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Review article

Statins decrease the risk of stroke in individuals with heterozygous familial hypercholesterolemia: A systematic review and meta-analysis

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ABSTRACT

Background: Familial hypercholesterolemia (FH) is undoubtedly associated with premature coronary heart disease, but it is debatable whether FH increases the risk for stroke.
Objective: To meta-analyze available evidence regarding the incidence of stroke in individuals with heterozygous (He) FH.
Methods: We conducted a systematic review and a meta-analysis of epidemiological studies, including English-language publications until June 2015; four observational studies, with 3374 participants with HeFH, were included in the analysis. Cerebrovascular disease comprised of ischemic stroke or transient ischemic attack. Since studies did not include any control subjects, the corresponding general population of the same reference area and period of time for each HeFH study served as control group. Analyses were performed according to the period of time during which the studies were conducted: prestatin and statin era (before and after 1987 when lovastatin was launched).
Results: In the prestatin era, individuals with HeFH exhibited a higher risk for stroke compared with the general population [odds ratio (OR) = 7.658, 95% confidence interval (CI): 6.059–9.678, $p < 0.01$]. In contrast, FH subjects had a lower odds for stroke following the generalization of statin therapy (OR = 0.251, 95% CI: 0.176–0.358, $p < 0.01$).
Conclusions: Taking into account the small number of studies and methodological issues, HeFH was associated with a higher risk of cerebrovascular disease compared with the general population in the prestatin era, which was significantly reduced after the introduction of statin therapy.

1. Introduction

Heterozygous (He) familial hypercholesterolemia (FH) is the most common inherited metabolic disease causing lifelong elevated serum low-density lipoprotein cholesterol (LDL-C) levels [1]. FH is an autosomal dominant disorder caused by mutations in genes encoding proteins involved in the LDL receptor endocytic and recycling pathways, leading to decreased cellular uptake of LDL and increased plasma LDL-C levels [2]. Thus, individuals with heterozygous and homozygous FH have twofold and fourfold higher LDL-C levels, respectively, compared with the general population [1]. In this article, we discuss only HeFH patients, since there is a lack of relevant data regarding homozygous FH. The worldwide prevalence of HeFH is estimated 1:500 [3]. However, a direct screening in Netherlands has recently indicated a higher prevalence (1:200–250) [2]. Undoubtedly, untreated FH is related with premature coronary artery disease (CAD) and, especially in men, with early acute myocardial infarction (AMI) and cardiac death [3]. It is well established that statins have changed the prognosis of FH, since the incidence of cardiovascular events in FH patients is almost equal to that of the general population after 10 years of treatment [4]. Nonetheless, there is limited information regarding the association of FH and cerebrovascular disease [5,6].

Stroke is the second cause of death and a major cause of severe disability worldwide [7]. Age, smoking, hypertension, diabetes, male gender, family history of premature cardiovascular disease, prior heart or vascular disease, dyslipidemia, along with a non-balanced diet and physical activity are recognized as principal risk factors for ischemic stroke, which accounts for 80% of cerebrovascular disease [7,8]. There are only a few studies showing controversial results regarding the mortality or morbidity of stroke in individuals with HeFH [5,6]. What is more, a debate whether

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hypercholesterolemia per se comprises a risk factor for ischemic stroke still holds [9–11]. Indeed, there is a body of conflicting data regarding the association of plasma cholesterol levels and stroke [10,12–15].

The aim of the present meta-analysis was to evaluate the association between HeFH and incidence of stroke.

2. Methods

2.1. Outcomes and study eligibility

The outcome of interest was the incidence of cerebrovascular disease in patients with FH. Studies were considered as eligible if they were: a) full-length publications in peer-reviewed journals and b) investigating the incidence of cerebrovascular disease in patients with FH. No restriction criteria were imposed with regard to the size of the population studied.

Review articles and nonhuman studies were excluded. For the purposes of the present analysis, cerebrovascular disease comprised of ischemic stroke or transient ischemic attack. In addition, studies investigating MRI atherosclerotic lesions or regional cerebral flow among patients with FH were not included in the present meta-analysis.

2.2. Literature search

Studies evaluating relationships of FH with incidence of stroke were drawn from a systematic review of the English literature in PubMed until June 2015. The search terms were: 'inherited dyslipidemia' or 'familial hypercholesterolemia' or 'brain infarction' or 'cerebrovascular disease' or 'ischemic stroke' or 'statin treatment'. Studies were also identified through scrutinizing the references of articles.

2.3. Extraction of data

The literature search, selection of studies, the extraction and presentation of data were performed independently by two reviewers (F.B., H.M.). Mean levels of cholesterol, age, follow-up duration and origin of each study were recorded. Incidence related with cerebrovascular disease were recorded as annual rates per 1000 persons [(number of individuals diagnosed with cerebrovascular disease × 1000)/(total study population × follow-up duration)]. Due to the fact that eligible studies did not include control subjects, we used the corresponding general population of the same reference area and period of time for each FH study as control groups. Analyses were performed according to the period of time during which the studies were conducted: prestatin and statin era (i.e. before and after the year 1987 when lovastatin was launched). Disagreements between the two reviewers were resolved by consensus.

2.4. Statistical analysis

Fixed-effects and random effects meta-analysis of the selected studies was applied on the basis of within-study comparisons, thereby avoiding any biases being caused by methodological differences between studies. The Cochran's Q test and I-squared (I^2) statistic method were used to determine heterogeneity between studies [16,17]. These indices were used to assess the percentage of variability across studies, which is due to heterogeneity rather than chance. Heterogeneity was considered significant when $p < 0.10$ for the Q test or $I^2 > 50\%$. All statistical analyses were conducted using the Comprehensive Meta-analysis software version 2.2.064 (Biostat, Englewood, NJ).

3. Results

Our search identified 15 studies matching our criteria (Fig. 1). Of those, we excluded: a) 4 studies having stroke mortality as primary endpoint, b) 6 studies evaluating MRI atherosclerotic lesions or regional cerebral flow and c) 1 study investigating the incidence of cerebrovascular disease in HeFH subjects with carotid stenosis (Fig. 1). Finally, 4 studies providing data for 3374 HeFH patients were included in our meta-analysis [18–21]. These cohorts were retrospective. Neither case-control nor studies longitudinal interventional studies were found to report stroke outcomes in those patients. Details of the individual studies are presented in Table 1. No major differences were found regarding the subjects' baseline cholesterol levels of each study. The participants included in the studies conducted during prestatin era were younger compared with those of the statin era (Table 1). Finally, the study participants of Kaste et al. had the longest follow-up duration and the majority of those were diagnosed with cardiovascular disease at the baseline visit (Table 1).

A higher incidence of stroke was noticed in HeFH patients compared with the general population during the prestatin era, whereas no difference was found during the statin era (Figs. 2 and 3). In the prestatin era, individuals with HeFH exhibited a higher risk for stroke compared with the general population [odds ratio (OR) = 7.658, 95% confidence interval (CI): 6.059–9.678, $p < 0.01$]. No differences in the pooled data from random-effects models were noted. However, significant trial heterogeneity was detected (Q value = 4.43, p = 0.03, $I^2 = 77.4\%$).

In contrast, FH subjects had a lower odds for stroke following the generalization of statin therapy (OR = 0.251, 95% CI: 0.176–0.358, $p < 0.01$). Again, no differences in the pooled data from random-effects models were noted, but significant trial heterogeneity was detected (Q-value = 4.54, p = 0.03, $I^2 = 78\%$).

4. Discussion

The present meta-analysis shows that patients with HeFH were at higher risk of stroke in the prestatin era. Following the generalization of statin therapy in patients with HeFH, the risk of stroke was eliminated in these individuals.

Data indicate a higher stroke incidence in FH individuals during the prestatin era and are in line with other studies not included in the present meta-analysis [22,23]. A study including FH patients with carotid stenosis (n = 34) demonstrated a higher incidence

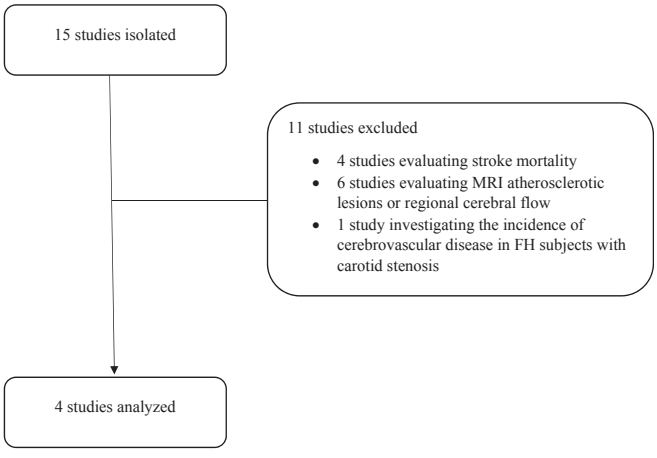

Fig. 1. Flow diagram of the procedure followed to determine studies to be in included in the meta-analysis.