential interactions with each other. A study by Tikhonoff et al. [64] has confirmed that the β-adducin C1797T allele may be associated with increased blood pressure in populations with high salt intake. However, Zhou et al. reported that the study of the Yi and Hani ethnic groups with the lowest incidence of EH in China and found that there was no distribution of mutant homozygotes (TT) in both the case group and the control group of the two ethnic groups, and the T allele mutant of β-adducin was very low [65], suggesting that the lack of C1797T polymorphism in the Yi and Hani ethnics in China may not be related to the onset of EH. Additionally, Kato et al. discovered a new SNP locus C/A variant of the β-adducin gene (rs3755351). The experimental results show that it has a significant correlation with EH, but after a strict Bonferroni correction, the conclusion became negative [66]. Therefore, at the present stage, larger sample sizes and high-quality researches are needed.

4.3. γ-Adducin A386G Polymorphism with Hypertension. Apart from C1797T β-adducin polymorphism, some studies have reported the connection of γ-adducin A386G polymorphism with EH, usually combined with the polymorphic loci of ADD1 and ADD2. In 2005, Cwynar et al. studied European Caucasians and found that, in α-adducin Trp allele carriers, the increase in peripheral and central pulse pressure was associated with the γ-adducin 386G allele, suggesting that two genes may have an epistatic effect that is consistent with the heterodimeric structure of the cytoskeletal protein and its influence on transmembranous sodium transport [67]. In the same year, Lanzani et al. studied the association of the adducin family gene polymorphism with EH and verified the presence of epistatic effects among mutated Trp ADD1 allele and ADD3 G allele. After a combined analysis of the mutant population of ADD1 and ADD3, it was concluded that there was a high correlation with EH [68]. However, in 2006, Chinese scholars reported that there is no 386G allele distribution in the Yi and Hani populations and that the A386G mutation of γ-adducin may not be an important determinant associated with EH [65]. Due to the lack of separate studies on the association between γ-adducin gene polymorphism and EH, the combined analyses of ADD2 and ADD3 gene variants are also scarce, so the association with blood pressure variability or hypertension is not fully affirmed. Large-scale and in-depth studies are still needed in different populations.

Studies have found that diuretics (especially hydrochlorothiazide, HCTZ) have a better antihypertensive effect in hypertensive patients with adducin gene mutation than nonmutated patients, which indirectly confirmed that adducin gene variation is closely related to volume-dependent hypertension and may be a useful predictor of the antihypertensive effect of diuretics [21, 69, 70]. However, the study by Suonsyrjä et al. found no correlation between adducin gene mutation and EH, presumably because the subjects enrolled in the study were all patients who received antihypertensive drugs and only had a 30-day washout period, so the interference of previous treatment effects on the experiment cannot be excluded [71]. Davis et al. also did not find a predictive effect of the Gly460Trp allele mutation on diuretics, which may be masked by other antihypertensive methods, such as lifestyle adjustments [72]. Schelleman et al. reported a large observational study involving 3,025 hypertensive patients. The results showed that the α-adducin Gly460Trp polymorphism had no significant association with the antihypertensive effect of diuretics, but the study did not rule out possible bias and confounding factors and the credibility of the results remains to be evaluated [73]. Due to the lack of relevant research in this field, more high-quality, large-sample studies are needed to further clarify the relationship between adducin family gene polymorphism and the antihypertensive effect of antihypertensive drugs.

5. Prospects

Adducin is an important candidate gene for EH though it still faces many controversies. Previous studies had reached inconsistent results; we speculate that there are several reasons as follows: (1) Racial difference: this is because essential hypertension is a highly genetic heterogeneous disease associated with multiple factors, and the majority of studies have found that the onset of

essential hypertension is related to the alpha-adducin gene polymorphism mainly in Asian population. (2) Sample size: the small sample size of most case-control studies may be one of the potential limitations. (3) Gene-environmental interactions: most studies do not take into account environmental factors such as geographical location, climate, diet, and lifestyle, all of which are associated with the risk of hypertension. Hence, it is an urgent need to identify gene-environmental interactions in the future. For these reasons, we believe that even if the results are controversial, studies about ADD gene polymorphism will help guide the discovery of the pathogenesis and therapeutic targets of hypertension in the future. As mentioned above, multiple SNPs in adducin family gene are related to the onset of EH, and some new gene mutation loci have been discovered and verified [74, 75]. These studies are helpful to elucidate the genetic mechanism of EH and provide a newer and stronger theoretical basis and practical evidence for the prevention, diagnosis, and treatment of EH. As is shown in the case of rostafuroxin, a newly developed antihypertensive agent targeted endogenous ouabain and mutant adducin and downregulates the Src-epidermal growth factor receptor-(EGFR-) dependent signaling pathway, which leads to the phosphorylation and activation of Na^+-K^+-ATPase and ERK tyrosine, thereby selectively inhibiting the activity and expression of renal tubular Na^+-K^+-ATPase, suppressing sodium reabsorption in renal tubules, and lowering blood pressure. As described above, a 30-day washout period is not enough to remove the influence of previous treatment. Hence, Lanzani et al. conducted clinical trials in newly discovered and untreated patients to determine whether genetic profile could predict the response to the pharmacological treatment with rostafuroxin [76]. They found in these clinical studies that the relevance of adducin gene variants is able to predict the response to the new antihypertensive medication. Additionally, rostafuroxin reduced blood pressure in these patients who responded to rostafuroxin while inhibiting hypertension-related organ damage, thereby reducing cardiovascular risk factors. Given their involvement in essential hypertension, adducin gene variants represent attractive therapeutic target and it is reasonable to believe that they can be used to predict the response to rostafuroxin. Our collective hope is that by identifying positive genes for EH, we will be able to better predict those at risk and, perhaps most importantly, develop new treatments and use them in more precise ways.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This study was supported by grants from the National Natural Science Foundation of China (No. 81700271) and the Hebei Provincial Natural Science Foundation (No. H2018105054).

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Hindawi
Cardiology Research and Practice
Volume 2019, Article ID 2748035, 7 pages
https://doi.org/10.1155/2019/2748035

Research Article

Low-Dose Aspirin as Primary Prophylaxis for Cardiovascular Events in Rheumatoid Arthritis: An Italian Multicentre Retrospective Study

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Received 27 December 2018; Revised 14 March 2019; Accepted 1 April 2019; Published 2 May 2019

Guest Editor: Rajesh Tota-Maharaj

Objective. To investigate the role of acetylsalicylic acid (ASA) in reducing the incidence of cardiovascular (CV) events in an Italian multicentre rheumatoid arthritis (RA) inception cohort. *Methods*. The clinical charts of RA patients consecutively admitted to 4 Italian centres for their 1st visit from November 1, 2000, to December 31, 2015, and followed up till December 2016 were retrospectively investigated for the incidence of CV events. Patients were subdivided into two groups, namely, ASA- and non-ASA-treated groups. The Kaplan–Meier curve and log-rank test were used to investigate differences in event-free survival. Cox regression analysis was carried out to identify factors associated with CV event occurrence. *Results*. Seven hundred forty-six consecutive RA patients were enrolled and followed up for a median of 5.6 years (range 2.9–8.9 years). The incidence rate (IR) of CV events was 8/1000 person-years (p-ys) in the overall cohort. The IR of CV events was significantly lower in the ASA-treated group with respect to the non-ASA-treated group (IR 1.7 vs. 11.8/1000 p-ys; $p = 0.0002$). The CV event-free rate was longer in ASA-treated patients than in non-ASA-treated patients (log-rank test 12.8; $p = 0.0003$). At multivariable analysis, arterial hypertension (HR 9.3) and hypercholesterolemia (HR 2.8) resulted to be positive predictors and ASA (HR 0.09) and hydroxychloroquine (HCQ) (HR 0.22) to be negative predictors. *Conclusion*. The IR of CV events in our Italian multicentre cohort was lower than that reported in other European and non-European cohorts. Low-dose ASA may have a role in the primary prophylaxis of CV events in RA patients.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder associated with increased mortality from all-causes and in particular from cardiovascular disease (CVD). Actually, myocardial infarction (MI) and stroke are recognized as leading causes of mortality in patients with RA [1]. Nevertheless, the pathophysiological mechanism underlying the increased CV risk in RA patients is not fully understood. In point of fact, traditional CV risk factors do not fully explain the increased incidence of CV events, observed in these patients [2]. Therefore, RA-associated CV risk seems to be the consequence of the combined effects of chronic systemic inflammation (included platelet activation) and increased traditional CV risk factors and of the treatment with disease-modifying antirheumatic drugs

(DMARDs), corticosteroids, and nonsteroidal anti-inflammatory drugs [3–5].

We have recently demonstrated that low-dose acetylsalicylic acid (ASA) and hydroxychloroquine (HCQ) decreased the incidence of CV events in patients with systemic lupus erythematosus (SLE), who are at high risk for atherosclerosis [6, 7].

On this basis, we undertook the present retrospective study to investigate, the role, if any, of ASA in reducing CV morbidity. To that aim, we investigated the Italian multicentre RA cohort, from 4 GIRRCS (*Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale*) centres.

2. Methods

2.1. Patients. From our database, which includes RA patients consecutively admitted for their 1st visit, from November 1, 2000, to December 31, 2015, to 4 GIRRCS tertiary centres (Academic Rheumatology Units of Naples, l'Aquila, Rome, and Foggia), we selected patients with the following criteria:

(i) Those who at the first visit satisfied 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA [8]

(ii) Those who at the first visit had not experienced any prior CV event

(iii) Those who were subsequently assessed at least annually during follow-up

The duration of follow-up was defined as the time from the first visit (baseline visit) to the first CV event or to the last observation in patients without any thrombotic event.

A written informed consent had been obtained by each patient at admission and during follow-up for any new treatment, according to the Declaration of Helsinki. The study was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli" (CE 278).

2.2. Clinical and Laboratory Data. Our database contains information about each patient from admission to throughout follow-up and includes sex, age, disease duration (in years, from onset), autoantibodies profile (serum rheumatoid factor, RF test, cutoff 20 units/mL and anti-citrullinated cyclic peptide antibodies, ACPA, ELISA test, cut off 25 units/mL), disease activity (assessed by Simplefied Disease Activity Index (SDAI)) [9], disability (assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI)) [10], extra-articular manifestations and radiological features (erosions and joint narrowing), and smoking status (previous/current use of at least one cigarette/day). Concomitant comorbidities and concomitant treatments, as derived from medical records, had been noticed at baseline and from 6-monthly to yearly thereafter. Each patient was investigated for arterial hypertension (prior/ongoing and/or antihypertensive therapy use), diabetes mellitus (fasting glucose level >126 mg/dL in at least two tests and/or ongoing treatment with insulin or oral hypoglycaemic agents), hypercholesterolemia (total cholesterol, TC > 200 mg/dl and/or low-density lipoprotein, LDL > 130 mg/dl and/or high-density lipoprotein, HDL < 40 mg/dl and/or ongoing treatment for hypercholesterolemia), and obesity (body mass index (BMI) > 30 kg/m^2) [11].

Follow-up intervening treatments, i.e., biological and nonbiological DMARDs (methotrexate, leflunomide, sulfasalazine, and hydroxycloroquine), steroids, and statin use, were registered. Moreover, ASA treatment was recorded if prescribed at any time. In this regard, ASA therapy is currently administered to patients taking glucocorticoids, admitted to the Naples Unit, while in all other centres, ASA was prescribed only to patients with a high CV risk as assessed by traditional risk factors (in both cases, it was not administered to patients in whom it was contraindicated or it was stopped to those experienced side effects) [12]. Patients were then subdivided into two groups, namely, ASA- and non-ASA-treated, considering any patients undergoing ≥1 year ASA treatment as an ASA treated subject.

2.3. Outcome Variables. At each visit, any new-onset CV event was recorded. A CV event was defined as the presence of at least one of the following [13]:

(1) Ischemic heart disease (IHD), including angina pectoris (confirmed by exercise stress test) or MI (confirmed by electrocardiography and cardiac enzymes)

(2) Ischemic cerebrovascular disease (ICVD), including transient ischemic attack (TIA) or stroke supported by an imaging procedure (i.e., computed tomography angiography or magnetic resonance angiography)

(3) Ischemic peripheral vascular disease (IPVD): intermitted claudication or peripheral arterial thrombosis, confirmed by an imaging procedure (angiography or Doppler flow studies)

Any intervening event, as defined above, was recorded, and the diagnosis was confirmed by hospital discharge records and/or specific laboratory and diagnostic examinations (i.e., cerebral or myocardial imaging techniques, such as central nervous system computed tomography or magnetic resonance, echocardiography, or myocardial scintigraphy). Causes of death were identified from clinical records, hospital discharge or, when unavailable, by contacting the patient's relatives and obtaining from them written information (i.e., patient's general practitioner report).

On 31 December 2016, the incidence of CV events during follow-up and the vital status of each patient was recorded. Demographic, clinical features and incidence rate of CV events were compared between the two groups.

2.4. Statistical Analysis. Continuous variables were analyzed with Student's unpaired *t*-test or with the Mann–Whitney *U* test as appropriate. The chi-squared test or Fisher's exact test was applied for categorical variables. The incidence of CV events was calculated as incidence rate (IR: number of events/person years of observation). Kaplan–Meier curves and the log-rank test were used to analyze differences in

event-free survival. Univariable Cox regression analysis served to identify factors associated with CV event occurrence in the overall cohort. The factors found to be significant in univariable analysis were entered in the multivariable stepwise model.

We also derived a propensity score to account for the lack of randomization of ASA treatment. Using logistic regression, we found the predicted probability for the two different groups (ASA vs. non-ASA) using the following confounders: age > 60, smoke, hypertension, hypercholesterolemia, cumulative dose of steroids, and treatment centre. These propensity scores were then used as covariates in a Cox proportional hazards model to establish the relationship between ASA use and CV events.

A value of $p < 0.05$ was considered significant. Analysis was performed with MedCalc, version 12.7.0.0.

3. Results

3.1. Baseline Data. Seven-hundred forty-six consecutive patients were admitted during the study period.

Table 1 shows epidemiological, serological, and clinical features of the 746 patients of our cohort. Most patients were women (84.8%), with a mean (±standard deviation, SD) age of 59.5 (±13) years and a median disease duration of 11.9 years (interquartile range, IQR 7.37–18). As far as disease features are concerned, 436 patients (58.9%) were positive for RF; 371 patients (52%) were positive for ACPA; 429 patients (60%) had an erosive disease, while 86 patients (11.9%) presented extra-articular manifestations.

As assessed at the first visit, the median SDAI was 14 (IQR 7.2–22.9) and the median HAQ-DI was 1 (IQR 0.5–1.5).

Three-hundred twenty-five patients (45%) were smokers, 367 patients (49.5%) were affected by arterial hypertension, 96 (13.5%) suffered from diabetes, 276 (38%) suffered from hypercholesterolemia, and 112 (15%) were obese.

During the follow-up, all the patients had been managed according to the Treat to Target Strategy; in particular, 456 patients had been treated with biological DMARDs, as we expected in a tertiary centre, with or without conventional synthetic DMARDs (cs DMARDs) and 87% of whole cohort had been treated with steroids (mean cumulative dose: 1.08 g). Furthermore, 149 patients (19.2%) were treated with statins.

3.2. Follow-Up Data and CV Events. Patients were followed up for a median of 5.6 years (IQR 2.9–8.9). On 31 December 2016, 33 patients were lost to follow-up (4.4%). These patients were contacted by phone to ascertain vital status and the potential occurrence of CV events. Out of them, 4 patients were died, one for CV events (IMA) and 3 for other causes (2 for respiratory disease and 1 for cancer). At that time, we recorded 38 CV events: 29 MI, 4 stroke, 1 unstable angina, 1 heart failure, 2 atherosclerotic peripheral ischemia, and 1 death due to CV cause.

The IR of CV events in the overall cohort was 8/1000 person-years (38 events/4720 person-years).

3.3. ASA Role. Patients were then subdivided into two groups, namely, ASA-treated (242 patients) and non-ASA-treated (504 patients). Patients in the ASA group showed an older age, longer disease duration, higher prevalence of RF, ACPA, erosions, and higher HAQ. Regarding traditional risk factors, patients treated with ASA were more likely to suffer from arterial hypertension, diabetes, hypercholesterolemia, and obesity. On the other hand, SDAI were lower in the ASA group. As far as treatments during follow-up, ASA-treated patients showed a higher prevalence of treatments with methotrexate (MTX) and HCQ and as expected with steroids, as compared to the non-ASA group. As far as cardiovascular events are concerned, only three events occurred in the ASA group (3 events/1758 person-years) vs. 35 in the non-ASA group (35 events/2961 person-years). The IR of CV events was significantly lower in the ASA-treated group with respect to the non-ASA-treated group (IR ASA (1.70/1000) vs. IR non-ASA group (11.8/1000) person-years; $p = 0.0002$).

Furthermore, at the Kaplan–Meier curve, the CV event-free rate was higher in ASA-treated patients than in non-ASA-treated patients (log-rank test 12.8; $p = 0.0003$) (Figure 1).

Out of the 242 patients taking ASA, four patients (1.6%) developed menorrhagia, six (2.5%) epigastric pain, and one (0.4%) mild thrombocytopenia, but none of them discontinued ASA.

3.4. Predictors of CV Events. Age at first visit, SDAI > 11, arterial hypertension, hypercholesterolemia, and statins resulted to be independent predictors of CV events in univariable analysis as investigated by Cox regression analysis. As far as statins, we think that this result depends on a confounding for indication bias as statins have been prescribed to patients with hypercholesterolemia. On the other hand, biological treatment, HCQ, and ASA treatment were found to have a protective role (Table 2). At multivariable stepwise analysis the independent predictors of CV events were age at first visit (HR 2.82, 95% CI: 1.06–7.49; $p = 0.004$), arterial hypertension, and hypercholesterolemia (HR 9.11, 95% CI: 2.08–39.84; $p = 0.003$ and HR 3.15, 95% CI: 1.25–7.88; $p = 0.014$) as positive predictors; ASA treatment and HCQ treatment as negative predictors (HR 0.09, 95% CI: 0.02–0.37, $p = 0.0009$ and HR 0.21, 95% CI: 0.06–0.71, $p = 0.012$).

After adjustment for propensity score, results were very similar for ASA treatment: HR 0.09, 95% CI 0.02–0.39, $p = 0.001$.

Furthermore, we included in regression models the four treatment centres to account for variations in patients and treatment approaches by the study site. We could not find any significant differences at multivariable analysis (HR 1.29, 95% CI: 0.88–1.89, $p = 0.188$).

4. Discussion

We carried out a retrospective analysis of the rate of CV events in 746 patients consecutively admitted to 4 GIRRCS

Table 1: Baseline features and treatment during follow-up of the overall cohort.

Baseline features	
Sex: F/M ratio (%)	633/113 (84.8%)
Age (years)	
Median (IQR)	60.9 (52–68.6)
Mean ± SD	59.5 ± 13
Disease duration, years from onset	
Median (IQR)	11.9 (7.37–18)
RF+/−, *n* (%)	436/304 (58.9%)
ACPA+/−, *n* (%)	371/349 (52%)
Erosion+/−, *n* (%)	429/282 (60%)
SDAI baseline	
Median (IQR)	14 (7.2–22.9)
HAQ-DI baseline	
Median (IQR)	1 (0.5–1.5)
Smoke+/−, *n* (%)	325/397 (45%)
Hypertension+/−, *n* (%)	367/379 (49%)
Diabetes+/−, *n* (%)	96/650 (13%)
Hypercholesterolemia+/−, *n* (%)	276/449 (38%)
Obesity+/−, *n* (%)	112/631 (15%)
Treatment during follow-up	
Anti-TNF, *n* (%)	393/353 (52.6%)
Mean duration (years)	5.23
Non-anti-TNF-bDMARDs, *n* (%)	209/536 (28%)
Mean duration (years)	3.68
MTX+/−, *n* (%)	649/97 (87%)
Mean duration (years)	6.16
Other csDMARDs+/−, *n* (%)	Leflunomide 182/564 (24.4%); yrs 4.06 Sulfasalazine 127/617 (17%); yrs 2.8 Hydroxychloroquine 288/458 (38.6%); yrs 4.25
Mean duration (years)	
Low-dose steroids (2.5–5 mg), *n* (%)	651/95 (87.2%)
Mean duration (years)+	6.88
Cumulative dose of steroids (g)	
Mean ± SD	1.08 ± 1.07
Statin+/−, *n* (%)	149/494 (19.2%)
Mean duration (years)	5.15

IQR: interquartile range; SD: standard deviation; RF: rheumatoid factor; ACPA: anti-citrullinated cyclic peptide antibodies; SDAI: Simplified Disease Activity Index; HAQ-DI: Health Assessment Questionnaire-Disability Index; TNF: tumor necrosis factor; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; bDMARDs: biological disease-modifying antirheumatic drugs; MTX: methotrexate; ASA: acetylsalicylic acid.

centres, who, at admission, had not experienced any CV event. The IR of CV events in our cohort was significantly lower in the ASA-treated with respect to the non-ASA-treated group (IR ASA group (1.70/1000) vs. IR non-ASA group (11.8/1000) person-years; $p = 0.0002$), and CV event-free rate was higher in ASA-treated than in non-ASA-treated patients (log-rank test 12.8; $p = 0.0003$). These results might depend on the lower disease activity and the higher prevalence of MTX and HCQ-treated patients in the ASA-treated with respect to the non-ASA-treated group. Nevertheless, the higher prevalence of steroid-treated patients, the older age and the longer disease duration, the higher prevalence of RF and ACPA positivity, erosions, arterial hypertension, diabetes, hypercholesterolemia, and obesity in the ASA group seem to indicate a protective role of ASA itself. Actually, ASA intake resulted to be an independent protective factor at multivariable analysis (HR 0.09; 95% CI: 0.02–0.37; $p = 0.0009$), whereas the presence of arterial hypertension and hypercholesterolemia (HR 9.11, 95% CI: 2.08–39.84; $p = 0.003$ and HR 3.15, 95% CI: 1.25–7.88; $p = 0.014$) was independent predictive factors of CV events. These latter results confirm the already reported role of arterial hypertension and hypercholesterolemia as risk factors for CV disease in RA patients [14]. Intriguingly, smoke was not found to exert a promoting role of CV events in our RA cohort. We are inclined to think it depends on a reporting bias; the smoking habit has been reported in only 397 patients from the overall cohort. Finally, a high percentage of our patients were treated with bioDMARDs, this feature depending on the tertiary role of the 4 centres. In any case, the absence of significant difference in the use of bioDMARDs between ASA and non-ASA-treated patients makes a role of these drugs on our results unlikely.

As far as general population, the role of ASA in decreasing the incidence of CV events is debated [15]. Clinical benefits of aspirin for secondary prevention of CV events are well established. However, its use in primary CV prevention remains controversial [16].

The most recent meta-analysis about primary CV prevention pointed out a modest beneficial effect, particularly in

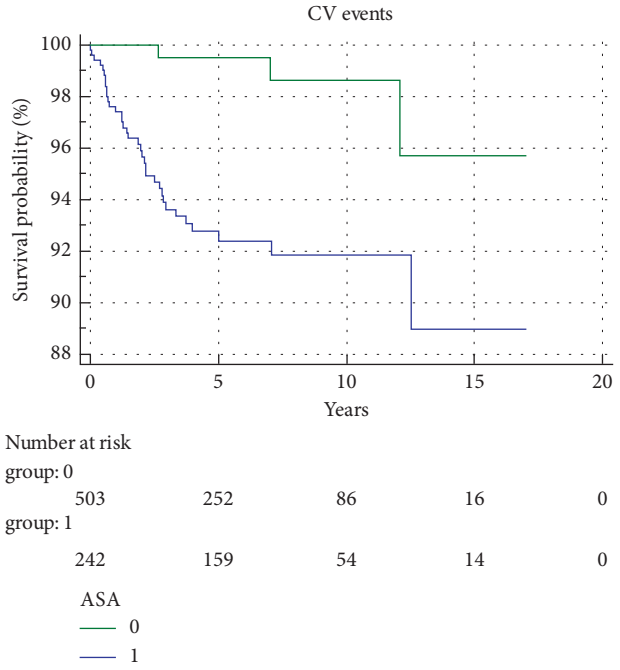

Figure 1: Kaplan–Meier curve: CV event-free rate for ASA-treated group vs. non-ASA-treated group. CV: cardiovascular; ASA: acetylsalicylic acid.

Table 2: Univariate analysis: factors associated with cardiovascular event occurrence.

Features	HR (CI)	p
Sex (F)	1.21 (0.43–3.09)	0.693
Age > 60 years	4.75 (1.98–11.35)	**0.0005***
RF+	0.91 (0.52–1.62)	0.752
ACPA+	1.80 (0.92–3.52)	0.08
Erosion	1.11 (0.56–2.20)	0.76
SDAI > 11	2.40 (1.03–5.59)	**0.0004***
Smoke	0.58 (0.28–1.18)	0.1334
Hypertension	19.3 (4.65–80.18)	**0.0001***
Diabetes	2.14 (1.01–4.52)	0.046
Hypercholesterolemia	5.13 (2.33–11.3)	**<0.0001***
Obesity	1.29 (0.56–2.95)	0.543
Biological treatment	0.42 (0.22–0.82)	**0.01***
HCQ	0.12 (0.04–0.39)	**0.0005***
MTX	0.99 (0.98–1.01)	0.940
Statins	3.68 (1.88–7.23)	**0.0001***
ASA	0.15 (0.05–0.51)	**0.002***
Cumulative dose of steroids	1 (0.99–1)	0.186

HR: hazard ratio; CI: confidence interval; RF: rheumatoid factor; ACPA: anti-citrullinated cyclic peptide antibodies; SDAI: Simplified Disease Activity Index; HAQ-DI: Health Assessment Questionnaire-Disability Index; HCQ: hydroxychloroquine; MTX: methotrexate; ASA: acetylsalicylic acid. *A p value < 0.05 was considered for factors associated with cardiovascular event occurrence (positive predictor if HR > 1, negative if HR < 1).

older adults as confined to MI [17]. In Italy, it is recommended in patients at high CV risk, like those with RA who are not at increased risk of bleeding [18]. On the other hand, a recent meta-analysis on the role of ASA in the primary prevention of CV events in patients with diabetes did not point out a definite role in the prophylaxis of a first atherosclerotic event or mortality [19]. In conclusion, no agreement has been reached.

As far as RA, in 1978, Linos et al. reviewed clinical charts of high-dose ASA-using RA patients and compared the incidence of CV events with that detected in the general population from Rochester County [20]. These authors failed to find any difference between the 2 groups and interpreted the result as a proof of the absence of any CV protective ASA effect. However, in 1978, despite the previous report by Cobb et al. pointing out an increased mortality by CV events in RA patients [21], accelerated atherosclerosis was not yet recognized as a distinct aspect of the disease [22].

As this aspect is well documented at present, detecting in RA patients an incidence of CV events similar to that in the general population could be regarded as a support to the role of ASA in the prophylaxis of CV events in RA. On the other hand, low-dose ASA in RA patients, using chronic non-steroidal anti-inflammatory drugs (NSAIDs) and esomeprazole, was not reported to affect the risk of major NSAID toxicity and major adverse CV events [23]. However, our study was not designed for this purpose, and in our cohort, patients were taking neither NSAIDs nor cyclooxygenase-2 inhibitors. Moreover, Durán et al. found no protective role of ASA as primary prophylaxis in a small group of RA patients. Nevertheless, in this study, they included subjects ≥60 years old (mean age 73.5), i.e., significantly older than those from our cohort (mean age 59.5) [24].

We also detected a significant protective role of HCQ for CV events occurrence in RA (HR 0.23, 95% CI: 0.067–0.77; $p = 0.0172$). In that regard, recent evidences in the literature demonstrated that HCQ has a positive impact on metabolic and cardiovascular outcomes in patients with RA, both by decreasing modifiable factors for CVD, namely, lipid profile, diabetes incidence, and glycosylated hemoglobin level and by decreasing the incidence of CV events [25]. Moreover, Sharma et al. have recently studied the association of HCQ use with incident cardiovascular disease (CVD) in a retrospective inception cohort of RA patients, reporting a 72% reduction in the risk of CVD in HCQ users [26]. We cannot rule out a concomitant role of HCQ in reducing the cardiovascular risk of ASA-treated patients. Nevertheless, the significance of Cox regression analysis points out an independent role of ASA.

Our study has some limitations. First of all, it is an observational retrospective study even if patients were prospectively enrolled. Secondly, the IR of CV events recorded in our cohort was 8/1000 person-years (38 events/4720 person-years), that is lower than that reported in other European and non-European cohorts [3]. The small number of CV events in the ASA group underlines the need to investigate the role of low-dose ASA in the prophylaxis of CV events in RA patients from countries with a higher burden of CV disease.

5. Conclusion

Our study suggests that low-dose ASA may have a role in the primary prophylaxis of CV events in RA patients. Further larger prospective studies are needed.

Abbreviations

RA:	Rheumatoid arthritis
CVD:	Cardiovascular disease
MI:	Myocardial infarction
DMARDs:	Disease-modifying antirheumatic drugs
ASA:	Acetylsalicylic acid
PGI/Tx2:	Prostaglandin I/thromboxane A2
SLE:	Systemic lupus erythematosus
GIRRCS:	Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale
ACR/ EULAR:	American College of Rheumatology/European League Against Rheumatism
TIA:	Transient ischemic attack
RF:	Rheumatoid factor
ACPA:	Anti-citrullinated cyclic peptide antibodies
SDAI:	Simplified Disease Activity Index
HAQ-DI:	Health Assessment Questionnaire-Disability Index
TC:	Total cholesterol
LDL:	Low-density lipoprotein
HDL:	High-density lipoprotein
BMI:	Body mass index
IR:	Incidence rate
SD:	Standard deviation
IQR:	Interquartile range
MTX:	Methotrexate
HCQ:	Hydroxychloroquine
HR:	Hazard ratio
CI:	Confidence interval
NSAID:	Nonsteroidal anti-inflammatory drug.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of the information that could compromise the research participant privacy/consent.

Additional Points

Significance and Innovations. (i) CV morbidity and mortality are significantly greater in RA. (ii) Cardiovascular morbidity is lower in ASA-treated RA patients. (iii) ASA may have a role as primary prophylaxis of CV events in RA.

Ethical Approval

The study was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli."

Consent

Informed consent was obtained from all individual participants included in the study, according to the Declaration of Helsinki.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

DI collected, analyzed, and interpreted data and was a major contributor in writing the manuscript. SF analyzed and interpreted data and was a contributor in writing the manuscript. IP, VD, PR, DPEM, LN, and NM collected data. RDG, FPC, AA, and RG were contributors in interpreting data. GV interpreted data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Hindawi
Cardiology Research and Practice
Volume 2019, Article ID 5931975, 7 pages
https://doi.org/10.1155/2019/5931975

Research Article

Non-HDL-c/TC: A Novel Lipid-Related Marker in the Assessment of Severity of Coronary Artery Lesions and Cardiovascular Outcomes

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Received 24 October 2018; Revised 16 February 2019; Accepted 17 March 2019; Published 23 April 2019

Guest Editor: Rajesh Tota-Maharaj

Background. Non-high-density lipoprotein cholesterol (non-HDL-c) predicts the severity of coronary artery lesions in patients not treated with statin. The association between non-HDL-c and severity of coronary artery lesions in patients treated with lipid-lowering therapy has been unknown. *Hypothesis*. We hypothesize a novel marker of non-HDL-c/TC predicts the severity of coronary artery lesions and clinical outcomes in 12 months in the patients treated with statin. *Method*. 473 subjects who met inclusion criteria were eligible for inclusion. Coronary artery angiography (CAG) was performed, and the Gensini score (GS) was calculated in all the subjects divided into three subgroups of low risk, medium risk, and high risk by the tertiles of GS. The non-HDL-c value was calculated as TC minus HDL-c, while non-HDL-c/TC was the ratio of non-HDL-c and TC. *Results*. The concentration of non-LDL-c differed between non-obstructive-CAD group and obstructive-CAD group ($P < 0.05$), and non-HDL-c/TC was elevated in the obstructive-CAD group ($P < 0.05$). Increased GS was associated with increasing non-HDL-c/TC ($P < 0.05$). Non-HDL-c/TC (OR: 108.50, 95% CI: 1.57–7520.28; $P = 0.030$) remained as an independent predicting factor of high risk under GS stratification. In unadjusted Cox model, high non-HDL-c/TC (RR: 1.976, 95% CI: 1.155–3.382; $P = 0.013$) predicted the occurrence of adverse events. After multivariate adjustment, high non-HDL-c/TC (RR: 1.921, 95% CI: 1.105–3.339; $P = 0.021$) was an independent predictor of poor outcomes. *Conclusion*. High level of non-HDL-c/TC presented an excellent prognostic value compared with other lipid-related markers in CAD patients treated with statin.

1. Introduction

Cardiovascular disease (CVD), as one of the most common causes of death worldwide, caused 17.3 million deaths worldwide which is more than twice that caused by cancer [1, 2]. In Europe, over 4 million people die of cardiovascular disease (CVD) each year [3]. A total of over 16.5 million Americans aged over 20 years have coronary artery disease (CAD) between 2011 and 2014 with prevalence of 6.3% in U.S. [4].

The link between blood lipids and CAD risks was initially discovered nearly 80 years ago, and many studies centered on the diagnosis or prognosis of CAD suggested dyslipidemia might be associated with severity of atherosclerosis [5, 6]. These results improved our understanding of CAD by suggesting that blood lipid levels increase cardiovascular risk. Recently, multiple risk assessment systems including Framingham model, Systemic Coronary Risk Estimation (SCORE), and Prospective Cardiovascular Münster Study (PROCAM) which included multiple lipid-related markers of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-c) were recommended to assess total CAD or CV risks in several current national guidelines [7–9].

Multiple guidelines from China, Europe, USA, or Canada recommended that low-density lipoprotein cholesterol (LDL-c) be used as the primary risk estimation for CVD and low HDL-c be an independent risk marker [10–13]. In addition, several novel cholesterol-associated markers such as non-

HDL-c and non-HDL-c/HDL-c are also considered as alternative analysis for risk estimation [14]. While statins reduce LDL-c and raise HDL-c, few studies have evaluated cardiovascular risk in persons already treated with statins [11]. Therefore, identifying the best cholesterol-related marker to judge the severity of atherosclerosis seems essential in patients treated with statins.

Non-HDL-c, calculated as the difference between TC and HDL-c, predicts CVD risk equivalent to or more robustly than LDL-c for capturing a more complicated pattern of dyslipidemia in those patients combined with high triglyceride [15, 16].

Previously, literatures have revealed that elevated lipoprotein levels like TG, LDL-c, intermediate HDL-c, and small HDL-c indicated severe coronary artery lesions [11, 17]. However, non-HDL-c is affected by baseline TC level and lipid-lowering drug. Non-HDL-c may not accurately predict the severity of coronary artery lesions in patients already treated with lipid-lowering therapy before. To the best of our knowledge, few studies have studied the association between non-HDL-c and severity of coronary artery lesions in patients treated with lipid-lowering drugs.

In this study, we evaluated the prognostic ability of a novel marker, the ratio of non-HDL-c to TC. We hypothesize that non-HDL-c/TC is a better cardiovascular risk marker in patients treated with statins. Our study aims to compare non-HDL-c/TC with non-HDL-c in predicting the severity of coronary artery lesions and outcomes in 12 months.

2. Materials and Methods

2.1. Study Design and Population. A clinical retrospective study was designed for evaluating non-HDL-c or non-HDL-c/TC to severity of coronary artery lesions and prognosis of CAD. A total of 629 consecutive individuals with chest pain were evaluated for inclusion in our study between September 2014 and October 2016. 493 subjects were eligible for inclusion. Persons were included in the study if (1) there were clinical findings suggestive of possible CAD including stable angina pectoris, unstable angina pectoris, non-ST segment elevated myocardial infarction (NSTEMI), and ST segment elevated myocardial infarction (STEMI); (2) the patient had coronary angiography performed; (3) medical history including statins at least 3 months before entering this study; and (4) test of lipid metabolism including TC, HDL-c, as well as VLDL-c, or LDL-c. Exclusion criteria included (1) prior PCI therapy, (2) unavailable clinical data especially TC or HDL-c, and (3) comorbidity of thyroid dysfunction, severe liver dysfunction, and/or renal insufficiency or malignant tumor. The Ethical Committee Board of Tianjin Union Medical Center approved this study protocol.

2.2. Clinical Data Collection. The demographic characteristics and medical history were recorded at the time of hospitalization. Fasting blood samples were obtained in precooled EDTA and centrifuged at 3600 rpm for over 10 min. Laboratory indices including creatinine kinase (CK), creatinine kinase-MB (CK-MB), high-sensitivity-C reactive protein (hs-CRP), creatinine (Cr), hemoglobin A1c (HbA1c), TC, total triglyceride (TG), HDL-c, LDL-c, and very-low-density lipoprotein cholesterol (VLDL-c) were tested by the biochemistry analyzer (Abbott Architect C-16000 system, Chicago, U.S). Briefly, the TC level was detected by the CHOD-PAP method (cholesterol reagent; Shanghai Fosun Long March Medical Science Co., Ltd) with a coefficient variation (CV) of less than 4%. The GPO-PAP method was performed to test TG (triglycerides reagent; Shanghai Fosun Long March Medical Science Co., Ltd) combined with CV of <5%. In addition, the HDL-c (HDL-cholesterol reagent kit; Shanghai Fosun Long March Medical Science Co., Ltd) and LDL-c (LDL-cholesterol reagent kit; Shanghai Fosun Long March Medical Science Co., Ltd) levels were determined by the clearance method (HDL-cholesterol reagent kit) with a CV of <3% or 4%, respectively. The relative deviation of all kits was not more than 10%. The non-HDL-c value was calculated as TC minus HDL-c, and meanwhile non-HDL-c/TC was the ratio of non-HDL-c and TC.

2.3. Evaluation of Severity of Coronary Artery Lesions. Coronary artery angiography (CAG) was performed in all patients using the Judkins technique by 2 experienced cardiac interventional physicians [18]. Based on the coronary artery angiographic results, Gensini score (GS) was calculated in all the participants for quantifying the degree of coronary artery lesions. The specific computing method of GS score has been depicted in the literature previously [19]. Briefly, both the severity of coronary artery stenosis and its geographic location are incorporated in the GS model. All the patients were classified into low-risk, medium-risk, and high-risk subgroups by the tertiles of GS. Coronary stenosis over 50% in one of three main coronary arteries was considered as CAD.

2.4. Follow-Up and Outcomes. Clinical follow-up data were obtained by clinic visits every 1 month, telephone interviews every 2 weeks, and analysis of readmission. The primary outcomes included all-cause mortality or cardiovascular mortality. The secondary outcomes included the reoccurrence of chest pain or rehospitalization for PCI or CABG. Follow-up continued until reaching the combined outcomes or censoring on October 31, 2017. Patients showed primary outcome or secondary outcome and were recorded as adverse events.

3. Results

From September 2014 through October 2016, a total of 629 patients with suspected chest pain or distress were screened (Figure 1). 493 consecutive individuals were finally included in this study with the exclusion of 136 subjects. Of these, 46 persons had prior PCI, 20 persons had a diagnosis of a malignant tumor or thyroid dysfunction, and 70 persons had incomplete clinical data or no treatment with statins. 493 patients met the inclusion criteria and were divided into

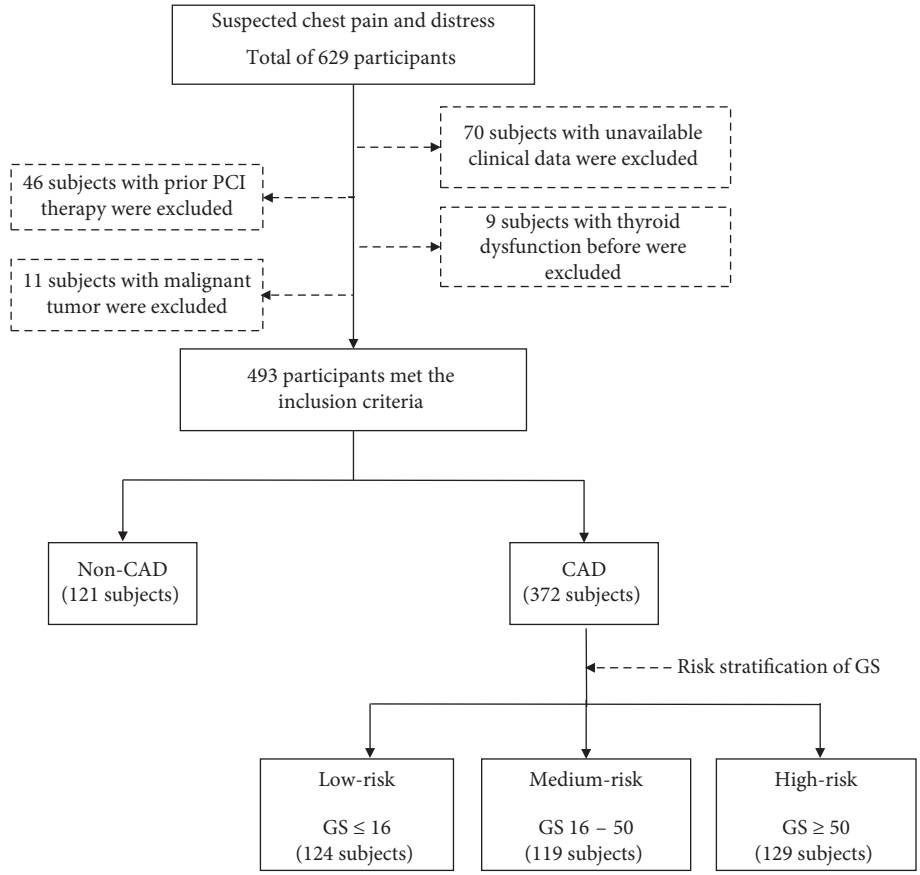

Figure 1: Study flow chart: participant selection in the study. PCI: percutaneous coronary intervention; CAD: coronary artery disease; GS: Gensini score.

non-obstructive-CAD group (121 subjects) or obstructive-CAD group (372 subjects). Patients with <50% of any major epicardial coronary artery were classified into non-obstructive-CAD group while patients ≥50% stenosis were classified as obstructive-CAD group. In the next analysis, patients in obstructive-CAD group were assigned into three subgroups (Low-risk, medium-risk, and high-risk) on the basis of tertiles of GS.

Patients in the non-obstructive-CAD group and different risk subgroups under GS stratification were balanced with regard to the majority of baseline demographic and clinical characteristics well (Table 1). There was no statistically significant different in either group with respect to medical history, and TC, LDL-c, or LVEF levels ($P > 0.05$). The mean age of CAD patients was higher than that of non-obstructive-CAD patients ($P < 0.05$), and the proportion of males increased in the obstructive-CAD group compared to the non-obstructive-CAD group ($P < 0.05$). The laboratory indices including CK, CK-MB, hs-CRP, Cr, HbA1c, TG, and VLDL-c ($P < 0.05$) were increased significantly in patients with CAD. LDL-c level showed no difference between non-obstructive-CAD group and obstructive-CAD group ($P > 0.05$). However, HDL-c levels were lower in patients with CAD ($P < 0.05$). The left ventricular ejection fraction (LVEF) was comparable in both groups ($P > 0.05$). The concentration of non-HDL-c was significantly increased in obstructive-CAD group ($P < 0.05$), and non-HDL-c/TC elevated in obstructive-CAD group compared to non-obstructive-CAD group ($P < 0.05$). The comparison among distinct risk subgroups under the GS stratification was also analyzed. Increased GS was associated with increasing age, male sex, Cr, HbA1c, HDL-c, and non-HDL-c/TC ($P < 0.05$).

Ordered logistic regression analysis was performed for evaluating risk factors for severity of coronary artery lesions. Univariate and multivariate-adjusted RRs are presented in Table 2. On univariate analysis, male, age, HDL-c, HbA1c, and non-HDL-c/TC were possible confounding factors for high GS. After multivariate ordered logistic regression analysis, non-HDL-c/TC (OR: 108.50, 95% CI: 1.57–7520.28; $P = 0.030$) remained as independent predicting factor of high risk under GS stratification, as well as male (OR: 2.95, 95% CI: 1.86–4.69; $P < 0.001$), age (OR: 1.05, 95% CI: 1.02–1.08; $P = 0.001$), and HbA1c (OR: 1.43, 95% CI: 1.20–1.71; $P < 0.001$), while HDL-c was no longer statistically significant ($P > 0.05$).

The incidence of adverse events was recorded during the 12-month follow-up in our obstructive-CAD group. The baseline characteristics of nonadverse events and adverse events subgroups are shown in Table 3. The percentage of smoking elevated significantly in obstructive-CAD patients with adverse events subgroup with 63.6% (VS nonadverse events subgroup: 45.1%, $P = 0.011$); however, the ratio of hypertension decreased with 43.6% (VS nonadverse events

Table 1: Baseline characteristics of the study population.

	Non-CAD (n = 121)	CAD			P_1 value	P_2 value
		Low risk (n = 124)	Medium risk (n = 118)	High risk (n = 129)		
Age (years)	59.47 ± 8.07	61.27 ± 8.45	63.11 ± 7.62	63.81 ± 8.04	<0.001**	0.036*
Male (n (%))	39 (32.2%)	48 (38.7%)	71 (60.2%)	82 (63.6%)	<0.001**	<0.001**
Smoking (n (%))	38 (31.4%)	54 (43.5%)	67 (56.8%)	57 (44.2%)	0.001**	0.056
Medical history (n (%))						
Hypertension	61 (50.4%)	67 (54.0%)	64 (54.2%)	83 (64.3%)	0.113	0.166
DM	43 (35.5%)	48 (38.7%)	50 (42.4%)	60 (46.5%)	0.324	0.454
Dyslipidemia	57 (47.1%)	70 (56.5%)	64 (54.2%)	78 (60.5%)	0.194	0.603
Laboratory index						
CK (U/L)	77 (55, 104)	77 (52, 120)	84 (58, 117)	85 (60, 151)	0.038*	0.142
CK-MB (U/L)	10 (8, 12)	12 (9, 15)	12 (9, 16)	13 (9, 18)	<0.001**	0.163
hs-CRP (U/L)	1.01 (0.51, 2.10)	1.82 (0.67, 3.20)	1.40 (0.60, 2.98)	2.28 (0.90, 5.15)	0.001**	0.057
Cr (mg/dL)	0.67 ± 0.14	0.71 ± 0.16	0.74 ± 0.16	0.81 ± 0.21	<0.001**	0.001**
HbA1c (%)	6.11 ± 0.74	6.25 ± 0.98	6.48 ± 1.11	6.85 ± 1.46	<0.001**	0.001**
TC (mg/dL)	4.36 (3.87, 5.22)	4.69 (4.13, 5.32)	4.70 (4.11, 5.28)	4.70 (4.11, 5.30)	0.141	0.724
TG (mg/dL)	1.39 (0.99, 1.92)	1.66 (1.10, 2.27)	1.54 (1.18, 1.97)	1.72 (1.24, 2.43)	0.006**	0.099
HDL-c (mg/dL)	1.17 (1.07, 1.38)	1.19 (1.06, 1.40)	1.15 (0.98, 1.30)	1.08 (0.96, 1.27)	0.006**	0.005**
LDL-c (mg/dL)	2.85 ± 0.85	3.03 ± 0.84	3.01 ± 0.86	3.05 ± 0.92	0.241	0.950
VLDL-c (mg/dL)	0.65 (0.45, 0.89)	0.74 (0.52, 1.05)	0.70 (0.54, 0.92)	0.79 (0.57, 1.11)	0.008**	0.079
LVEF (%)	59 (57, 62)	58 (57, 60)	58 (57, 61)	58 (56, 60)	0.109	0.213
Non-HDL-c (mg/dL)	121.78 (104.58, 154.64)	135.70 (108.34, 159.09)	134.92 (113.47, 155.80)	137.63 (119.65, 158.51)	0.049*	0.629
Non-HDL-c/TC	0.74 (0.70, 0.77)	0.75 (0.71, 0.78)	0.75 (0.70, 0.78)	0.76 (0.73, 0.79)	0.006*	0.016*
Adverse events (n (%))	0	7 (5.6%)	16 (13.6%)	32 (24.8%)	NS	<0.001**

Values are mean ± SD (standard deviation), median (percentiles 25th–75th), or n (%). P_1 value indicates comparison among distinct Gensini risk and non-CAD groups. P_2 value indicates comparison among distinct Gensini risk subgroups. *$P < 0.05$ and **$P < 0.01$. DM: diabetes mellitus; CK: creatinine kinase; CK-MB: creatinine kinase-MB; hs-CRP: high-sensitivity-C reactive protein; Cr: creatinine; HbA1c: hemoglobin A1c; TC: total cholesterol; TG: total triglyceride; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; VLDL-c: very-low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction.

Table 2: Independent correlates of severity of coronary artery lesion according to Gensini score stratification.

	Odds ratio	95% CI	P value
Univariate regression			
Male	2.16	1.47–3.17	<0.001**
Age	1.03	1.01–1.06	0.012*
HDL-c	0.45	0.23–0.88	0.019**
HbA1c	1.40	1.17–1.67	<0.001**
Non-HDL-c/TC	138.31	4.67–4095.95	0.004**
Multivariate regression			
Male	2.95	1.86–4.69	<0.001**
Age	1.05	1.02–1.08	0.001**
HDL-c	1.48	0.62–3.50	0.376
HbA1c	1.43	1.20–1.71	<0.001**
Non-HDL-c/TC	108.50	1.57–7520.28	0.030*

Multivariate model adjusted for male, age, HDL-c, HbA1c, and Non-LDL. CI = confidence interval. *$P < 0.05$ and **$P < 0.01$. HDL-c, high-density lipoprotein cholesterol; HbA1c: hemoglobin A1c.

subgroup: 43.6% $P = 0.024$). No difference was shown in other medical history including DM or dyslipidemia ($P = 0.050$, 0.919) as well as male sex ($P = 0.093$) and age ($P = 0.827$). The laboratory indices are also shown in Table 3; there were no differences in both subgroups except HDL-c ($P = 0.011$). In addition, Gensini score and non-HDL-c/TC elevated in adverse event subgroup compared with that of nonadverse events subgroup ($P < 0.001$, 0.031), while no difference was seen in non-HDL-c level and LVEF ($P = 0.785$, 0.054).

The present study suggested non-HDL-c/TC might be an independent factor for predicting the occurrence of adverse events. All the patients with obstructive CAD were divided into high non-HDL-c/TC level or low non-HDL-c/TC based on the median value (0.751) of non-HDL-c/TC. Survival analysis using the Cox regression model was performed to evaluate the independent risk factor for adverse events (Table 4 and Figure 2). In unadjusted Cox model, high non-HDL-c/TC (RR: 1.976, 95% CI: 1.155–3.382; $P = 0.013$), smoking (RR: 1.779, 95% CI: 1.024–3.092; $P = 0.041$), hypertension (RR: 1.737, 95% CI: 1.020–2.960; $P = 0.042$), and Gensini score (RR: 1.779, 95% CI: 1.024–3.092; $P = 0.041$) predicted the occurrence of adverse events. After adjusting for these factors, high non-HDL-c/TC (RR: 1.921, 95% CI: 1.105–3.339; $P = 0.021$), smoking (RR: 2.276, 95% CI: 1.289–4.022; $P = 0.005$), hypertension (RR: 1.873, 95% CI: 1.088–3.227; $P = 0.024$), and Gensini score (RR: 1.012, 95% CI: 1.007–1.016; $P < 0.001$) were independent risk factors for predicting poor outcomes. The unadjusted Kaplan–Meier curves presented slight difference ($P = 0.041$) of prognosis between high HDL-c/TC and low HDL-c/TC, while this difference was further amplified after adjusting for hypertension, smoking, and GS ($P = 0.017$) (Figure 3).

Table 3: Baseline characteristics of CAD patients with adverse and nonadverse events.

	Nonadverse events ($n = 317$)	Adverse events ($n = 55$)	P value
Age (years)	62.79 ± 8.12	63.06 ± 7.97	0.827
Male (n (%))	177 (55.8%)	24 (43.6%)	0.093
Smoking (n (%))	143 (45.1%)	35 (63.6%)	0.011*
Medical history (n (%))			
Hypertension	190 (59.9%)	24 (43.6%)	0.024*
DM	128 (40.4%)	30 (54.5%)	0.050
Dyslipidemia	181 (57.1%)	31 (56.4%)	0.919
Laboratory index			
CK (U/L)	81 (57, 126)	72 (51, 155)	0.993
CK-MB (U/L)	12 (9, 16)	11 (8, 17)	0.964
hs-CRP (mg/L)	1.70 (0.67, 3.27)	1.38 (0.66, 5.17)	0.760
Cr (mg/dL)	0.71 (0.62, 0.87)	0.72 (0.62, 0.85)	0.687
HbA1c (%)	6.1 (5.7, 6.8)	6.3 (5.8, 7.3)	0.063
TC (mg/dL)	175.70 (157.90, 202.01)	181.50 (144.74, 200.85)	0.947
TG (mg/dL)	138.94 (102.66, 184.97)	147.80 (105.32, 181.43)	0.896
HDL-c (mg/dL)	45.67 (39.86, 53.79)	41.80 (37.93, 46.83)	0.011*
LDL-c (mg/dL)	114.55 ± 31.35	112.62 ± 27.86	0.684
VLDL-c (mg/dL)	27.48 (20.51, 37.93)	27.09 (20.90, 35.22)	0.792
LVEF (%)	58 (57, 61)	58 (56, 60)	0.054
Gensini score	26 (10, 50)	64 (33, 104)	<0.001**
Non-LDL-c (mg/dL)	132.47 ± 32.40	133.80 ± 33.07	0.785
Non-LDL-c/TC	0.74 (0.70, 0.78)	0.77 (0.72, 0.78)	0.031*

Values are mean ± SD (standard deviation), median (percentiles 25th–75th), or n (%). P value indicates comparison between nonadverse events and adverse events subgroup. DM: diabetes mellitus; CK: creatinine kinase; CK-MB: creatinine kinase-MB; hs-CRP: high-sensitivity C-reactive protein; Cr: creatinine; HbA1c: hemoglobin A1c; TC: total cholesterol; TG: total triglyceride; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; VLDL-c: very-low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction.

Table 4: Unadjusted and adjusted survival analysis for predicting adverse events.

Smoking	1.779	1.024–3.092	0.041*	2.276	1.289–4.022	0.005**
Hypertension	1.737	1.020–2.960	0.042*	1.873	1.088–3.227	0.024*
Gensini score	1.011	1.007–1.016	<0.001**	1.012	1.007–1.016	<0.001**
Non-HDL-c/TC (>0.751)	1.976	1.155–3.382	0.013*	1.921	1.105–3.339	0.021*

Multivariate model adjusted for smoking, hypertension, Gensini score, and non-HDL-c/TC. RR: relative risk; CI: confidence interval. *$P < 0.05$ and **$P < 0.01$.

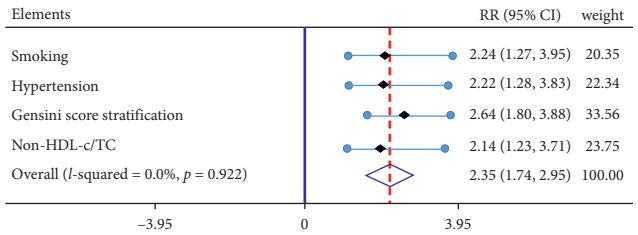

Figure 2: Forest plots of adjusted RR for the adverse events. RR: relative risk; CI: confidence interval.

4. Discussion

This study shows that, in patients with CAD who are treated with statins, high level of non-HDL-c/TC, while not non-HDL-c, is associated with high GS. Non-HDL-c/TC is an independent risk factor in estimation of severity of coronary atherosclerosis. Accordingly, increased non-HDL-c/TC, which predicts more severe coronary artery lesions, is associated with a poor outcome in 1-year follow-up. After adjusting for several confounders, high level of non-HDL-c/TC indicated poorer prognosis. Overall, these findings support the hypothesis that, in patients treated with statins, non-HDL-c/TC may be a superior predictor of events at one year.

This study focused on the predicting value of lipid-related markers in the assessment of coronary artery lesions and clinical outcomes. In several clinical conditions, series of lipid markers such as TC, LDL-c, HDL-c, and non-HDL-c have been utilized in predicting the risk of CVD [11]. In addition, non-HDL-c and HDL-c can predict the severity of coronary artery lesions. Non-HDL-c indicates a total of cholesterol within all the apolipoprotein B (Apo B) particle including LDL-c and remnant cholesterol [20]. From a prospective study of CGPS, the remnant cholesterol, composed of VLDL-c and intermediate-density lipoproteins (IDL-c), is also a causal risk factor for ischemic heart disease (IHD) [21]. Thus, LDL-c level alone can definitely underestimate the real cardiovascular risk, or severity of atherosclerosis, and further overestimate the prognosis of CAD. Non-HDL-c representing harmful cholesterol could accurately assess the cardiovascular risk and severity of coronary artery lesions in CAD.

However, these lipid-related markers are altered by numerous classes of lipid-lowering drugs which may be one of the confounding factors in predicting severity of coronary

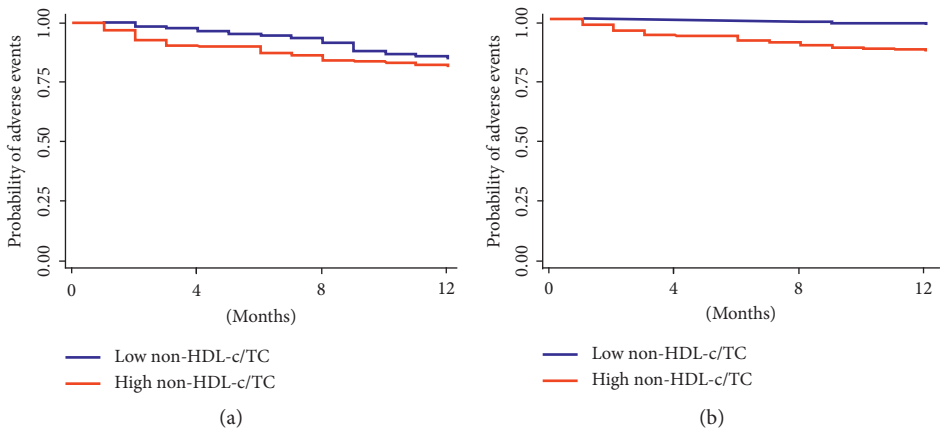

Figure 3: (a) Unadjusted and (b) Adjusted Kaplan–Meier survival curves of non-HDL-c/TC. This model is adjusted for smoking, hypertension, and Gensini score.

artery lesions and short-term clinical outcomes. Statins, as a first line in the treatment of CAD, can significantly reduce serum TC and LDL-c levels or even inhibit VLDL synthesis as well as increase HDL-c levels slightly. In patients with suspected CAD, intensified statins therapy has been recommended by numerous national guidelines [22–24].

Non-HDL-c is calculated as the difference between TC and HDL-c, which can be increased after using statins through reducing LDL-c level. Therefore, statins therapy may underestimate the severity of coronary artery lesions and finally overestimate the clinical prognosis in the real world. A retrospective study enrolled a total of 1757 consecutive patients, and all the participants were divided into four groups based on the GS stratification [17]. Patients with high GS presented elevated non-HDL-c, and non-HDL-c may be a better predictor compared with LDL-c. All the participants in that retrospective study recruited only those treated without any lipid-lowering drugs, thus no confounding from statins insisted on in this study. In the real world, more patients have accepted treatment of statins before CAD. Despite this, the association between lipid-related markers and severity of coronary artery lesions has been unknown in patients treated with statin.

Statin could affect the non-HDL-c and TC value through lowering LDL-c, which may underestimate the cardiovascular risks. Non-HDL-c/TC, as the ratio of non-HDL-c and TC, may weaken this confounding. Non-HDL-c/TC, compared to non-HDL-c, could better reflect the basal lipid level and study the association with severity of coronary artery lesions and clinical outcome in the real world. Although non-HDL-c and non-HDL-c/TC were both increased in patients with CAD in our study, only non-HDL-c/TC differed in the high-risk subgroup. There was no significant difference of non-HDL-c seen among distinct GS risk subgroups. No systemic retrospective study has presented the true association between non-HDL-c level and coronary artery lesions in patients treated with statins.

In our study, high level of non-HDL-c/TC, but not non-HDL-c, showed poor outcomes in 1-year follow-up. Our findings are similar to previously published studies [25, 26]. In those studies, statin might be one of the major confounding factors which could affect the non-HDL-c level. Even though statins were used for all the participants, the ratio of non-HDL-c and TC could weaken a bit of this confound. Patients with non-HDL-c level of over 0.751 might predict poor outcomes.

Several limitations are present in this study. It was only a cross-sectional study of patients with ischemic symptoms and acceptance of CAG; however, those with asymptomatic CAD could not be enrolled into our study. The small sample size and single center preclude application of the study's findings to the general population. Only 1-year follow-up is a relatively short time for assessment of prognosis, and a longer follow-up period will be needed for definitive conclusions.

5. Conclusion

This current study supported the hypothesis that non-HDL-c/TC is more useful than non-HDL-c in predicting the severity of coronary artery lesions in patients treated by statin. High level of non-HDL-c/TC had excellent prognostic value compared with other lipid-related markers in CAD patients treated with statin.

Data Availability

The original article data used to support the findings of this study are included within the article. Data generated during the study are from clinical data or follow-up information. Several specific data can be accessed by contacting the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported by the Foundation of Health and Family Planning Commission of Tianjin, China (Grant no. 2015KG110) and Science and Technology Program of Tianjin (Grant no. 16ZXMJSY00060).

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Hindawi
Cardiology Research and Practice
Volume 2019, Article ID 7689208, 7 pages
https://doi.org/10.1155/2019/7689208

Research Article

Concordance between the Different Cardiovascular Risk Scores in People with Rheumatoid Arthritis and Psoriasis Arthritis

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Received 29 November 2018; Revised 28 January 2019; Accepted 24 February 2019; Published 14 March 2019

Guest Editor: Rajesh Tota-Maharaj

Aim. To determine the cardiovascular risk and the concordance between the different scores in people with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). *Methods*. Observational descriptive study of prevalence. Performed in the Rheumatology Service and the Clinical Epidemiology and Biostatistics Unit of the University Hospital Complex of A Coruña (Spain). Patients diagnosed with RA or PsA, older than 18 years of age were included. Measurements: sociodemographic, anthropometric variables of the disease, comorbidity, cardiovascular risk, and therapeutic management. *Results*. 151 subjects (75 RA and 76 PsA) were studied. The average age was 57.9 ± 12.2 years, 61.6% being women. The average of the Charlson index was 2.8 ± 1.5. 43% were overweight. 46.5% were classified as cardiovascular risk, and the average percentage was 33.3% by Framingham. The best agreement has been between Framingham and Dorica ($k = 0.709$; $p < 0.001$), classifying more than 80% of the cases in the same risk categories. *Conclusions*. The most prevalent risk factors were overweight and obesity, followed by smoking and hypertension. The prevalence of patients with moderate/high cardiovascular risk varies according to the score used, the levels of concordance being the scores of Framingham and Dorica.

1. Introduction

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are two of the most prevalent rheumatic diseases which have an impact on the health system [1]. Among the repercussions of these diseases, their relationship with an increase in cardiovascular disease (CVD) [2, 3], morbidity, and mortality [1] stands out, owing to the role played by inflammation in both pathologies [4]. Thus, it has been observed that the CVD condition is the main cause of death, both in people with RA and in people with PsA [5, 6]. In the case of RA, life expectancy has been reduced from 3 to 10 years compared with the general population [7]. The cardiovascular risk (CVR) factors described in the literature are cholesterol, diabetes, hypertension, genetic inheritance, stress, tobacco, physical inactivity, obesity, and heart rate [8]. The CVD establishes the probability of suffering in a given period of time, generally 5 or 10 years, a cardiovascular episode [9]. The scientific literature reveals that the risk factors described and attributed to RA are hypertension, dyslipidemia [3], physical inactivity, obesity, and diabetes [10, 11], defined as highly prevalent in this population [12]. These factors can be fed back by the disease itself, as in the case of pain, which contributes to physical inactivity and obesity. Furthermore, it has been seen that the increase in CVR in people with RA has an effect similar in magnitude to that of diabetes [13]. A higher prevalence of heart failure [14, 15] and of acute myocardial infarction (41–68%) has also been found with respect to the general population [16, 17].

People with PsA [18] have more CVR factors than people with RA [19], constituting one of the most relevant causes of death [6].

In this way, the magnitude of the problem induces the interest of studying the recognized increase in CVR in these diseases [5], if it is also taken into account that it constitutes the main cause of death in these populations [20].

Therefore, the aim of the present research was to determine the CVR and the concordance between the different scores in people with RA and PsA.

2. Methods

An observational descriptive study of prevalence was carried out in the Rheumatology Service and in the Clinical Epidemiology and Biostatistics Unit of the University Hospital Complex of A Coruña (CHUAC) (A Coruña, Spain). Patients diagnosed with RA or PsA were included in the study who went consecutively to the Rheumatology Service during the study period (December 2016 to July 2017) and who gave their written informed consent to participate in the study. The study was approved by the Clinical Research Ethics Committee of Galicia (CEIC 2016/544). The following variables were studied for each person included in the research: sociodemographic variables (age, sex, family history, smoking habit, level of studies, work situation, and type of activity); anthropometric variables (body mass index (BMI)); abdominal circumference (cm), hip (cm), and neck (cm); waist circumference index (WCI) (cm); waist height index (WHI) (cm)); disease variables (type of time evolution of the disease); comorbidity variables (Charlson comorbidity index [21], systolic blood pressure (SBP), diastolic blood pressure (DBP), ankle-brachial index (ABI), total cholesterol level, HDL-cholesterol, left ventricular hypertrophy, and diabetes mellitus); cardiovascular risk (Framingham–Wilson, Score, Dorica, and Regicor) [22]; and therapeutic management variables (medication at the time of the interview). An electrocardiogram was performed on all participants in the study. The data were obtained from the examination and the clinical history and through the analytical parameters.

To perform the ABI, the patient was placed in the supine position. A cuff was used for the arm and another for the ankle of at least 40% of the circumference of the limb. The sleeve should be clean and dry. Doppler tube from 8 to 10 MHz was used. The blood pressure was taken simultaneously in the 2 arms with the validated automatic device Microlife WATCH BP OFFICCE ABI®, which determines differences between the 2 arms, making 3 measurements separated by one minute each, and making, the same device, an average of the 3 measurements in each arm. The device is validated for patients with atrial fibrillation and to perform the ABI automatically. It was measured in the posterior tibial artery (in the lower limbs) and the cuff was placed above the malleoli. ABIs with values <0.99 and ≥1.30 were considered pathological. The process was always performed by the same nurse in all patients.

To perform the electrocardiogram, the patient was placed on the stretcher, with the thorax, ankles, and wrists exposed, with arms and legs separated from the body. The corresponding electrodes were placed. The speed of the paper was adjusted to 25 mm/second and the tension to 10 mm/mv, and the way to do it in automatic mode was selected. The PageWriter TC20/TC30 electrocardiograph was used.

To avoid the variability of these measuring instruments, the recommendations of the manufacturers were followed. The devices were checked every 6 months. The measurements were always carried out by the same nurse, using the same procedure.

A descriptive study of the variables was carried out. The comparison of means between two groups was carried out using the Student's t-test or the Mann–Whitney test as appropriate after verification of normality with the Kolmogorov–Smirnov test. The association of qualitative variables was determined with the chi-square or Fisher's test as appropriate. The p value <0.05 has been considered as statistically significant. The concordance between the different scores was analyzed through the kappa concordance index.

3. Results

The general and comorbidity characteristics are shown in Table 1. The mean age at the time of the interview was 57.9 ± 12.2 years, 61.6% being women. The mean evolution of the disease was 9.2 ± 7.6 years, and the Charlson comorbidity index was 2.8 ± 1.5. In terms of BMI, a high percentage of overweight (43%) and obesity (28.5%) was observed. 19.9% declared to be a smoker and 31.8% ex-smoker. 71.5% did not present a family history of the study pathologies (RA and PsA).

The people diagnosed with RA showed greater age at diagnosis (51.1 ± 12.2 vs 46.4 ± 13, $p = 0.024$), predominance of the female sex (77.3% vs 46.1%, $p < 0.001$), and of basic studies (64% vs 45.3%, $p = 0.022$). Both groups showed similar BMI and comorbidity index. In contrast, a higher Charlson index adjusted for age was observed in patients with RA (3.1 ± 1.5 vs 2.5 ± 1.4, $p = 0.020$).

Table 2 shows the CVR of the sample studied and its factors. The most prevalent pathology in our sample was hypertension (39.6%), followed by diabetes (10.3%), 8.1% being without target organ damage. Ventricular hypertrophy was present in 4.6% of cases. As for various anthropometric measurements, the mean of the WCI was 0.9 ± 0.1 and that of the WHI of 0.6 ± 0.1. None of these measurements showed statistically significant differences between the study pathologies. The patients presented total cholesterol of 205.2 ± 37.8 mg/dl, with mean values of LDL 122.1 ± 31.9 mg/dl and HDL 57.2 ± 15.4 mg/dl, showing no differences between the RA and PsA.

The mean of the ABI was 1.2 ± 0.1 and the heart rate in the sample studied was 71.3 ± 13.4, without finding significant differences between the two pathologies studied. Table 3 shows the CVR classified according to the different scores as well as the concordance between them. Thus, it has been classified as moderate/high by 46.5% according to Score, by 33.3% according to Framingham, by 24.1% according to Dorica, and by 4.3% according to Regicor. A good concordance between Framingham and Dorica is observed ($k = 0.709$; $p < 0.001$), classifying more than 80% of

Table 1: General characteristics and comorbidity of the global sample and according to the type of arthritis.

	Global, $n = 151$ Mean ± SD	Rheumatoid arthritis, $n = 75$ (49.7%) Mean ± SD	Psoriatic arthritis, $n = 76$ (50.3%) Mean ± SD	p
Age dx (years)	48.7 ± 12.8	51.1 ± 12.2	46.4 ± 13	**0.024**
Age interview (years)	57.9 ± 12.2	60 ± 12.4	55.8 ± 11.8	**0.037**
BMI (kg/m^2)	28 ± 5.1	27.7 ± 4.8	28.3 ± 5.3	0.445
Charlson index	1.4 ± 0.8	1.4 ± 0.8	1.3 ± 0.7	0.320
Adjusted Charlson index	2.8 ± 1.5	3.1 ± 1.5	2.5 ± 1.4	**0.020**
	n (%)	n (%)	n (%)	p
Sex				**<0.001**
Male	58 (38.4)	17 (22.7)	41 (53.9)	
Female	93 (61.6)	58 (77.3)	35 (46.1)	
Family history				**<0.001**
No	108 (71.5)	68 (90.7)	40 (52.6)	
Yes	43 (28.5)	7 (9.3)	36 (47.4)	
BMI (kg/m^2)				0.910
Normal (BMI < 25)	41 (27.2)	20 (27.4)	21 (27.6)	
Overweight (25 ≥ BMI < 30)	65 (43)	33 (45.2)	32 (42.1)	
Obesity (BMI ≥ 30)	43 (28.5)	20 (27.4)	23 (30.3)	
Smoking habit				0.066
Nonsmoker	73 (48.3)	36 (48)	37 (48.7)	
Ex-smoker	48 (31.8)	29 (38.7)	19 (25)	
Smoker	30 (19.9)	10 (13.3)	20 (26.3)	
Studies				**0.022**
No/primary	82 (54.3)	48 (64)	34 (45.3)	
Superior	68 (45)	27 (36)	41 (54.7)	
Employment situation				0.148
Inactive	94 (62.3)	51 (68)	43 (56.6)	
Active	57 (37.7)	24 (32)	33 (43.4)	
Type of activity				0.509
Seated	18 (11.9)	7 (14.9)	11 (21.2)	
Standing/movement	51 (33.8)	27 (57.4)	24 (46.2)	
Mixed	30 (19.9)	13 (27.7)	17 (32.7)	
Medication				
Methotrexate	77 (56.6)	40 (57.1)	37 (56.1)	0.899

Age dx: age at diagnosis; BMI: body mass index.

the cases in the same risk categories. Also, the agreement was good between Framingham and Score ($k = 0.464$; $p < 0.001$), classifying more than 70% of the cases in the same risk categories. The characteristics and CVR factors were compared between the general population and rheumatic diseases in Table 4. The BMI observed in the general population is higher than that observed in patients with rheumatic disease, there being significant differences in the case of RA. (29.2 ± 4.7 vs. 27.7 ± 4.8, $p = 0.006$). A lower comorbidity was observed in the general population, being significantly lower in relation to the present one in RA (2.2 ± 1.8 vs 3.1 ± 1.5, $p < 0.001$). The general population showed significantly higher LDL cholesterol values than those observed in patients with rheumatic disease. The most prevalent pathology in the general population was hypertension (36.5%), showing a similar percentage to that observed in RA (34.7%) and PsA (43.4%).

4. Discussion

In our study, the mean age of the patients at the time of diagnosis of arthritis was 48.7 years, with a predominance of females: data similar to those observed in the CARMA [23] project and a more recent study by Castañeda [24]. In the comparison between patients with RA and PsA, results were found in agreement with those obtained in the CARMA multicenter project, with a greater age at diagnosis in patients with RA, mostly women. In the literature, we find articles [20, 25–28] that deal with the topic of study, revealing the influence of cardiovascular diseases in rheumatic diseases, and thus exposing their importance. Research on CVR factors in PsA is scarcer than that in RA or with psoriasis [29].

The literature concludes the increase in CVR in these diseases, as well as in morbidity and mortality, constituting the systemic inflammation itself as an independent CVR factor [30–32], not forgetting the contribution of traditional risk factors (which can be modified by medication) [2, 26].

In general, the traditional factors of hypertension, diabetes, and obesity have a great association with RA and PsA (and this is also in case with hyperlipidemia) [32–34]. In relation to the BMI, we found high data of overweight (44.0%) and obesity (26.7%) in our article. Accordingly, Kitas and Gabriel [5] affirm that the relationship between BMI and mortality in people with RA is remarkable, due to

Table 2: Cardiovascular risk factors and scores.

	Global, $n = 151$ Mean ± SD	Rheumatoid arthritis, $n = 75$ (49.7%) Mean ± SD	Psoriatic arthritis, $n = 766$ (50.3%) Mean ± SD	p
Perimeter (cm)				
Abdominal	97.8 ± 13.8	97.6 ± 13.0	98.1 ± 14.7	0.823
Hip	102.4 ± 10.4	103.1 ± 10.2	101.8 ± 10.6	0.454
Neck	37.8 ± 4.5	37.8 ± 4.2	37.9 ± 4.7	0.861
WCI (cm)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.768
WHI (cm)	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.423
Total cholesterol	205.2 ± 37.8	208.6 ± 40.7	201.9 ± 34.7	0.133
HDL	57.2 ± 15.4	59.0 ± 16.7	55.3 ± 13.8	0.158
LDL	122.1 ± 31.9	121.8 ± 33.7	122.5 ± 30.9	0.904
Ankle-brachial index	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.929
Heart rate	71.3 ± 13.4	70.7 ± 14.5	71.8 ± 12.3	0.684
Cardiovascular risk scores				
Framingham	9.8 ± 8.6	9.6 ± 8.1	9.9 ± 9.1	0.807
Regicor	3.9 ± 3.1	3.7 ± 2.7	4.0 ± 3.6	0.640
Dorica	6.4 ± 5.9	5.9 ± 5.5	6.8 ± 6.3	0.386
Score	1.9 ± 2.2	2.1 ± 2.2	1.7 ± 2.1	0.281
	n (%)	n (%)	n (%)	p
LVH				0.276
No	144 (95.4)	70 (93.3)	74 (97.4)	
Yes	7 (4.6)	5 (6.7)	2 (2.6)	
Arterial hypertension				0.330
No	90 (60.4)	47 (64.4)	43 (56.6)	
Yes	59 (39.6)	26 (35.6)	33 (43.4)	
Charlson index				
PAD	1 (0.7)	1 (100.0)	0 (0.0)	0.515
Cerebrovascular disease	1 (0.7)	1 (100.0)	0 (0.0)	0.515
Heart failure	2 (1.5)	1 (50.0)	1 (50.0)	0.737
AMI	3 (2.2)	2 (66.7)	1 (33.3)	0.522
Diabetes	14 (10.3)	7 (50.0)	7 (50.0)	0.979
Without organ damage	11 (8.1)	5 (45.5)	6 (54.5)	0.459
With organ injuries	3 (2.2)	2 (66.7)	1 (33.3)	0.522

WCI: waist circumference index; WHI: waist height index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVH: left ventricular hypertrophy; PAD: peripheral arterial disease; AMI: acute myocardial infarction.

Table 3: Classification of cardiovascular risk according to the different scores and concordance.

	Framingham n (%)	Dorica n (%)	Regicor n (%)	Score n (%)
Low risk	94 (66.7)	107 (75.9)	135 (95.7)	77 (53.5)
Moderate-high risk	47 (33.3)	34 (24.1)	6 (4.3)	67 (46.5)
Concordance study		Dorica	Regicor	Score
		K (p)	K (p)	K (p)
	Framingham	0.709 (<0.001)	0.163 (<0.001)	0.464 (<0.001)
	Dorica		0.245 (<0.001)	0.296 (<0.001)
	Regicor			0.066 (0.067)

K: kappa concordance index; p: p value.

the greater accumulation of body fat (known as rheumatoid cachexia) [35], unlike other investigations [33, 36] that claim to see that some patients have a low BMI associated with higher CVD mortality [30]. Likewise, no data have been found in other studies on the results of the different anthropometric data shown in this article (such as the waist–hip index), which is highly recommended [36], but it is noteworthy that abdominal fat is associated with insulin resistance, cardiometabolic risk, and the inflammatory load [5]. For its part, despite the scarcity of studies on body composition in PsA, it is reported that excess adiposity increases the CV [35] risk, being closely related to obesity [28], being associated with a greater metabolic risk than RA, and constituting obese BMI as a risk factor for psoriasis [37].

In our study, we found almost 20% of smokers; similar results in other researches (15.6%) [38]were observed. This smoking habit is associated with an increased risk of developing RA and increased activity of the disease [30]. In relation to hypertension, 35.6% RA and 43.4% PsA suffered it in the study sample. Lower percentages were objectified in other studies in RA (7.3%) [13]. Regarding PsA, Panoulas

Table 4: Characteristics of the general population and rheumatic disease cases (RA and PsA).

	General population $n = 1844$ Mean ± SD	Rheumatoid arthritis, $n = 75$ (49.7%) Mean ± SD	p^1	Psoriatic arthritis, $n = 76$ (50.3%) Mean ± SD	p^2
BMI (kg/m^2)	29.2 ± 4.7	27.7 ± 4.8	**0.006**	28.3 ± 5.3	0.103
Adjusted Charlson index	2.2 ± 1.8	3.1 ± 1.5	**<0.001**	2.5 ± 1.4	0.630
Abdominal perimeter (cm)	95.5 ± 12.7	97.6 ± 13.0	0.160	98.1 ± 14.7	0.082
LDL	132.0 ± 31.4	121.8 ± 33.7	**0.006**	122.5 ± 30.9	**0.009**
Ankle-brachial index	1.2 ± 3.5	1.2 ± 0.1	0.999	1.2 ± 0.1	0.999
	n (%)	n (%)	p^1	n (%)	p^2
Charlson index					
PAD	74(4.1)	1(1.3)	0.384	0(0.0)	0.139
Cerebrovascular disease	74(4.1)	1(1.3)	0.384	0(0.0)	0.139
Heart failure	31(1.7)	1(1.3)	0.818	1(1.3)	0.831
AMI	87(4.8)	2(2.7)	0.583	1(1.3)	0.267
Diabetes	244 (13.4)	7 (9.3)	0.326	7 (9.2)	0.308
Without organ damage	217(11.9)	5(6.7)	0.242	6(7.9)	0.395
With organ injuries	27(1.5)	2(2.7)	0.723	1(1.3)	0.702
Arterial hypertension	663(36.5)	26(34.7)	0.916	33(43.4)	0.228
Smoking habit					
Nonsmoker	1008(55.0)	36(48)	0.308	37(48.7)	0.363
Ex-smoker	505(27.6)	29(38.7)	**0.044**	19(25)	0.744
Smoker	320(17.5)	10(13.3)	0.454	20(26.3)	**0.064**

BMI: body mass index; LDL: low-density lipoprotein; PAD: peripheral arterial disease; AMI: acute myocardial infarction; ^1p value for contrasts general population vs RA; ^2p value for contrasts general population vs PsA.

et al. [39] state that it is superior in patients with RA, ranging from 4 to 73%, being the cause of the sample sizes, the definition of hypertension, or the study population. Therefore, it is not clear that there is a higher prevalence of this pathology than in the RA or general population. More similar data with other investigations correspond to those of DM and RA (prevalence of 10%) [38], with a higher prevalence of this condition in PsA (23%) [31].

On the other hand, the literature shows inconsistent findings about lipid levels as the disease evolves, with a clear alteration of the lipid profile [35]. In our study, with an average time of evolution of the disease of 9.2 years, we obtain an average of total cholesterol of 208.6 and LDL 121.8. This LDL value is lower than that found in the general population, as in other investigations [40], which can be explained by the evolution of the disease [41] and questioning its clinical relevance in RA [40].

Reviewing the literature, Jurcut et al. [42] found an increased risk of myocardial infarction in people with RA. Regarding PsA, it is related to higher prevalences of heart diseases (heart failure or cerebrovascular disease) [29]. In line with the above, we have not found data to contrast our results on left ventricular hypertrophy in the study populations, as well as to relate the Charlson comorbidity score with the pathologies under study. It could be mentioned in this discussion that antirheumatic drugs, especially methotrexate and/or biologics, appear to reduce CVR by effectively decreasing systemic inflammation [41].

In relation to the CVD scores, Arts et al. [43], after reviewing the literature, state that the risk score of Framingham, Reynolds, and Score classify 60% of patients with RA as lower risk, agreeing with other investigations in which they underestimate CVR in RA [43]. Liao and Solomon [11] describe the need to develop scores that include inflammatory markers in addition to traditional cardiovascular risk factors so as not to underestimate CVR in these conditions [44, 45]. In our study, the scores show higher prevalences in a low CVR, which may be due to the time of evolution of the disease or the treatment received [43], since the events are more common within the first 7 years of the disease.

5. Conclusions

Cardiovascular risk factors have a great impact on people with RA and PsA. The most prevalent were overweight and obesity, followed by smoking and hypertension. The prevalence of moderate/high cardiovascular risk varies according to the score used, the Framingham and Dorica scores being the most concordant. The control of the disease in an integral way constitutes a fundamental field in the reduction of CVD risk in both diseases, fundamental for the quality of life of people with RA and PsA.

Data Availability

The data used to support the findings of this study are restricted by the Clinical Research Ethics Committee of Galicia in order to protect patient privacy. Data are available from Cristina González-Martín, Research Group in Clinical Epidemiology, Department of Health Sciences, Faculty of Nursing and Podiatry, University of A Coruña (UDC), Ferrol Campus, Ferrol, Spain, for researchers who meet the criteria for access to confidential data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors acknowledge the multidisciplinary work team formed by rheumatologists, nurses, and podiatrists.

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