Familial hypercholesterolemia in Chinese patients with premature ST-segment-elevation myocardial infarction: Prevalence, lipid management and 1-year follow-up

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Abstract

Background

Familial hypercholesterolemia (FH), characterized by elevated plasma low-density lipoprotein-cholesterol (LDL-C) levels and premature coronary artery disease (CAD), remains mostly underdiagnosed and undertreated. We investigated the prevalence of clinical FH among Chinese patients with premature ST-segment-elevation myocardial infarction (STEMI) and one-year follow-up on their lipid management and cardiovascular events.

Methods

Four hundred and ninety-eight premature STEMI patients (363 men) were enrolled. FH patients were identified using the Dutch Lipid Clinic Network Criteria. Lipid management and cardiovascular events in all patients were assessed.

Results

Nineteen patients (3.8%) were diagnosed as definite/probable FH, 211 (42.4%) as possible FH and 268 (53.8%) as unlikely FH. All patients were divided into two main groups: unlikely FH (0–2 points) and possible FH (>3 points). Possible FH patients were younger (50.1 years vs. 53.5 years) with higher NT-proBNP level (3014.15 pg/mL vs. 2326.25 pg/mL), occurrence of multi-vessel CAD (37.4% vs. 18.3%), lower LVEF (47% vs. 49%) and more severe Killip classification (Class 3, 20.0% vs. 9.7%). Follow-up data were available for 203 patients from the possible FH group and 243 patients from the unlikely FH group. High intensity statin intake status (%) of possible FH vs. unlikely FH was as follows: 1) on admission: 4.8% vs. 0.4%; 2) at discharge: 10.4% vs. 1.6% and 3) at one year follow-up: 5.4% vs. 0.8%. A significantly low percentage of possible FH patients (18.7% vs. 51.4%) achieved target LDL-C levels. There were no significant differences in MACE defined as a composite
of cardiogenic shock or Class IV heart failure, recurrent MI, cardiovascular-related rehospitalization, TLR and CV death between the two groups. However, the proportion of cardiogenic shock or Class IV heart failure was significantly higher in possible FH patients group (5.9% vs. 1.2%).

Conclusion
Clinical diagnosis of possible FH is common in Chinese patients with premature STEMI. A low proportion of FH patients were prescribed high intensity statins. Despite aggressive cholesterol-lowering drugs, a significantly lower proportion of FH patients achieved LDL-C targets compared to unlikely FH patients. Possible FH patients were younger with a significantly higher occurrence of multi-vessel CAD and impaired cardiac function.

Introduction
Familial Hypercholesterolemia (FH) is considered to be a genetic disorder of lipid metabolism attributed to defects in the LDL-receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin/kexin type 9 (PCSK9), and LDL receptor adaptor protein 1 (LDLRAP1)[1]. It is characterized by impaired metabolism of low-density lipoprotein-cholesterol (LDL-C) causing severe hypercholesterolemia and consequently leading to accelerated atherosclerosis and premature coronary artery diseases (CAD)[2]. The prevalence of FH in the general population is now estimated to be between 1 in 200 ~ 300 [3–5]. While genetic evaluation can confirm a diagnosis of FH, clinical estimation based on measured cholesterol (mainly LDL-C) levels, physical examination (presence of tendon xanthomas, xanthelasmas and corneal arcus), personal and familial history of CAD is also widely accepted. Recent data show that clinical diagnosis of FH is relatively common in hospitalized patients with premature acute coronary syndrome (ACS) [6–10].

Patients with FH have a 20-fold increased lifetime risk of CAD compared to the general population, if FH is not identified and treated at an early age [11]. Lifestyle modification and appropriate lipid-lowering therapy are recommended and have proved their contribution in reducing this risk[12]. However, FH remains widely underdiagnosed and undertreated worldwide [13, 14] thereby predisposing FH patients to a higher risk in CAD. Clinical trials support the effectiveness and safety of statins in decreasing CAD events in both primary and secondary settings [15] and intensive lipid lowering treatment for FH patients decreases the risk of developing CAD and onset of myocardial infarction (MI) [16]. The adverse effects of FH have also been recognized in China. However, few studies have focused on lipid management and follow up outcomes specifically in FH patients and thus, strategies that can be most effective and efficient in promoting lipid goal attainment for FH patients remain unknown.

This study aimed to investigate the prevalence of clinical FH among Chinese patients with premature ST-segment-elevation myocardial infarction (STEMI) and one-year follow-up on their lipid management and cardiovascular events.

Materials and methods
Study population
Our study complied with the Declaration of Helsinki and was approved by the hospital’s ethical review board (Shanghai Tenth People’s Hospital, Tongji University, Shanghai, China).
Informed written consent was obtained from all patients enrolled in this study. STEMI patients at <55 years of age for male and <60 years of age for female admitted to Shanghai Tenth People’s Hospital and Chongming Second People’s Hospital were consecutively enrolled from January 2013 to October 2015. The diagnosis of STEMI was based on the presence of characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic ST-segment elevation in at least two contiguous leads and subsequent release of biomarkers of myocardial necrosis.

Patients with significant hematologic disorders, infectious or systemic inflammatory diseases, thyroid dysfunction, severe liver and/or renal insufficiency, and malignant disease were excluded.

All patients underwent cardiac catheterization with stent implantation during hospitalization and significant coronary artery stenosis was defined as >50% reduction in lumen diameter of any of the three coronary arteries or their main branches. Troponin I, creatine kinase-MB (CK-MB) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured for every patient on admission. Peripheral blood samples were collected within 24h from patients for assessing fasting lipids, apolipoproteins, lipoprotein (a) [LP (a)], glucose and high sensitive CRP (hs-CRP) levels. Smoking habit, Hypertension, Diabetes mellitus (DM) and body mass index (BMI) were also evaluated. All clinical data were collected via medical records or direct interview of the patients by trained nurses.

**Diagnosis of Familial hypercholesterolemia**

Clinical FH was diagnosed using the Dutch Lipid Clinic Network Criteria (DLCN) criteria including personal and family history of premature atherosclerosis, LDL-C levels and xanthomas.

Trained cardiologists examined the cutaneous or tendous xanthomas from the skins and joints of the patients. Patients on lipid-lowering medications with their pretreatment LDL-C unavailable had their untreated LDL-C levels conservatively adjusted by a relative correction factor, here 1.43, which depended on their dose and potency of statins [17].

Based on the DLCN criteria, numerical scores were assigned as follows: (1) family history of a first-degree relative with known premature CAD or vascular disease (<55 years for men, <60 years for women) (1 point) and/or a first-degree relative with known hypercholesterolemia (1 point) or xanthomas (2 points) or offspring(s) with known hypercholesterolemia (2 points). (2) personal history of premature CAD (ages as above, 2 points) or cerebral/peripheral vascular disease (ages as above, 1 point) or xanthomas (6 points); untreated LDL-C>8.5 mmol/L (8 points), 6.5–8.4 mmol/L (5 points), 5.0–6.4 mmol/L (3 points), or 4.0–4.9 mmol/L (1 point); (3) corneal arcus and genetic diagnosis were not available, and these missing information were counted as zero. Finally, a diagnosis of definite FH was considered if the total score was >8 points, probable if the score was 6–8 points, possible if the score was 3–5 points and unlikely if the score was <3 points.

**Follow-up**

After discharge all patients were followed-up for 12 months by trained cardiologists at Shanghai Tenth People’s Hospital and Chongming Second People’s Hospital. Those unable to attend their appointment were followed by an interview on the phone. If any patient reported an admission due to recurrent coronary event, they were asked to bring or send by fax the discharge summary. Additionally, all patients were contacted by telephone to assess their clinical status. If patients were not found, information was obtained through family members or patients’ treating physician. The primary end point was major adverse cardiac events (MACE)
defined as the composite of cardiogenic shock or Class IV heart failure, recurrent MI, cardiovascular-related rehospitalization, target lesion revascularization (TLR) and cardiovascular death.

**Statistical analysis**

The values were expressed as mean±SD or median (interquartile range) for continuous variables and number (percentage) for categorical variables. Differences in clinical and biochemical parameters between groups were analyzed using independent t test, Mann–Whitney U test, and Chi-squared tests where appropriate. A P value <0.05 was considered statistically significant. The statistical analysis was performed with SPSS version 22.0 software (SPSS Inc., Chicago, IL).

**Results**

Four hundred and ninety-eight premature STEMI patients (363 men) were enrolled. During data collection and analysis, of 14 patients who were unable to provide clear family history as they had deceased first degree relatives without available cause of death, 1 patient was from the definite/probable FH group (≥6 points), 11 patients were from the possible FH group (3–5 points) and 2 from the unlikely FH group (<3 points). According to the DLCN criteria, the prevalence of definite/probable FH was 3.8% (19 in 498 patients), possible FH was 42.4% (211 in 498 patients) and that of unlikely FH was 53.8% (268 in 498 patients). As only 19 definite/probable FH were identified, its data was merged with possible FH group for further statistical analysis and all patients were divided into two main groups according to the score obtained: unlikely FH (0–2 points) and possible FH (≥3 points). Unavailability of family history of those 12 patients (1 from definite/probable FH group and 11 from the possible FH group) does not affect their group classification as they already have a score of ≥3 points regardless of family history.

The baseline characteristics of the patients according to FH diagnosis are shown in Table 1. There was no significant difference between the groups when factors such as sex, smoking habits, hypertension or DM were considered. Possible FH patients were younger (50.1 years vs. 53.5 years) and had higher proportion of family history of premature CAD (62.2% vs. 0.7%). Patients with possible FH had higher total cholesterol, LDL-C, triglycerides and Lp(a) levels and were more likely to develop multivessel CAD (37.4% vs. 18.3%) compared to the unlikely FH patients. There was no significant difference between the groups in levels of Troponin I and CK-MB while possible FH patients had significantly higher NT-proBNP level (3014.15 pg/mL vs. 2326.25 pg/mL), lower LVEF (47% vs. 49%) and more severe Killip classification (Class 3, 20.0% vs. 9.7%). During the hospitalization period no recurrent MI and TLR occurred in all patients. There was no significant difference in the CV deaths between the groups.

The cholesterol-lowering medication intake status of the patients is described in Table 2. The high intensity statin intake status % (n) [Ezetimibe % (n)] of the possible FH group vs. unlikely FH group was as follows: 1) on admission 4.8% (11) [0.9% (2)] vs. 0.4% (1) [0.4% (1)]; 2) at discharge, 10.4% (23) [2.3% (5)] vs. 1.6% (4) [0.8% (2)] and 3) one-year follow-up 5.4% (11) [2.0% (4)] vs. 0.8% (2) [0.8% (2)].

One year after their cardiovascular event, 203 patients from the possible FH group and 243 patients from the unlikely FH group came for follow-up. LDL-C and TC levels of both groups decreased significantly. Despite being treated more aggressively with cholesterol-lowering drugs, a lower percentage of possible FH patients (18.7%) achieved targeted LDL-C levels (LDL-C <1.8mmol/L or a decrease >50% of the LDL-C levels on admission) compared to
51.4% of unlikely FH patients. At 1 year follow-up, the two groups showed no significant difference in MACE which was defined as a composite of cardiogenic shock or Class IV heart failure, recurrent MI, cardiovascular-related rehospitalization, TLR and CV death. However, the proportion of cardiogenic shock or Class IV heart failure was significantly higher in possible FH patients group (5.9% vs.1.2%). Recurrent MI occurred in 3 of the possible FH group and all 3 were from the 19 definite/probable FH patients while only 1 case occurred in the unlikely FH group. The proportion of TLR in the possible FH group was 3.4% compared to 1.2% in the unlikely FH group and although there was no significant difference between the groups, possible FH group showed an increasing trend in TLR. Cardiovascular-related rehospitalization

Table 1. Baseline characteristics of the study population.

|                          | Possible FH (n = 230) | Unlikely FH (n = 268) | P value |
|--------------------------|-----------------------|-----------------------|---------|
| Age (y)                  | 50.1±3.9              | 53.5±4.2              | <0.001  |
| Men, % (n)               | 72.6(167)             | 73.1(196)             | 0.981   |
| Current smokers, % (n)   | 60.4(139)             | 62.7(168)             | 0.664   |
| Former smokers, % (n)    | 9.6(22)               | 8.2(22)               | 0.696   |
| Hypertension, % (n)      | 50.0(115)             | 51.5(138)             | 0.807   |
| Diabetes mellitus, % (n) | 25.7(59)              | 23.9(64)              | 0.719   |
| Family history of CAD, % (n) | 62.2(143)          | 0.7(2)                | <0.001  |
| Systolic Blood Pressure(mmHg) | 132±12.9         | 130±14.1             | 0.101   |
| Diastolic Blood Pressure(mmHg) | 74±10.0            | 75±8.6               | 0.231   |
| Body mass index (kg/m²)  | 25.6±3.7              | 25.2±3.4              | 0.210   |
| Hypertriglyceridemia, % (n) | 34.8(80)              | 25.4(68)              | 0.029   |

Laboratory analysis

|                                      | Possible FH (n = 230) | Unlikely FH (n = 268) | P value |
|--------------------------------------|-----------------------|-----------------------|---------|
| Total cholesterol (mmol/L)           | 7.38±0.93             | 4.10±1.02             | <0.001  |
| Triglycerides (mmol/L)               | 1.72±1.31             | 1.67±1.14             | 0.649   |
| HDL cholesterol (mmol/L)             | 0.98±0.28             | 1.03±0.38             | 0.010   |
| LDL cholesterol (mmol/L)             | 5.77±0.36             | 2.69±0.41             | <0.001  |
| Apolipoprotein A-I (mg/dL)           | 123.1±21.3            | 119.6±22.9            | 0.080   |
| Apolipoprotein B (mg/dL)             | 112.3±25.8            | 88.7±25.3             | <0.001  |
| Lipoprotein(a) (mg/dL)               | 37.0±18.8             | 33.4±17.1             | 0.026   |
| Glucose (mmol/L)                     | 5.81±1.21             | 6.0±1.30              | 0.094   |
| HbA1C (%)                            | 6.33±1.12             | 6.24±1.41             | 0.436   |
| Troponin I(μg/L)                     | 201.33±21.54          | 199.35±19.87          | 0.287   |
| CK-MB (μg/L)                         | 224.51±22.97          | 220.33±26.85          | 0.065   |
| NT-proBNP(pg/mL)                     | 3014.15±281.74        | 2326.25±212.94        | <0.001  |
| Hs-CRP (mg/L)                        | 1.71(0.85–7.14)       | 1.58(0.41–5.37)       | 0.138   |
| Multivessel CAD, % (n)               | 37.4(86)              | 18.3(49)              | <0.001  |
| Left ventricle ejection fraction (%) | 47±9                  | 49 ± 6               | 0.003   |

Abbreviations: CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; HbA1C, hemoglobin A1c; CK-MB, creatine kinase-MB; NT-proBNP, N-terminal pro-brain natriuretic peptide; Hs-CRP, high sensitive CRP; CV, cardiovascular.

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Discussion

Our study investigated the status of clinical diagnosis of FH in Chinese patients with premature STEMI and one-year follow-up on their lipid management and cardiovascular events. The major findings were 1) Clinical diagnosis of possible FH is relatively common in Chinese patients with premature STEMI, 2) A low proportion of FH patients were prescribed high-intensity statins. Despite aggressive cholesterol-lowering drugs, a significantly lower proportion of FH patients achieved LDL-C targets compared to unlikely FH patients, 3) Possible FH patients were younger with significantly higher occurrence of multi-vessel CAD and impaired cardiac function.

Phenotypic diagnosis of FH is more appropriate for clinical use as genetic screening is not easily endorsed in the clinical setup. It is only after the occurrence of their first cardiovascular event that FH patients can be identified based on lipid profiles and diagnostic criteria such as

Table 3. One-year follow-up data of patients.

|                         | Possible FH (n = 203) | Unlikely FH (n = 243) | P value |
|-------------------------|-----------------------|-----------------------|---------|
| Body mass index (kg/m²) | 24.0±2.1              | 23.7±2.4              | 0.165   |
| Laboratory analysis    |                       |                       |         |
| Total cholesterol (mmol/L) | 5.54±1.21            | 3.89±0.98             | <0.001  |
| Triglycerides (mmol/L)  | 1.65±0.92             | 1.54±1.02             | 0.236   |
| HDL cholesterol (mmol/L) | 1.10±0.46            | 1.18±0.59             | 0.116   |
| LDL cholesterol (mmol/L) | 3.47±0.97            | 2.11±0.88             | <0.001  |
| Apolipoprotein A-I (mg/dL) | 117.4±20.1        | 114.8±17.3            | 0.142   |
| Apolipoprotein B (mg/dL) | 90.0±18.2             | 86.0±15.4             | 0.012   |
| Lipoprotein(a) (mg/dL)  | 30.1±2.9              | 29.7±3.1              | 0.163   |
| <1.8mmol/L or a decrease >50% of initial LDL-C levels available on admission, % (n) | 18.7 (38) | 51.4 (125) | <0.001 |
| Cardiogenic shock or Class IV heart failure, % (n) | 5.9 (12) | 1.2 (3) | 0.013 |
| Recurrent MI, % (n) | 1.5 (3)               | 0.4 (1)               | 0.471   |
| Cardiovascular-related rehospitalization, % (n) | 6.4 (13) | 4.5 (11) | 0.499 |
| TLR, % (n) | 3.4 (7) | 1.2 (3) | 0.210 |
| CV death, % (n) | 4.9 (10) | 4.5 (11) | 0.979 |
| MACE, % (n) | 9.4 (19) | 6.2 (15) | 0.277 |

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; MI, myocardial infarction; TLR, target lesion revascularization; CV, cardiovascular; MACE, major adverse cardiovascular events.

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the DLCN algorithm and the Simon Broome criteria. Therefore, the hospital is considered as a useful setup in the identification of FH. STEMI in young patients is a life threatening condition and identification of FH in this subpopulation is of vital importance as premature ACS is one of the important clinical manifestations of the disease. Recently, studies have investigated the prevalence of FH in patients with premature ACS. The reported prevalence of phenotypic diagnosis of FH based on the DLCN algorithm varies from study to study due to the cut-off age used to define AMI. A study by Rallidis et al. which investigated the prevalence of FH in patients <35 years with first STEMI identified 20.3% with definite/probable FH and 50.9% with possible FH[7]. In a larger multicenter cohort study in Switzerland among 1451 young patients with premature ACS, 4.8% had probable/definite FH and 47.1% had possible FH [6]. From a larger population, Mortensen et al. identified 6.9% probable/definite FH patients among the 291 (21%) patients with premature MI[18]. The EUROASPIRE IV study [19] also found a high prevalence of FH among patients with premature coronary heart diseases (<50 years) while a smaller study by Pang et al. [8] showed that the prevalence of probable/definite FH was 14.3% among premature CAD patients in a CCU setting. A similar trend was seen in a Chinese study in which 48.2% of the study population had premature MI and when the prevalence of FH was assessed, 7.1% of them were diagnosed with definite/probable FH [10]. These data reflect the increasing burden of FH and therefore emphasizes the need for mandatory phenotypic screening of FH in such populations. Results from our study, together with other studies carried out on the Chinese population show that FH is not rare in the Chinese population [17] but is undertreated and underdiagnosed. The prevalence of definite/probable FH in our present study was found to be 3.8% and is lower than the percentage reported by Li et al [10]. This disparity could be explained by the poor availability of information about the family history of some of our patients. Of 14 patients who were unable to provide clear family history as they had deceased first degree relatives without available cause of death, 11 patients were from the possible FH group (3~5 points). Availability of family history about these possible FH patients could lead to some of them to be in the definite/probable group thereby increasing the prevalence of definite/probable FH.

The 2013 European Atherosclerosis Society recommends high intensity statins in treating FH and if necessary supplemented by Ezetimibe [13]. Our results showed that a relatively low proportion of FH patients were given high intensity statins and although they were treated more aggressively with cholesterol-lowering drugs, the control of LDL-C levels in FH patients is poor compared with patients with unlikely FH. Several reasons might account for the low percentage of FH patients achieving recommended LDL-C levels in the present study. The first was under diagnosis of FH by physicians due to their lack of knowledge about the disease and the treatment of underdiagnosed FH patients as usual STEMI patients in such cases. The second reason might be that FH patients were not treated with intensive LDL-C lowering medications due to lack of knowledge of physicians about intensive LDL-C lowering drugs and concern of side effects of drugs. These can explain for the low percentage of patients being on high intensity statin and Ezetimibe on admission and a slightly higher percentage at discharge. A third but equally important reason might be non-compliance in Chinese patients, who were not taking the required doses of cholesterol-lowering drugs as prescribed and did not implement any lifestyle modifications such as a diet low in cholesterol and exercise. This can be seen in the one-year follow-up by the decreased rates of possible FH patients being on high intensity therapy and Ezetimibe as compared to the prescribed doses at discharge. In addition, it has been seen that despite being on maximum doses of statin with the addition of Ezetimibe, a low percentage ranging from 10.4~22% of heterozygous FH patients reached the less stringent levels of <2.5mmol/L of LDL-C levels [20, 21]. A previous study showed that there was no difference in intensive vs. standard statin treatment in patients with elevated LDL-C levels in Asian
population[22] and increasing the statin dose by two-fold had only shown a further 6.4% decrease in LDL-C levels in Chinese population[23]. Accordingly, a low proportion of FH patients achieved LDL-C targets despite statin treatments.

FH causes severe hypercholesterolemia consequently leading to accelerated atherosclerosis and premature CAD as individuals with FH are born with a high LDL-C cholesterol level in contrast to those who acquire hypercholesterolemia later in life. Clinical FH among patients with first MI was strongly related with MI occurring prematurely by as much as 15 years[18] and 10 years[10]. We also found a significant difference between the ages of onset of premature MI between the two groups with MI occurring 2–3 years earlier in possible FH group. Our study also showed that patients with possible FH exhibited a higher prevalence of multivessel CAD confirming the critical role of FH in the development of atherosclerosis [24]. However, the present data did not show any significant difference in MACE, recurrent MI, cardiovascular-related rehospitalization, TLR and CV death between the two groups at one-year follow-up. A previous study showed no significant differences in the rate of recurrent MI of the first two years and all-cause mortality in a median follow-up of 3.3 years in premature STEMI patients diagnosed with FH[9]. However, in the same study, the unadjusted and adjusted event rates of recurrent MI were higher in patients with possible FH compared with unlikely FH after the first two years[9]. In the present study, all 3 recurrent MI in possible FH group were from 19 definite/probable FH patients. The proportion of TLR was 3.4% in possible FH group compared to 1.2% in unlikely FH group showing an increasing trend in TLR in possible FH patients. In addition, possible FH patients had higher levels of NT-proBNP on admission and impaired cardiac function both on admission and at one year follow-up. Higher levels of NT-proBNP[25] and impaired cardiac function both represent a higher risk of subsequent adverse cardiac events. Based on these data, we deduce that there would be a significant difference in the incidence of MACE between the two groups with the extension of follow-up.

Limitations

Several limitations need to be considered in the present study. First, we did not use the criteria relating to corneal arcus and molecular genetic testing for FH identification. Second, the LDL-C levels for FH diagnosis might have a certain bias: we used the estimated values rather than the true untreated LDL-C for the medical-treated patients; MI status has been demonstrated to generate changes in levels of circulating cholesterol known as the acute phase response. In addition, small sample size, short period of follow-up and loss of follow-up could contribute to a bias of the present result in our study.

Conclusion

Clinically diagnosed FH is relatively common in Chinese patients with premature STEMI. A low proportion of FH patients were prescribed high intensity statins. Despite aggressive cholesterol-lowering drugs, a significantly lower proportion of FH patients achieved LDL-C targets compared to unlikely FH patients. Possible FH patients were younger with a significantly higher occurrence of multi-vessel CAD and impaired cardiac function. There was no difference in MACE between two groups at one-year follow-up, thus emphasizing the need for continuous follow-up.

Supporting information

S1 Checklist. STROBE-checklist-cohort.

(DOC)
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Those who contributed to the work and meet the authorship criteria are listed as authors of the article. We also are indebted to the participants of this study.

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References

1. Henderson R, O’Kane M, McGilligan V, Watterson S. The genetics and screening of familial hypercholesterolaemia. J Biomed Sci. 2016; 23:39. Epub 2016/04/17. https://doi.org/10.1186/s12929-016-0256-1 PMID: 27084339

2. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Familial hypercholesterolaemia and coronary heart disease: a HuGE association review. Am J Epidemiol. 2004; 160(5):421–9. https://doi.org/10.1093/aje/kwh237 PMID: 15321838

3. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012; 97(11):3956–64. https://doi.org/10.1210/jc.2012-1563 PMID: 22893714

4. Sjouke B, Kusters DM, Kindt I, Besseling J, Defesche JC, Sijbrands EJ, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. Eur Heart J. 2015; 36(9):560–5. Epub 2014/03/04. https://doi.org/10.1093/eurheartj/ehu058 PMID: 24585268

5. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). Circulation. 2016; 133(11):1067–72. https://doi.org/10.1161/CIRCULATIONAHA.115.018791 PMID: 26976914

6. Nanchen D, Gencer B, Auer R, Raber L, Stefanini GG, Klingenberg R, et al. Prevalence and management of familial hypercholesterolemia in patients with acute coronary syndromes. Eur Heart J. 2015; 36(36):2438–45. https://doi.org/10.1093/eurheartj/ehv289 PMID: 26142466

7. Rallidis LS, Triantafyllis AS, Tsireboulos G, Katsaras D, Ralli M, Moutsatsou P, et al. Prevalence of heterozygous familial hypercholesterolemia and its impact on long-term prognosis in patients with very early ST-segment elevation myocardial infarction in the era of statins. Atherosclerosis. 2016; 249:17–21. https://doi.org/10.1016/j.atherosclerosis.2016.03.023 PMID: 27062405
8. Pang J, Poulter EB, Bell DA, Bates TR, Jefferson VL, Hillis GS, et al. Frequency of familial hypercholesterolemia in patients with early-onset coronary artery disease admitted to a coronary care unit. J Clin Lipidol. 2015; 9(5):703–8. https://doi.org/10.1016/j.jacl.2015.07.005 PMID: 26350818

9. Rerup SA, Bang LE, Mogensen UM, Engstrom T, Jorgensen E, Pedersen F, et al. The prevalence and prognostic importance of possible familial hypercholesterolemia in patients with myocardial infarction. Am Heart J. 2016; 181:35–42. https://doi.org/10.1016/j.ahj.2016.08.001 PMID: 27823691

10. Li S, Zhang Y, Zhu CG, Guo YL, Wu NQ, Gao Y, et al. Identification of familial hypercholesterolemia in patients with myocardial infarction: A Chinese cohort study. J Clin Lipidol. 2016; 10(6):1344–52. https://doi.org/10.1016/j.jacl.2016.08.013 PMID: 27919351

11. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011; 5(3 Suppl):S1–8. https://doi.org/10.1016/j.jacl.2011.04.003 PMID: 21600525

12. Goldstein JK H H, Brown MS In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. Familial hypercholesterolemia. The Metabolic & Molecular Bases of Inherited Disease. 2001; 8th ed (New York: McGraw-Hill):2863–913.

13. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013; 34(45):3478–90a. https://doi.org/10.1093/euheartj/eht273 PMID: 23956253.

14. Knowles JW, O'Brien EC, Greendale K, Wilemon K, Genest J, Sperling LS, et al. Reducing the burden of disease and death from familial hypercholesterolemia: a call to action. Am Heart J. 2014; 168(6):807–11. https://doi.org/10.1016/j.ahj.2014.09.001 PMID: 25458642.

15. Gumbs PD, Verschuren MW, Mantel-Teeuwisse AK, de Wit AG, de Boer A, Klungel OH. Economic evaluations of cholesterol-lowering drugs: a critical and systematic review. PharmacoEconomics. 2007; 25(3):187–99. PMID: 17339395

16. Ellis A, Zhou R, Stein EA. Effect of lipid-lowering treatment on natural history of heterozygous familial hypercholesterolemia in past three decades. Am J Cardiol. 2011; 108(2):223–6. https://doi.org/10.1016/j.amjcard.2011.03.027 PMID: 21545982

17. Shi Z, Yuan B, Zhao D, Taylor AW, Lin J, Watts GF. Familial hypercholesterolemia in China: prevalence and evidence of underdetection and undertreatment in a community population. Int J Cardiol. 2014; 174(3):834–6. https://doi.org/10.1016/j.ij.card.2014.04.165 PMID: 24801084

18. Mortensen MB, Kulenovic I, Klausen IC, Falk E. Familial hypercholesterolemia among unselected contemporary patients presenting with first myocardial infarction: Prevalence, risk factor burden, and impact on age at presentation. J Clin Lipidol. 2016; 10(5):1145–52 e1. https://doi.org/10.1016/j.jacl.2016.06.002 PMID: 27678431

19. De Backer G, Besseling J, Chapman J, Hovingh GK, Kastelein JJ, Kotseva K, et al. Prevalence and management of familial hypercholesterolaemia in coronary patients: An analysis of EUROASPIRE IV, a study of the European Society of Cardiology. Atherosclerosis. 2015; 241(1):169–75. https://doi.org/10.1016/j.atherosclerosis.2015.04.809 PMID: 25997074

20. Pijlman AH, Huijgen R, Verhagen SN, Imholz BP, Liem AH, Kastelein JJ, et al. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. Atherosclerosis. 2010; 209(1):189–94. https://doi.org/10.1016/j.atherosclerosis.2009.09.014 PMID: 19818960

21. Huijgen R, Kindt I, Verhoeven SB, Slijbrandt EJ, Vissers MN, Kastelein JJ, et al. Two years after molecular diagnosis of familial hypercholesterolemia: majority on cholesterol-lowering treatment but a minority reaches treatment goal. PLoS One. 2010; 5(2):e9220. https://doi.org/10.1371/journal.pone.0009220 PMID: 20169164.

22. Kawada-Watanabe E, Ogawa H, Koyanagi R, Arashi H, Yamaguchi J, Matsui K, et al. Rationale, design features, and baseline characteristics: The Heart Institute of Japan-PROper level of lipid lowering with Pitavastatin and Ezetimibe in acute coronary syndrome (HJU-PROPER). J Cardiol. 2017; 69(3):536–41. https://doi.org/10.1016/j.jcc.2016.05.002 PMID: 27349705

23. Zhao SP, Yu BL, Peng DQ, Huo Y. The effect of moderate-dose versus double-dose statins on patients with acute coronary syndrome in China: Results of the CHILLAS trial. Atherosclerosis. 2014; 233(2):707–12. https://doi.org/10.1016/j.atherosclerosis.2013.12.003 PMID: 24603217

24. Neefjes LA, Ten Kate GJ, Alexia R, Nieman K, Galema-Boers AJ, Langendonk JG, et al. Accelerated subclinical coronary atherosclerosis in patients with familial hypercholesterolemia. Atherosclerosis. 2011; 219(2):721–7. https://doi.org/10.1016/j.atherosclerosis.2011.09.052 PMID: 22018443
25. Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA. N-terminal fragment of the pro-hormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. Jama. 2007; 297(2):169–76. Epub 2007/01/11. https://doi.org/10.1001/jama.297.2.169 PMID: 17213400.